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Prehospital statin therapy and one-year mortality in patients with stable coronary artery disease undergoing percutaneous coronary intervention

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ABSTRACT

Background: Statins have multiple effects in patients with coronary artery disease. No studies have investigated whether chronic statin pretreatment before percutaneous coronary intervention (PCI) has an impact on long-term mortality in patients with stable angina.
Methods: The study included 8041 patients with stable angina. At the time of PCI, 5939 patients (73.8%) were receiving statins for ≥1 month before procedure and 2102 patients (26.2%) were not receiving statins. The primary outcome analysis was 1-year mortality.
Results: There were 192 deaths during the follow-up: 119 deaths among patients receiving statins and 73 deaths among patients not receiving statins (Kaplan–Meier estimates of 1-year mortality 2.06% and 3.59%; unadjusted hazards ratio [HR] = 0.56, 95% confidence interval [CI] 0.42–0.75; P<0.001). Landmark analysis showed that almost all mortality benefit occurred in the first 30-days after PCI: 10 deaths among patients receiving statins and 22 deaths among patients not receiving statins (Kaplan–Meier estimates of 30-day death, 0.17% and 1.06%, respectively; HR = 0.16, 95% CI 0.08–0.34, P<0.001). No significant difference in mortality according to statin pretreatment between 30 days and 1 year was observed (109 deaths among patients receiving statins vs 51 deaths among patients not receiving statins; Kaplan–Meier estimates 1.89% and 2.53%; HR = 0.75, 95% CI 0.53–1.05, P = 0.095). After adjustment in the Cox proportional hazards model, statin pretreatment was associated with a 35% reduction in the adjusted risk for 1-year mortality (adjusted HR = 0.65, 95% CI 0.44–0.98, P = 0.039).
Conclusions: Pretreatment with statins before PCI was associated with a significant reduction of 1-year mortality in patients with stable angina.

1. Introduction

Earlier observational studies have shown that statin pretreatment in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) significantly reduced periprocedural complications including myocardial infarction [1] and early mortality mostly in patients with unstable CAD [2]. Stable angina is the commonest form of CAD [3] and the most frequent indication for performing PCI [4]. In the last decade several randomized studies have investigated the impact of pretreatment with statins on the outcome of patients with stable angina undergoing PCI [5–12]. Most of these studies [5–10] but all of them [11,12] showed a benefit from the statin pretreatment before PCI especially in terms of reduction of the peri-PCI myocardial infarction. Nevertheless, a recent meta-analysis of randomized statin trials that included patients with stable and unstable angina showed that short-term statin pretreatment before PCI was associated with a significant decrease of peri-PCI myocardial infarction and 30-day incidence of major adverse cardiac events, with no impact on 30-day incidence of death [13]. Several characteristics of these studies deserve concern. First, these studies included small numbers of patients (from 42 patients in the study by Kinoshita et al. [9] to 573 patients in the study by Briguori et al. [8]) Second, all these trials used high-dose statin therapy for short treatment intervals before PCI (from 12 h to 2 weeks before PCI) which were too short to produce significant effects on cholesterol level. Third, all these studies investigated the impact of statin therapy on peri-PCI complications or short-term outcome (mostly 30-day outcome). No studies so far have investigated whether statin pretreatment before PCI has an impact on long-term mortality of patients with stable angina. Thus, we undertook this study to investigate whether statin pretreatment before PCI has an impact on 1-year mortality in patients with stable angina.

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2. Materials and methods

2.1. Patients

Between March 2000 and December 2009, 8041 consecutive patients with stable CAD underwent coronary angiography and PCI in the Deutsches Herzzentrum, Munich, Germany. To be included in the study patients had to have chest pain that did not change its pattern within the last 2 months, angiographic documentation of CAD and information on statin use before admission available. Patients presenting with acute coronary syndromes, acute infections, advanced kidney disease (serum creatinine ≥2 mg/dl) and known malignancies with life expectancy <1 year were excluded. Data on the statin use before admission were collected in every patient. Definitions of risk factors including hypercholesterolemia, arterial hypertension, smoking and diabetes are provided in a prior publication from our group [14]. Body mass index was calculated using patients' weight and height measured during the hospital course. The glomerular filtration rate was estimated using the Cockcroft–Gault formula [15]. The study conforms with the Declaration of Helsinki and has been approved by the institutional ethics committee.

