

The Role of Statin Therapy to Acutely Prevent Myocardial Damage in Patients Undergoing Percutaneous Coronary Intervention

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BACKGROUND:

Myocardial damage, or necrosis, can be assessed by elevated levels of creatine kinase-MB (CK-MB), troponin-I, and myoglobin in the blood when cellular injury has occurred. Elevation of these cardiac markers from damage during percutaneous coronary intervention (PCI) occurs in up to 31% of cases.¹ These peri-procedural elevations may occur for several reasons, including distal embolization of plaque or thrombus compromising coronary collaterals, increased sympathetic vasoconstrictor release, and side-branch occlusion, all of which can cause small zones of necrosis in the myocardium due to lack of coronary blood flow, referred to as a myocardial infarction (MI).² Elevated cardiac markers after PCI are associated with an increased risk of cardiac death, mortality, bypass surgery, and repeat coronary interventions.²

HMG-CoA reductase inhibitors “statins” have been proven safe and effective for the long-term reduction of cholesterol through their inhibitory actions in cholesterol synthesis. Statins have other cardioprotective, cholesterol-independent actions that occur within 24 hours of administration, including an increase in the formation of nitric oxide (NO) and vasodilatation, down-regulation of endothelial adhesion molecules, and decreased platelet recruiting and aggregation which can protect against myocardial damage.³⁻⁵

CLINICAL TRIAL SUMMARY:

The use of atorvastatin was assessed in a randomized, double-blind, placebo-controlled trial of 153 patients with chronic stable angina without previous statin treatment undergoing elective percutaneous coronary intervention (PCI).⁶ Patients received atorvastatin 40 mg daily or placebo for 7 days before undergoing PCI. Characteristics of the treatment groups were comparable, and included smokers, diabetes mellitus (DM), previous MI, PCI, or bypass surgery, hypercholesterolemia, hypertension, and ejection fraction (EF) >30%. The primary endpoint was occurrence of MI, defined as post-procedural increase of CK-MB >2 times above upper limit of normal (ULN) defined as 4ng/ml. MI was detected in 5% (4/76) of the atorvastatin group and 18% (14/77) of the placebo group (p=0.025). Fewer patients treated with atorvastatin showed an increase above the ULN in cardiac markers than placebo, elevation of CK-MB occurred in 12% (9/76) in the atorvastatin group versus 35% (27/77) in placebo (p=0.001), troponin-I 20% (15/76) versus 48% (37/77) (p=0.0004), and myoglobin 22% (17/76) versus 51% (39/77) (p=0.0005), respectively. After PCI, peak values of all cardiac markers were significantly lower in atorvastatin group versus placebo group: CK-MB 2.9±3 ng/mL versus 7.5±18 ng/mL (p=0.007), troponin-I 0.09±0.2 ng/mL versus 0.47±1.3 ng/mL (p=0.0008), and myoglobin 58±36 ng/mL versus 81±49 ng/mL (p=0.0002), respectively. Multivariate analysis showed that pretreatment with atorvastatin is associated with a reduced risk of peri-procedural MI (Odds Ratio [OR] 0.19, 95% Confidence Interval [CI] 0.05-0.57). The authors concluded that pretreatment with atorvastatin 40 mg daily for 7 days reduced peri-procedural myocardial damage in PCI patients with stable angina.⁶

Atorvastatin was also assessed in a randomized, prospective, double-blind, placebo-controlled trial of 171 patients with non-ST-segment elevation acute coronary syndrome (unstable angina or NSTEMI) sent to coronary angiography in <48 hours to undergo PCI.⁷ Patients received atorvastatin 80

