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Failure to achieve recommended LDL cholesterol levels by suboptimal statin therapy relates to elevated cardiac event rates

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Abstract

Objectives: The majority of patients with myocardial infarction (MI) and hypercholesterolaemia does not achieve guideline recommended low-density lipoprotein cholesterol (LDL) levels. Suboptimal dosages of statins explain this dilemma in most patients.
Design and setting: We evaluated the relationship between statin treatment quality (optimal: LDL<115 mg/dl, suboptimal: LDL≥115 mg/dl, no statin therapy despite hypercholesterolaemia) and the subsequent incidence of coronary events (coronary death, nonfatal MI, bypass surgery) over a 30 months follow-up in a large cohort of post MI patients with hypercholesterolaemia (n=2045). Analysis was performed in a nested case–control manner comparing 173 cases with a coronary event and 346 matched controls.
Results: Patients who developed a coronary event were treated optimally in 11.0%, suboptimally in 43.4% (p<0.05 vs. optimal treatment) and were untreated in 45.7% (p<0.001 vs. optimal treatment). Respective numbers in event-free patients were 21.4%, 47.7%, and 30.9%. After adjustment for most potential confounders, including all cardiovascular risk factors and medication, the relative risk of future non-fatal MI and coronary death associated with a suboptimal statin treatment was 2.02 (95% CI 1.04 to 4.18) compared to optimal statin treatment. Moreover, the statin equivalent dose in optimally treated individuals was significantly higher than in suboptimally treated individuals (0.85±0.03 vs. 0.78±0.02, p<0.05).
Conclusion: In this community-based study, a lipid lowering therapy with statins into the recommended target range of LDL levels may be associated with decreased cardiovascular risk compared to a statin therapy without titrating the LDL level below 115 mg/dl. Thus, the quality of statin treatment was identified as an independent predictor of coronary events in post MI patients.

Keywords: Statins; Myocardial infarction; Secondary prevention; Routine care; Quality of health care

1. Introduction

Numerous epidemiological studies established the relationship between elevated low-density lipoprotein cholesterol (LDL) levels and cardiovascular morbidity and mortality [1–3]. Complementary to these findings, clinical trials indicate beneficial effects of HMG-CoA reductase inhibitors (statins) by LDL lowering [4–8]. Consequently, recommendations for LDL target levels and statin treatment are included in European and American guidelines for both, primary and secondary prevention of coronary artery disease.

Despite the clear benefits achieved by the reduction of LDL, in the overall population the majority of patients with myocardial infarction (MI) and hypercholesterolaemia fails to reach recommended LDL levels [9–17]. Suboptimal dosages of statins have been identified as the main reason for this failure [12–17].

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The aim of this study attempts to answer the question whether insufficient LDL-cholesterol lowering with statin therapy relates to elevated event rates by studying a large cohort of MI patients from a population-based registry.

2. Subjects and methods

2.1. Study population

A cohort of post MI patients was selected from a German MI family registry, in which subjects were identified by screening of patient charts from 17 cardiac rehabilitation centers distributed throughout Germany. Specifically, patients with a first MI under the age of 60 years and a positive family history for coronary artery disease were invited to participate in the study.

From all study participants, a standardized questionnaire was obtained by specially trained telephone interviewers regarding medical history, presence of coronary risk factors, clinical events, medication, anthropometric data and socio-economic background. These information were validated by analyzing retrospectively medical records from hospital stays and primary physicians. Additionally, all patients underwent measurements of weight, height, heart rate and blood pressure as well as a venous blood collection during a visit scheduled at their primary care doctors' office. Blood pressure was measured in a standardized fashion in sitting position after 5 min of rest on the right arm using a standard mercury sphygmomanometer (mean of three readings). Blood samples were immediately centrifuged and serum samples were sent standardized to a single clinical chemistry laboratory for lipid analysis (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides).

For the present investigation, post MI patients with hypercholesterolaemia were enrolled if a history of documented MI for >6 months but <5 years before enrollment in the study existed, if they remained event-free during this time interval and if they did not complain about any cardiac-specific symptoms for >6 months.

The resulting study cohort consisted of 2045 patients with documented previous MI and hypercholesterolaemia. While 1396 patients were treated with statins on a regular basis since the MI, 649 patients never received a statin treatment despite hypercholesterolaemia. All patients participating in this investigation were followed-up for 30 months by telephone interviews.

2.2. Definition of hypercholesterolaemia and other risk factors

Cardiovascular risk factors were defined according to the guidelines for secondary prevention of the European Society of Cardiology [18]. Hypercholesterolaemia was diagnosed when the total cholesterol level was above 190 mg/dl and/or when the LDL level was above 115 mg/dl or when lipid lowering therapy was administered. LDL levels were determined using the Friedewald formula when triglycerides were below 400 mg/dl (4.52 mmol/l). Arterial hypertension was considered when systolic blood pressure was above 140 mm Hg and/or diastolic blood pressure above 90 mm Hg or when subjects either were currently using antihypertensive medication or were known to have a history of arterial hypertension. Diabetes mellitus was considered with the history of diabetes or the intake of antidiabetic medication or glycosylated haemoglobin levels above 6.5%. Smokers were current smokers when they consumed five or more cigarettes per day on a regular basis.

2.3. Follow-up investigation

At follow-up, clinical outcomes were recorded and a detailed history of current medication was documented. For all possible events, clinical information was sought directly from hospital or general practitioners' charts. All details of ECG, hospital admissions, enzymes, surgical operations, and treatment were collected and classified according to MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) criteria as described previously [19]. After 2.5 years, follow-up was achieved in >95% of the cohort.

Outcome was defined by a combined endpoint that included coronary events (nonfatal myocardial infarction, coronary deaths as well as the need and accomplishment of a coronary artery bypass grafting). All events were checked by a medical committee to provide independent validation of the event.

2.4. Design

We used the nested case–control approach, which has the advantage of allowing for statistically efficient analysis of data from a cohort with substantial savings in cost and time. A total of 173 MI patients within the cohort who subsequently developed an event enlisted above were selected as cases. For each confirmed case, two MI patients who remained free of any event were randomly selected, matched by sex, age (±5 years), and duration of coronary artery disease before study enrollment (±1 year). As objective information on left ventricular function was frequently not available, we used the intake of diuretics as rough indication for symptoms of heart failure [20]. Subsequently, cases were additionally paired with controls matched for the intake of diuretic agents.

2.5. Definition of optimal, suboptimal and untreated patients

The treatment was predominantly managed by the primary physicians of the patients (63% general practitioners, 32% specialists for internal medicine or cardiology, 5% other specialists) and reflects the treatment practice in European population based registries [11]. Patients who permanently