The prevalence and prognostic importance of possible familial hypercholesterolemia in patients with myocardial infarction

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Aims Familial hypercholesterolemia (FH) is a common genetic disorder causing accelerated atherosclerosis and premature cardiovascular disease. The aim of this study was to examine the prevalence and prognostic significance of possible FH in patients with myocardial infarction (MI).

Methods and results By individual-level linkage of data from the Eastern Danish Heart Registry and national administrative registries, a study population of patients referred for coronary angiography due to MI was selected. The study population was divided into "unlikely FH" and "possible FH" based on the Dutch Lipid Clinic Network criteria, which included a plasma low-density lipoprotein cholesterol (LDL-C) and age for onset of cardiac disease. A score of ≥3 points was used as the cutpoint between the 2 groups.

Among the study population of 13,174 MI patients, 1,281 (9.7%) had possible FH. These patients were younger (59.1 vs 65.7 years, $P \leq .0001$), had similar levels of comorbidities, and were treated more aggressively with cholesterol-lowering drugs compared with patients with unlikely FH. During a median of 3.3 years of follow-up, the unadjusted and adjusted event rates of recurrent MI were higher in patients with possible FH compared with unlikely FH (16% vs 11%, adjusted hazard ratio 1.28, 95% CI 1.09-1.51, $P = .003$.). Differences in adjusted all-cause mortality were not statistically significant (17% vs 23%, adjusted hazard ratio 0.89 [0.74-1.04], $P = .1$).

Conclusion We found that MI patients with possible FH have higher risk of recurrent MI but similar risk of mortality compared with unlikely FH patients. Further studies on secondary prevention are warranted. (Am Heart J 2016;181:35-42.)

Familial hypercholesterolemia (FH) is a genetic disease associated with significantly increased risk of atherosclerotic disease including myocardial infarction (MI).[1,2] It is characterized by increased levels of plasma low density lipoprotein cholesterol (LDL-C) and is diagnosed using sets of clinical criteria and genetic testing for disease-causing mutations. The mode of inheritance is autosomal dominant and the disease covers a broad spectrum of genetic mutations mainly due to loss-of-function mutations in the low-density lipoprotein receptor, mutations in the LDL-receptor ligand apolipoprotein B, and gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 causing an increased degradation of LDL receptors. These mutations lead to an impaired uptake and accumulation of LDL-C in plasma, causing premature development of atherosclerosis and coronary artery disease (CAD).[3] If heterozygous FH patients are left untreated, it is estimated that 50% of men at the age of 50 years and 30% of women at the age of 60 years will have had an MI.[4]

The prevalence of heterozygous FH has been estimated to be 1:500 in Western populations with no founder effect, but a Danish study published in 2012 estimated a prevalence of 1:200.[5] Intensive LDL-C–lowering treatment for FH patients before the development of clinical cardiovascular disease significantly decreases the risk of developing CAD and can lower the risk of MI to that of the general population.[6,7] However, there is still a severe underdiagnosis and undertreatment of FH, and hence,

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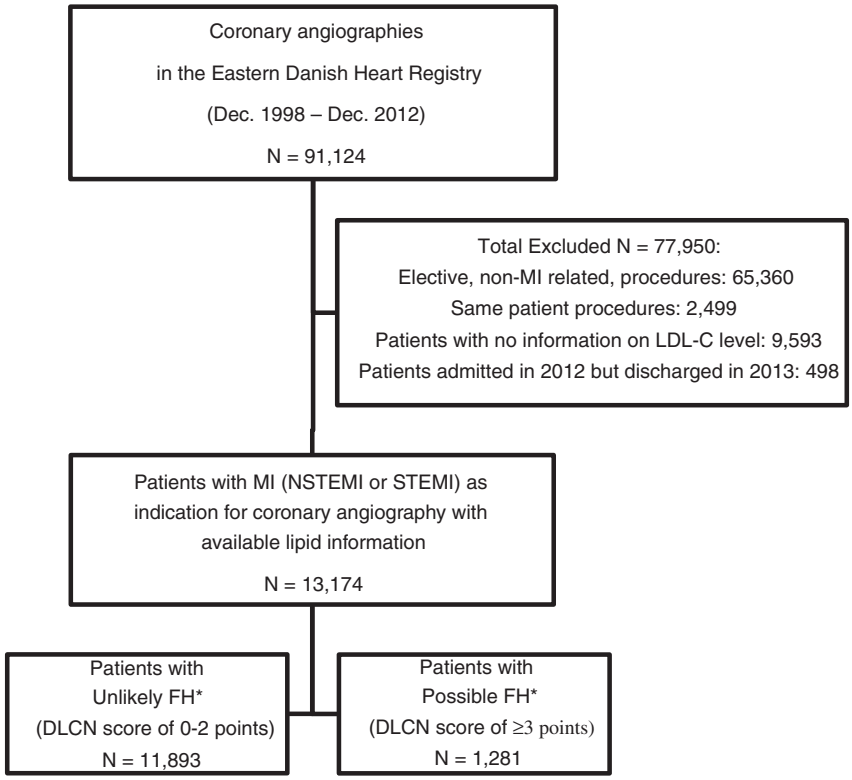
Figure 1



Flowchart displaying the selection of the study population. *For patients who were on lipid-lowering medication, the LDL-C value was multiplied by a drug and dose dependent correction factor.

there are a large proportion of patients with FH who develop severe CAD.[8] One study has investigated the standardized mortality ratio and showed FH in recent times to be associated with a coronary heart disease (CHD) with a standardized mortality ratio of 2.13.[9] However, data regarding clinical outcomes on the long-term for patients with possible FH are sparse, which led us to investigate the prevalence of possible FH among patients with MI and examine the prognostic significance.

Methods

Data sources

The data used in this study were gathered from multiple Danish registries and linked on individual-level by the unique civil registration number that every citizen in Denmark is given by birth or immigration to the country. Information on cardiac procedures was obtained through the Eastern Danish Heart Registry, which is a quality improvement registry that has been collecting data from all patients in eastern Denmark undergoing coronary angiography and percutaneous coronary intervention since 1998.[10] Data regarding use of medication, including statins, were gathered from the Register of Medicinal Product Statistics, providing information on all prescribed drugs sold in Danish pharmacies. Details on the patients' medical history were collected from The Danish National Patient Registry via discharge diagnoses. The coding of diagnoses follows the *International Classification of Diseases* (*ICD-8* before 1994 and *ICD-10* thereafter). Information on cause of death was obtained from the Danish National Cause of Death Registry which includes all deaths in Denmark, based on death certificates filled in by physicians. Retrospective registry-based studies do not require ethical approval in Denmark. This study was approved by the Danish Data Protection agency.

Study population

The source of the study population was patients enrolled in the Eastern Danish Heart Registry from December 1998 to December 2012 (Figure 1). Having ST-elevation MI (STEMI) or non–ST-elevation MI (NSTEMI) as the cause for referral to coronary angiography, in addition to available information