mg loading dose 12 hours before angiography and an additional 40 mg 2 hours before angiogram/PCI procedure, or placebo at 12 hours and 2 hours before the procedure. After PCI, all patients received atorvastatin 40 mg daily for 30 days. Characteristics of the treatment groups were comparable, and included smokers, DM, previous MI, PCI, or bypass surgery, hypercholesterolemia, hypertension, and EF >30%, with 36% having NSTEMI and 64% having unstable angina. The primary endpoint was 30-day incidence of major adverse cardiac events, defined as death, MI (defined as post-procedural increase of CK-MB >2 times above ULN (4ng/ml) or >2 times baseline value) or unplanned revascularization (including bypass surgery or repeat PCI of target vessel). The primary endpoint occurred in 5% (4/86) in the atorvastatin group and 17% (14/85) in the placebo group ($p=0.01$), which consisted mainly of MI with the exception of one incidence of revascularization in the placebo group. After PCI, patients with elevated cardiac markers in atorvastatin versus placebo were: CK-MB 7% (6/86) versus 27% (23/85) ($p=0.001$), and troponin-I 41% (35/86) versus 58% (49/85) ($p=0.039$), respectively. Multivariable analysis identified pretreatment with atorvastatin as a predictor of decreased risk of major adverse cardiac events at 30 days (OR 0.12, 95% CI 0.05-0.50). The authors concluded that short-term pre-treatment with atorvastatin decreases the rate of adverse cardiac events in patients with unstable angina or NSTEMI.⁷

Atorvastatin was further assessed in a randomized, prospective, double-blind, placebo-controlled trial enrolling 383 patients on chronic statin therapy (>30 days) needing PCI who had stable angina with inducible myocardial ischemia, or non-ST-segment elevation acute coronary syndrome.⁸ Patients received atorvastatin 80 mg loading dose 12 hours before angiography and an additional 40 mg 2 hours before PCI, or placebo. After PCI, all patients received atorvastatin 40 mg daily for 30 days. Characteristics of the treatment groups were comparable, and included smokers, DM, previous MI, PCI, or bypass surgery, hypercholesterolemia, hypertension, and EF \geq 30%. The primary endpoint was 30-day incidence of major adverse cardiac events, defined as death, MI (defined as post-procedural increase of troponin or CK-MB >3 times above ULN (4ng/ml) or >3 times baseline value) or target vessel revascularization (including bypass surgery or repeat PCI of target vessels). The primary endpoint occurred in 3.7% (7/192) in the atorvastatin group and 9.4% (18/191) in the placebo group ($p=0.037$), which consisted mainly of MI with the exception of one death in the placebo group. Multivariable analysis showed atorvastatin reload as a predictor of decreased risk for 30-day major adverse cardiac events (OR 0.12, 95% CI 0.20-0.80). The authors concluded that short-term pre-treatment with high-dose atorvastatin before PCI is beneficial at preventing cardiac events in patients already on chronic statin therapy.⁸

Non-selective statin therapy was assessed in a randomized, controlled trial of 451 statin naïve patients scheduled for elective PCI.⁹ Patients received statin treatment 17 ± 8 (range 3-31) days before PCI, or no statin treatment. The statin therapies used were: 39% simvastatin (24 ± 9 mg/day), 29% atorvastatin (22 ± 9 mg/day), 29% pravastatin (32 ± 10 mg/day), and 3% fluvastatin (80 mg/day). Characteristics of the treatment groups were comparable, and included asymptomatic, stable or unstable angina, smokers, DM, previous MI, PCI, or bypass surgery, hypertension, and EF >40%. The primary endpoint was rate of a large non-Q-wave myocardial infarction, defined as a CK-MB elevation >5 times ULN (3.5 ng/ml) alone or associated with chest pain or ST segment or T wave abnormalities. The primary endpoint occurred in 8% (18/226) in the statin group and 15.6% (35/225) in the control group ($p=0.012$). There was no significant difference between the statins used and the primary endpoint in the statin group. Multivariable analysis identified statin pre-treatment as a predictor of decreased risk of CK-MB levels >5 times ULN (OR 0.33, 95% CI 0.13-0.86). The authors concluded that pre-treatment with a statin decreases the occurrence of large non-Q-wave myocardial infarctions after PCI.⁹

SUMMARY:

The short-term pre-procedural use of statins has been shown effective at reducing the 30 day occurrence of major adverse cardiac events in patients following PCI, most specifically cardiac marker elevation. Importantly these benefits have been shown in both elective and primary PCI as well as in statin naïve and chronically treated patients. Atorvastatin is the most extensively studied statin, but evidence suggests these benefits may extend to other statins as well. Longer term and larger studies are needed to truly demonstrate the long-term benefit of this strategy, but this evidence positions statins as a possible adjunct to optimize current perioperative drug therapy for patients undergoing PCI.

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