2.2. Angiographic evaluation and definitions

CAD was diagnosed in the presence of coronary stenoses ≥50% lumen obstruction in, at least, one of the three major coronary arteries. Coronary atherosclerotic burden was estimated using the Gensini score [16]. In brief, concentric lesions and eccentric plaques were scored by 1, 2, 4, 8, 16, and 32 in case of 25, 50, 75, 90, 99 and 100% lumen obstruction, respectively. The significance of the myocardial area supplied by a given coronary segment was also considered and quantified by a multiplying factor (from 1 to a maximal 5 if the lesion involves the left main segment). The final atherosclerotic burden score equals the sum of all segments scores, each derived from the severity of lumen obstruction multiplied by the factor of segment significance. The complexity of lesions was defined using the modified American College of Cardiology/American Heart Association grading system. Class B2 and C lesions were considered complex. In patients with preserved renal function, left ventricular ejection fraction was measured on left ventricular angiograms using the area length method. Side branch closure/compromise was defined as, at least, 1 grade reduction in the post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow grade compared with pre-procedural flow in the same artery. Digital angiograms were analyzed offline with an automated edge detection system (CMS; Medis Medical Imaging Systems, Nuenen, The Netherlands) in the core angiographic laboratory by staff unaware of statin use.

Stent implantation and periprocedural care were performed according to standard criteria. Antiplatelet therapy consisted of clopidogrel (300 mg or 600 mg as a loading dose followed by 75 mg/day for at least 4 weeks) and aspirin (200 mg/day administered orally and continued indefinitely). Coronary stents were used in 7162 patients (89%); the remaining 879 patients (11%) were treated with balloon angioplasty alone.

2.3. End point definition and follow-up

The primary outcome analysis was all-cause mortality at 1 year after PCI procedure. Secondary outcomes included incidence of cardiac death, myocardial infarction or stroke. The follow-up protocol consisted of a phone interview at 1 month, a visit at 6 months and a phone interview at 12 months following index procedure. Information on deaths was obtained from hospital records, death certificates or phone contact with relatives of the patient or referring physician. Cardiac death was defined according to the Academic Research Consortium criteria and included any death due to proximate cardiac cause (e.g., myocardial infarction, low-output failure and fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment [17]. The diagnosis of myocardial infarction was based on the development of new abnormal Q waves in >2 contiguous precordial or >2 adjacent limb leads; or, an elevation of creatine kinase-myocardial band (CK-MB) >2 times (>3 times for the 48 h after a PCI procedure) the upper limit of normal. Patients who had clinical events during the follow-up underwent a complete clinical, electrocardiographic and laboratory evaluation. Follow-up information and event adjudication were performed by staff unaware of clinical diagnosis or statin use before admission.

2.4. Statistical analysis

Data are presented as median (25th; 75th percentiles), number of patients/events or proportions (%). The normality of distribution of continuous data was assessed using the Kolmogorov–Smirnov test. Continuous data were compared with the Kruskal–Wallis rank-sum test. Categorical data were compared with Chi-square test. Survival analysis was performed with the use of the Kaplan–Meier method. Comparison between the groups according to statin use was performed with the log-rank test and by calculation of hazard ratios. Landmark analysis was performed to assess early and late risk of death or myocardial infarction. A 30-day time point after the PCI was selected as a landmark for conducting the analysis of survival by response. Only patients alive at the landmark time are included in the analysis [18]. The multivariable Cox proportional hazards model was used to assess the association between statin use before admission and 1-year mortality. All variables of Table 1 were entered into the model. All analyses were performed using S-plus statistical package (S-PLUS, Insightful Corp, Seattle, Washington). A two-tailed $P<0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

The study included 8041 patients with stable CAD. Of them, 5939 patients (73.8%) were on statin therapy for ≥1 month and 2102 patients (26.2%) were not on statin therapy at the time of admission. Baseline characteristics of patients according to statin use were shown in Table 1. With the exception of proportions of patients with arterial hypertension and diabetes (including those on insulin therapy) and body mass index, all other demographic and clinical characteristics appear to differ significantly between groups with and without statin therapy. Of note, patients receiving statins had a significantly higher atherosclerotic burden across all degrees of the Gensini score than patients who were not receiving statins at the time of admission (Fig. 1).

Post-procedural TIMI flow grade ≤2 was observed in 88 patients on statins (4.2%) versus 261 patients (4.4%) without statins ($P=0.411$). Side branch closure/compromise was observed in 135 patients on statins (2.3%) versus 61 patients (2.9%) without statins ($P=0.108$). Glycoprotein IIb/IIIa inhibitors (abciximab) were used as bail-out therapy in 367 patients on statins (6.2%) versus 240 patients (11.4%) without statins ($P<0.001$).

3.2. One-year outcome

There were 192 deaths during the 1-year follow-up. Differences in the baseline characteristics in survivors and nonsurvivors are shown in Table 2. There were 119 deaths among patients who were receiving statins and 73 deaths among patients who were not receiving statins at the time of admission (Kaplan–Meier estimates of 1-year mortality 2.06% and 3.59%; unadjusted hazards ratio [HR] = 0.56, 95% confidence interval [CI] 0.42–0.75; $P<0.001$; Fig. 2). Landmark analysis for the primary outcome with a prespecified landmark at 30 days was performed to assess early and late risk of death in groups with and without statins on admission. There were 32 deaths in the first month after index admission: 10 deaths among patients on statin therapy and 22 deaths