Acute Ischemic Heart Disease

The impact of smoking on long-term outcome of patients with premature (≤35 years) ST-segment elevation acute myocardial infarction

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Background There are few data regarding the long-term prognosis of young survivors of acute myocardial infarction (AMI). We explored the long-term outcome in individuals who had sustained a premature ST-segment elevation AMI.

Methods We recruited 257 consecutive patients who had survived their first AMI ≤35 years of age. Patients were followed up for up to 18 years. Clinical end points included all major adverse coronary events (MACE): cardiac death, readmission for acute coronary syndrome, arrhythmias, or coronary revascularization due to clinical deterioration.

Results The most prevalent risk factor at presentation was smoking (93.7%). Follow-up data were obtained from 237 patients (32.2 ± 3.7 years old). The median follow-up period was 9.1 years. During follow-up, 139 (58.6%) patients reported continuation of smoking. Ninety-one (38.4%) patients had recurrent MACE (13 deaths, 59 acute coronary syndromes, 2 arrhythmias, and 17 revascularizations). Multivariable Cox regression analysis showed that persistence of smoking, left ventricular ejection fraction (LVEF), and reperfusion therapy (fibrinolysis or primary coronary angioplasty) were independent predictors of MACE after adjustment for conventional risk factors. Continuation of smoking remained an independent predictor for MACE after additional adjustments for LVEF (hazard ratio 2.154, 95% CI 1.313-3.535, $P = .002$) or reperfusion treatment (hazard ratio 2.327, 95% CI 1.423-3.804, $P = .001$). Harrell *c* statistic showed that the model with persistent smoking had the best discriminatory power compared with models with LVEF or reperfusion treatment.

Conclusions In the era of statins and reperfusion treatment, continuation of smoking is the strongest independent long-term predictor for recurrent MACE in young survivors of premature AMI. (Am Heart J 2015;169:356-62.)

Acute myocardial infarction (AMI) is an uncommon entity in young adults. The incidence of premature AMI depends on the cutoff age used.[1-3] Schoenenberger et al[4] reported that 0.7% of patients with acute coronary syndrome (ACS) were 35 years or younger.

Patients with premature AMI have several characteristics that differentiate them from older patients. Young patients with AMI have a different risk factor profile compared with older patients, characterized by a higher proportion of heavy smoking and a lower proportion of hypertension and diabetes mellitus.[5] Another distinct characteristic of young patients is the less atheromatic burden in their epicardial coronary arteries, mainly due to the relatively high proportion of angiographically "normal" coronary arteries.[5,6]

Several studies have shown that young patients with AMI have a more favorable prognosis than older patients.[7,8] However, in most studies, the cutoff limit for premature AMI was set in the range of 40 to 55 years.[9-11] There is only one study performed ~40 years ago that enrolled very young survivors of AMI, that is, ≤45 years old, and provided data on a medium-term prognosis.[5] Therefore, it is challenging to explore the long-term outcome in individuals who had had an AMI at young age (ie, ≤35 years) in the era of widespread use of statins and reperfusion treatment with fibrinolysis or primary coronary angioplasty.

Methods

Study population

We enrolled 257 consecutive patients who had survived their first AMI occurring ≤35 years of age. They were recruited from the coronary care unit of 2 large hospitals (Attikon University Hospital in Athens and General Hospital of Nikea in Piraeus) between 1996 and

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2010. Only patients with ST-segment elevation AMI were enrolled. The diagnosis of ST-segment elevation AMI was based on the following criteria: history of typical chest pain lasting >30 minutes, electrocardiographic changes characterized by ST-segment elevation ≥1 mm in at least 2 adjacent leads, and diagnostic evolutionary pattern of markers of myocardial injury.

All patients underwent coronary angiography and left ventriculography prior to discharge. Coronary artery stenosis was defined as >50% reduction in lumen diameter of any of the 3 coronary arteries or their primary branches. Coronary arteries with smooth contours and no focal diameter reduction or with non-hemodynamically significant atherosclerotic lesions (<50% stenosis) were defined as "normal".

