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Prevalence of heterozygous familial hypercholesterolaemia and its impact on long-term prognosis in patients with very early ST-segment elevation myocardial infarction in the era of statins

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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is an important cause of early onset coronary artery disease. We assessed the prevalence of clinical heterozygous FH (HeFH) among patients with very early ST-segment elevation myocardial infarction (STEMI), its management and its impact on long-term prognosis in the era of widespread utilization of statins.

Methods: We recruited prospectively 320 consecutive patients who had survived their first STEMI ≤35 years of age. Using the Dutch Lipid Clinic Network algorithm patients having HeFH (possible, probable or definite) were identified.

Results: Sixty-five patients (20.3%) had definite/probable HeFH and 163 patients (50.9%) had possible FH. Two years after discharge among 51 patients with definite/probable HeFH and available lipid levels, 43 (84.3%) were taking statins of whom 10 (23.3%) were on high-intensity statin therapy but only 1 (2.3%) of the statin-treated patients had LDL cholesterol levels <1.8 mmol/L (70 mg/dL). After a median follow-up of 9.1 years, major adverse coronary events (MACE) occurred in 99 (38.8%) of 255 patients with available follow-up information. Definite/probable HeFH was associated with an excess risk for recurrence of MACE independently of statin use, continuation of smoking after the STEMI, hypertension, diabetes mellitus, and sex (hazard ratio = 1.615, 95% confidence interval, 1.038 to 2.512, p = 0.03).

Conclusions: One out of five patients who develop STEMI ≤35 years of age has definite/probable HeFH and despite the use of statins there is a therapeutic gap and a high recurrence rate of cardiac events during long-term follow-up.

1. Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant inherited disorder of lipoprotein metabolism characterized by a high risk of premature coronary artery disease (CAD). Heterozygous FH (HeFH) has a prevalence of 1/200 to 1/500 in the general population and is caused by mutations in the low density lipoprotein (LDL) receptor gene or less frequently by mutations in the genes encoding apolipoprotein-B and proprotein convertase subtilisin/kexin type 9 (PCSK9) [1,2]. Early identification of patients with FH is of utmost importance, since timely treatment may reduce the risk of premature CAD [3]. Statins, which lower serum LDL cholesterol (LDL-C) by 40–55%, are the cornerstone for reducing the risk of cardiovascular events in patients with FH [4–7].

Acute myocardial infarction (AMI) is an uncommon entity in young adults and its incidence depends on the cut-off age used. It has been reported that <1% of patients with acute coronary syndromes (ACS) are ≤35 years [8]. Young patients with AMI have a different risk factor profile than older patients, characterized by a higher proportion of heavy smoking and lower proportion of hypertension and diabetes mellitus (DM) [9]. Recent data suggest that a phenotypic diagnosis of HeFH is relatively common in hospitalized patients with premature ACS [10].

Given the fact that FH is widely underdiagnosed and

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undertreated, it becomes evident that prompt diagnosis and treatment should be sought, especially in younger patients, to minimize the duration of the exposure to high LDL-C levels [11]. In our study, we assessed a) the prevalence and lipid management of clinical HeFH among patients with very early (≤35 years of age) ST-segment elevation myocardial infarction (STEMI) and b) the impact of HeFH on long-term prognosis in the era of widespread utilization of statins.

2. Methods

2.1. Study population

We enrolled 320 (279 men) consecutive patients who had survived their first STEMI at ≤35 years of age. The diagnosis of STEMI was based on the presence of characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST-segment elevation and subsequent release of biomarkers of myocardial necrosis [12]. The patients were recruited prospectively from 2 tertiary large hospitals (Attikon University Hospital in Athens and General Hospital of Nikea in Piraeus) between 1996 and 2014.

All patients underwent cardiac catheterization during hospitalization and significant coronary artery stenosis was defined as >50% reduction in lumen diameter of any of the three coronary arteries or their main branches. Coronary arteries with smooth contours and no focal diameter reduction or with non-haemodynamically significant atherosclerotic lesions (<50% stenosis) were defined as “normal or near normal”.

Peripheral blood samples were collected from patients within 24 h from admission for assessing lipids, apolipoproteins and lipoprotein(a) [Lp(a)] levels. Hypertension was defined as blood pressure ≥140/90 mmHg or a history of previous antihypertensive treatment; DM was defined as fasting plasma glucose >6.94 mmol/L (125 mg/dL) or the use of glucose lowering treatment. Smoking habits and body mass index [BMI] (weight in kg/height^2 in m^2) were also evaluated.

