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Original article

Preloading with atorvastatin before percutaneous coronary intervention in statin-naïve Asian patients with non-ST elevation acute coronary syndromes: A randomized study

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ABSTRACT

Background: Data on atorvastatin pretreatment in Asian patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) are limited. However, there have been studies in other populations in Asia which demonstrated that statins can reduce the risk of periprocedural myocardial infarction (MI).

Methods and results: Statin-naïve patients with non-ST-segment-elevation (NSTE)-ACS scheduled for PCI were randomized to usual care or atorvastatin preloading groups. All patients received usual care including atorvastatin 40 mg/day. The atorvastatin group received atorvastatin 80 mg 12 h and 40 mg 2 h pre-PCI. Of 499 patients randomized, 247 were assigned to atorvastatin preloading. Following coronary angiography, 335 patients (163 atorvastatin) received PCI. During the 30 days post-PCI, major adverse cardiac events (death, MI, and target vessel revascularization) occurred in 24 (15%) atorvastatin and 27 (16%) usual care patients (p = NS). Post hoc analyses showed that at 8 h post-PCI, 3.82% of the atorvastatin group and 7.22% of the usual care group had a post-procedural creatine kinase-myocardial band (CK-MB) above 3 times the upper limit of normal (p = 0.27) and at 24 h post-PCI, the rate was 7.64% versus 9.47% (p = 1.0). Safety profile suggests that high-dose atorvastatin (40 mg) for up to 1 month, in conjunction with usual care, is relatively safe and well tolerated.

Conclusions: This study of statin-naïve Korean and Chinese patients with NSTE-ACS who received additional atorvastatin loading doses of 80 mg at 12 h, and 40 mg at 2 h, pre-PCI did not find a beneficial effect compared with usual post-PCI atorvastatin 40 mg/day treatment. Atorvastatin was found to be well tolerated in Asian patients with NSTE-ACS undergoing PCI. Results of the current study merit further investigation of the early use of statins in patients with NSTE-ACS to delineate patient subgroups who may benefit from this therapy.

Introduction

Recently, the potential of statin therapy to improve cardiovascular outcomes in acute coronary syndromes (ACS) or in association with percutaneous coronary interventions (PCI) has attracted increasing interest.

The earliest randomized trials of statin therapy in patients undergoing PCI—the Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA) studies—demonstrated beneficial effects of statin pretreatment on periprocedural major adverse cardiac events (MACE) in a range of acute patient groups [1–5]. Other trials have followed, also with largely positive results [6–11]. In a meta-analysis including 2088 statin-naïve PCI patients, periprocedural myocardial infarction (MI) occurred in significantly fewer patients after statin pretreatment than control [7]. Another meta-analysis comprising 4805 patients from 21 randomized, controlled trials demonstrated that pre-procedural statin use significantly reduced post-procedural MI after PCI and other surgery [8].

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While most studies have involved Western populations, some data in Asian patients have emerged [12–16]. In a Korean trial involving 445 ACS patients receiving PCI, MACE occurrence was 20.5% in the control group versus 9.8% in those who received pre-PCI rosuvastatin 40 mg [14]. Another study in 80 Chinese patients with non-ST-segment-elevation (NSTE)-ACS who received stent implantation established that high-dose, short-term pre-PCI atorvastatin was well tolerated with beneficial myocardial effects positively correlated with dose and frequency of atorvastatin administration [13].

Here, we report the results of the Asian Lipitor Pretreatment in ACS (ALPACS) study, which assessed the effect of pretreatment with atorvastatin on cardiovascular events in statin-naïve patients with NSTE-ACS scheduled for PCI in China and the Republic of Korea.

Methods

Study design

The protocol of ALPACS (NCT00728988, www.clinicaltrials.gov) has been described in detail previously [17]. This prospective, open-label study included statin-naïve Asian patients aged ≥18 years with NSTE-ACS (defined as unstable angina or NSTE-acute MI with coronary angiography to be undertaken within 72 h of the onset of symptoms) and low-density lipoprotein cholesterol (LDL-C) levels ≥2.07 mmol/L (80 mg/dL) at screening.

Key exclusion criteria included ST-segment elevation acute MI, NSTE-ACS with predefined features warranting emergency coronary angiography, left ventricular ejection fraction (LVEF) <30%, and previous or current statin treatment. Key prohibited medications were antilipidemic medication and cytochrome P450 inhibitors. See Appendix A for all exclusion criteria and prohibited medications.

The ALPACS study followed the Declaration of Helsinki and was approved by the ethics committee or institutional review board at each investigation site. Written informed consent was obtained from all patients.