Peripheral blood samples were collected from patients within 12 hours from admission for assessing lipid levels. All participants were interviewed during hospitalization, and the risk factors were recorded. *Hypercholesterolemia* was defined as total cholesterol >200 mg/dL (>5.2 mmol/L) or the use of cholesterol-lowering agents; *hypertension* was defined as blood pressure ≥140/90 mm Hg or a history of previous antihypertensive treatment; *diabetes mellitus* was defined as fasting plasma glucose >125 mg/dL (6.94 mmol/L) or the use of glucose-lowering treatment. Smoking habits (ie, number of cigarettes smoked per day, duration of smoking, continuation of smoking after AMI), and body mass index (BMI; weight in kg/height^2 in m^2) were also evaluated. *Obesity* was defined as BMI ≥30 kg/m^2, and metabolic syndrome (MS) was diagnosed using the criteria of the American Heart Association/The National Heart Lung and Blood Institute.[12] Before discharge, smokers had a 5- to 10-minute smoking cessation counseling by the attending cardiologist.

Follow-up

After discharge, all young coronary patients were followed up at 12-month intervals by trained cardiologists at Attikon Hospital. If they were unable to attend their appointment, data were obtained by telephone interview. If the patient reported an admission due to recurrent coronary event, he/she was asked to bring or send by fax the discharge summary of the hospitalization. In addition, between September 2013 and April 2014, all patients were contacted by telephone to assess their clinical status. If patients were not found, information was obtained by family members or patients' treating physician. Therefore, the follow-up period ranged between 4 and 18 years. End points included all major adverse coronary events (MACEs), that is, (*a*) coronary deaths and (*b*) readmissions for ACS, arrhythmias, or revascularization (coronary angioplasty or coronary artery bypass graft) due to clinical deterioration. Events occurred during their initial hospitalization were not included in clinical end points. In case of death, the cause of death was verified by verbal or written contact with the treating physician. Noncardiac deaths were not included in the analysis.

Regarding the smoking status, patients were classified as nonsmokers (patients who had never smoked), quitters (patients who were smoking at the time of the incident AMI, quit after the event, and reported nonsmoking at follow-up) and persistent smokers (patients who smoked before the onset of AMI and continued to smoke during follow-up regularly at least 5 cigarettes/d). In addition, persistent smokers were classified those who smoked until AMI, quit temporarily after AMI, and then resumed smoking. In case of recurrent coronary events, the patient was considered as smoker if he/she smoked at least 3 months prior to the event.

Finally, all patients underwent an echocardiographic study and the left ventricular ejection fraction (LVEF) was measured using the biplane method of disks (modified Simpson rule).

The study was approved by the ethics committee of our institution, and all subjects gave their informed consent.

Statistical analysis

Continuous variables are expressed as mean ± SD and were compared between groups of patients using Student *t* test or Mann-Whitney *U* test. Categorical variables are presented as absolute and relative frequencies, and associations between categorical variables were tested using the χ^2 test. Hazard ratios (HRs) and corresponding 95% CIs were calculated using Cox proportional hazards models. Proportionality of hazards was assessed using Schoenfeld residuals and the linear assumption using Martingale residuals. Event-free survival was analyzed by Kaplan-Meier method, and the log-rank test was used to evaluate differences in survival between groups. The Harrell *c* statistic was applied to compare the Cox regression models with LVEF, reperfusion, and persistent smoking.[13] Harrell *c* statistic is a rank-based measure that indicates the agreement of the fitted model between observed and predicted values. Higher values of the *c* statistic indicate higher predictive value of the model. The likelihood ratio test—by calculating the difference between −2log likelihood—was used to assess whether the Cox model with persistent smoking has better added predictive value compared with the model without persistent smoking. A *P* value <.05 was considered significant. The SPSS version 22 (SPSS Inc, Chicago, IL) statistical package was used for all statistical calculations.

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Results

Baseline characteristics

We initially recruited 257 consecutive patients who had survived their first AMI ≤35 years of age. Two patients