2.2. Diagnosis of familial hypercholesterolaemia

For the diagnosis of HeFH we used the Dutch Lipid Clinic Network (DLCN) algorithm which provides a numerical score to predict the probability of diagnosing HeFH. DLCN algorithm takes into consideration LDL-C levels, signs of physical examination (tendon xanthomas and arcus cornealis), personal and family history of premature cardiovascular disease (CVD), and molecular diagnosis of HeFH. Points are assigned for each characteristic as follows: 1 point for a family history of premature CVD (<55/60 years for men/women, respectively), 2 points for personal history of premature CVD (<55/60 years for men/women, respectively), 6 points for tendon xanthomas, 4 points for arcus cornealis at age ≤45 years, 1 point for an LDL-C of 4.0–4.9 mmol/L (155–189 mg/dL), 3 points for an LDL-C of 5.0–6.4 mmol/L (190–249 mg/dL), 5 points for an LDL-C of 6.5–8.4 mmol/L (250–329 mg/dL), 8 points for an LDL-C of ≥8.5 mmol/L (330 mg/dL) and 8 points for an identified FH mutation. A total point score of >8 is considered “definite” HeFH, 6–8 “probable” HeFH, 3–5 “possible” HeFH and 0–2 “unlikely” HeFH [11,13,14]. In our study we combined the categories “definite” HeFH and “probable” HeFH into one category (definite/probable HeFH).

2.3. Follow-up

After discharge all young coronary patients were followed-up at 12–24 months 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 was asked to bring or send by fax the discharge summary. Additionally, between June 2014 and December 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. Endpoints included all major adverse coronary events (MACE) i.e.: a) coronary deaths and b) readmissions for ACS, arrhythmias or revascularization (percutaneous coronary intervention or coronary artery bypass graft) due to clinical deterioration. Events that occurred during their initial hospitalization were not included in clinical endpoints. In case of death the cause of death was verified by verbal or written contact with the treating physician. Non-cardiac deaths were not included in the analysis.

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

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD and were compared between groups of patients using Student's *t*-test or Mann-Whitney test. Categorical variables were presented as percentages, and associations between categorical variables were tested using the chi-square test. Analysis of variance (ANOVA) for repeated measurements was used to compare the differences between groups followed by Bonferroni correction for multiple testing. The Kruskal-Wallis H test was applied as a non-parametric equivalent to test the differences of not normally distributed variables between groups. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated using Cox proportional-hazards models. Event-free survival was analysed by Kaplan-Meier method, and the log-rank test was used to evaluate differences in survival between groups. A p value < 0.05 was considered significant. The SPSS version 22 (SPSS Inc., Chicago, Illinois, USA) statistical package was used for all statistical calculations.

3. Results

3.1. Baseline characteristics

Among 320 patients with premature STEMI, 65 (20.3%) had definite/probable HeFH, 163 (50.9%) possible HeFH and 92 (28.8%) unlikely HeFH (Fig. 1).

Table 1 shows the baseline characteristics of the young patients according to HeFH diagnosis. Patients with definite/probable HeFH had higher total cholesterol, LDL-C, triglycerides and Lp(a) levels and higher proportion of family history of premature CAD compared to non-HeFH patients, i.e. patients with unlikely HeFH. There was no difference regarding the prevalence of sex, smoking, DM or hypertension.

All patients with definite/probable (n = 65) had hemodynamically significant CAD. In particular, 18 (27.7%) patients had 3 vessel-disease (VD), 12 (18.5%) had 2 VD and 35 (53.8%) had 1 VD. Patients with possible or unlikely HeFH (n = 255) had less atheromatic burden, i.e. 16 (6.3%) patients had 3 VD, 42 (16.5%) had 2 VD, 148 (58.0%) had 1 VD and 49 (19.2%) had “normal or near normal” coronary arteries.

Before hospitalization only two patients (3.1%) with definite/probable HeFH were taking statins. At discharge the vast majority (97.2%) were given statins. Two years after the event among 51 survivors with definite/probable HeFH who had available lipid levels, 43 (84.3%) were on statins but only 1 (2.3%) of them had achieved LDL-C levels <1.8 mmol/L (70 mg/dL). Of those on statins