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Familial hypercholesterolemia among unselected contemporary patients presenting with first myocardial infarction: Prevalence, risk factor burden, and impact on age at presentation

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BACKGROUND: Familial hypercholesterolemia (FH) is a hereditary disease carrying a substantial lifetime risk of coronary heart disease.

OBJECTIVE: To assess the prevalence of FH and its impact on age at presentation among unselected patients with first myocardial infarction (MI).

METHODS: In a multi-center cross sectional study, we identified 1381 unselected patients presenting with a first MI between 2010 and 2012. Clinical FH was assessed using both the Dutch Lipid Clinic Network (DLCN) criteria and the Simon Broome criteria.

RESULTS: Based on the DLCN criteria, 2.0% of patients with first MI had "probable/definite" FH, whereas 4.7% had "possible" FH according to the Simon Broome criteria. In the 291 (21%) patients with premature MI, 6.9% had "probable/definite" FH (DLCN criteria), and 11.0% had "possible" FH (Simon Broome criteria). Nearly all premature "probable/definite" and "possible" FH patients had at least one additional marker of high cardiovascular risk including current smoking (72%–80%) and hypertension (40%–44%). In multivariable-adjusted linear regression modeling, patients with "probable/definite" FH using DLCN criteria had their first MI 14.6 years (95% confidence interval [CI], 9.6–19.6 years) earlier than non-FH patients. Likewise, "possible" FH patients using Simon Broome criteria were associated with having an MI 9.1 years (95% CI = 6.3–12.4) earlier than non-FH patients.

CONCLUSION: Clinical FH is common and associated with markedly earlier age of first MI, especially when combined with additional markers of high risk, indicating an unmet need for earlier identification of FH to ensure global risk factor control. First MI constitutes a unique opportunity to detect families with unknown FH.

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Introduction

Familial hypercholesterolemia (FH) is a common autosomal-dominant disease characterized by impaired hepatic clearance of low-density lipoprotein (LDL) cholesterol causing severe hypercholesterolemia and, consequently, development of atherosclerosis and coronary

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heart disease (CHD).[1,2] FH can be caused by mutations in 1 of 3 genes encoding the LDL receptor, apolipoprotein B-100 (apoB100), or proprotein convertase subtilisin/kexin 9 (PCSK9). In clinical practice, the diagnosis of FH does not necessarily need identification of the disease-causing mutation (mutation diagnosis) but is based on measured LDL-cholesterol, physical examination, and personal and family history of CHD (clinical diagnosis).[1] Two validated algorithms for identification of clinical FH are widely used, namely the Dutch Lipid Clinic Network (DLCN) criteria and the Simon Broome criteria. The prevalence of clinical FH in the general population was previously considered to be 0.2% (1:500) but has recently been estimated to be as high as 0.5% (1:200).[1,3]

As recently highlighted, FH remains underdiagnosed and undertreated in the general population. This constitutes a considerable problem as individuals with FH have a more than 10-fold increased risk of CHD that, when timely identified, can be reduced effectively with lipid-lowering medication, primarily statins.[4] As FH is often asymptomatic until a first myocardial infarction (MI), screening for FH among such patients may be an effective way for identifying families with possible FH in whom to perform subsequent cascade screening to facilitate early identification and treatment of FH.

The prevalence of FH among patients with first MI, however, is unknown. Two recent studies have yielded very different results regarding the prevalence of clinical FH in patients with CHD ranging from 1.6% to 8.3%.[5,6] In the present study, we aimed to determine the prevalence of FH in unselected and contemporary patients presenting with a first MI as well as assessing their global risk factor burden and the relationship between FH and age at first MI.

Materials and methods

Study population

We designed a cross sectional study of contemporary and consecutive patients admitted with a first MI to 4 Danish hospitals (University Hospital Aarhus and the Regional Hospitals in Randers, Herning, and Horsens) in 2010–2012.[7,8] The universal definition of MI is implemented in Denmark, and patients were identified using the *International Classification of Disease, Tenth edition* codes I21.0 through I21.9. Plasma cholesterol was measured within 24 hours of admission to the hospital and/or from a prior contact the health care system. Family history was self-reported. The blood pressure was obtained before admission (if hospitalized previous year) or after recovery from MI (before hospital discharge or at the first visit to the rehabilitation clinic). Hypertension was defined as use of blood pressure–lowering medication before admission and/or a systolic blood pressure >140 mm Hg. The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.

Clinical FH diagnosis

We assessed clinical FH using 2 validated algorithms; the DLCN criteria and the Simon Broome criteria. These algorithms identify clinical FH based on age at CHD, LDL-cholesterol levels, and family history. As information on tendon xanthomas in the patients or in first-degree relatives was not available for this study, patients could not be identified as definite FH using the Simon Broome criteria.

Using the DLCN criteria (Supplementary Table 1), 1 point was given for a first-degree relative with premature CHD, 2 points were given for premature CHD in the index patient. Based on the LDL-cholesterol levels, 1 point was given for LDL-cholesterol in the interval: 4.0–4.9 mmol/L, 3 points for LDL-cholesterol: 5.0–6.4 mmol/L, 5 points for LDL-cholesterol: 6.5–8.4 mmol/L, and finally, 8 points were given if LDL-cholesterol was >8.5 mmol/L. In those on a statin at admission (simvastatin 40 mg in nearly all), we corrected the LDL-cholesterol levels by assuming a 37% reduction in LDL-cholesterol by statins.[9] The patients were diagnosed "no" FH if they had 0–2 points, "possible" FH if they had 3–5 points, "probable" FH if they had 6–8 points and "definite" FH if they had >8 points. For this study, we combined "probable" and "definite" FH into a single diagnosis called "probable/definite" FH.

Using the Simon Broome criteria, "possible" FH was diagnosed if LDL-C was >4.9 mmol/L plus personal or family (first-degree relative) history of premature CHD (age <60 years). Otherwise, the patients were "no" FH.

Statistical analysis

Baseline characteristics are presented as mean (±standard deviation). Baseline characteristics were compared with one-way ANOVA, Mann–Whitney test, or chi-square test. The proportion of patients with first MI diagnosed "possible" (Simon Broome) and "probable/definite" (DLCN) FH was calculated for the overall cohort and for patients with premature MI (age <60 years in women and <55 years in men).

The association of "possible" and "probable/definite" FH with age at first MI was assessed using multivariable linear regression analysis (age as the dependent variable). The variables included in the model were FH diagnosis, gender, smoking, diabetes, and statin use at baseline. The output of these analyses (β-coefficients) represents the change in age at first MI by presence vs absence of the covariate condition.

Finally, logistic regression analyses were used to assess the association of "possible" (Simon Broome) and "probable/definite" (DLCN) FH with development of premature MI. These results are presented as odds ratio with 95% confidence intervals (CIs).

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