Patients were randomized to either atorvastatin treatment (atorvastatin loading doses pre-PCI plus usual care) or usual care (usual care only). Screening occurred within 72 h prior to PCI. Enrolled patients were assessed at 12 and 2 h pre-PCI, 8 and 24 h post-PCI, and at end-of-study (30 days post-PCI). Assessments included physical examination; vital signs; electrocardiogram (ECG); and blood sampling for laboratory tests, including hematology, lipids, biochemistry, C-reactive protein (CRP), urinalysis, and cardiac biomarkers (troponin I, creatine kinase-myocardial band [CK-MB], and myoglobin).

Usual care treatments were in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) 2007 Guidelines for the Management of Patients with Unstable Angina/NSTE-MI [18]. Aspirin-naïve patients received aspirin according to local practice, 200–300 mg loading dose pre-PCI, and 100–200 mg/day thereafter. Patients taking aspirin at screening continued with their regimen. Clopidogrel 300 mg loading dose was administered at least 3 h pre-PCI and 75 mg/day thereafter. During hospitalization, patients also received subcutaneous heparin, enoxaparin (1 mg/kg every 12 h pre-PCI, every 12 h thereafter, or for at least 48 h post-PCI; or every 24 h if estimated creatinine clearance was <30 mL/min), or dalteparin [120 IU/kg (maximum 10,000 IU) every 12 h pre-PCI, every 12 h thereafter, or for a minimum of 48 h post-PCI]. Usual care also included atorvastatin 40 mg/day after PCI for 30 days. Patients in the atorvastatin group received all usual care treatments, plus atorvastatin loading doses of 80 mg at 12 h and 40 mg at 2 h pre-PCI.

Safety of atorvastatin was evaluated by the incidence, severity, and relationship to treatment of adverse events (AEs) including clinically significant changes in vital signs, ECG, and physical examination findings, also changes in laboratory parameters. Treatment-emergent AEs (TEAEs) of all-causality reported for ≥5% of patients in either treatment group were summarized.

Patient analysis sets and endpoints

Efficacy analysis was performed on the full analysis set (FAS: all patients who received ≥1 dose of study treatment and PCI) and per protocol (PP) analysis set. The FAS was the primary analysis set and was used for both primary and secondary efficacy analyses. The PP analysis set was used for the primary efficacy analysis only and included all patients who: (1) received ≥1 dose of study treatment; (2) were treated for ≥14 days, or discontinued before this time due to treatment failure; (3) were 80–120% compliant with the randomized treatment; (4) underwent PCI within 72 h of the onset of symptoms and 24 h of the first dose of atorvastatin; and (5) did not violate any inclusion or exclusion criteria that could affect the efficacy results.

The primary endpoint was the incidence of MACE (death, MI, and target vessel revascularization). By using the universal definition of MI [19], MI was defined biochemically as spontaneous [increased troponin exceeding 99th percentile of the upper reference limit (URL)] and PCI-associated (increased cardiac biomarker of more than 3 × 99th percentile of URL). Secondary endpoints included the incidence of MACE at 8 and 24 h post-PCI; the proportion of patients with any elevated biomarkers of myocardial injury (troponin I, CK-MB, and myoglobin) above the upper limit of normal (ULN) at 8 h, 24 h, and 30 days post-PCI; the change in CRP at these time points; and the safety and tolerability profile of atorvastatin in the presence of underlying usual care in this population.

Statistical methods

For each group, enrollment of 251 patients was planned to allow for approximately 158 evaluable (i.e. treated and received PCI) patients. The study was powered with 90% chance of detecting a difference in MACE incidence of 17% versus 5% between treatment groups within 30 days post-PCI. The difference in MACE (and its three components) incidence within 30 days post-PCI between the treatment groups was presented with a p-value and 95% confidence interval (CI) calculated by a 5% two-sided continuity-corrected chi-squared test. Fisher's exact test was used whenever the expected frequency of events was <5.

Unadjusted odds ratio (OR) and 95% CI for MACE (and its three components) at 30 days post-PCI were calculated by a logistic regression model using treatment group as the only covariate with the usual care group as the reference; adjusted OR and 95% CI were calculated by including treatment group and the following potential confounding covariates: age, gender, country, NSTE-MI, LVEF ≥40%, and use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel antagonists, or diuretics.

MACE- and MI-free comparison up to 30 days post-PCI between treatment groups was analyzed using Kaplan–Meier method with a log-rank test.

For secondary efficacy analyses, incidence rates of MACE within 8 and 24 h post-PCI and the proportions of patients with any elevated biomarkers of myocardial injury above the ULN from baseline at 8 h, 24 h, and 30 days post-PCI were compared by treatment group and visit. The difference in the proportions was analyzed using the same calculation method used for MACE analysis.

During the trial, the high sensitivity-CRP reagents used for 207 samples were found unstable, leading to an overall 20% positive bias for affected samples. To evaluate the impact of the affected samples, a sensitivity analysis was performed for the following sample