ABSTRACT

Background: Familial hypercholesterolemia (FH) is a common autosomal dominant disorder caused by loss-of-function mutations in the low-density lipoprotein (LDL) receptor or apolipoprotein B-100 gene, or gain-of-function mutations in proprotein convertase subtilisin/kexin type 9, resulting in very high blood cholesterol levels and premature cardiovascular disease (CVD).

Hypotheses/ Objectives:

1. FH patients who have developed CVD differ from those free of CVD by specific lipid and non-lipid risk factors.
2. The specific lipid and non-lipid risk factors differ in FH patients who develop CVD early(men<45, women<55 with evidence of CVD) and those resistant to CVD patients (men>60, women>70 with no evidence of CVD).
3. These risk factors risk factors differ between men and women.
4. These risk factors differ between ethnic groups.

Methods: A retrospective chart review of patients in the Prevention Clinic was carried out to find individuals with "definite" FH according to the Dutch Lipid Clinic Network Criteria (DLCNC) and determine which patients in this cohort developed CVD. Information regarding mortality and the cause of death in this cohort was obtained through the BC Vital Statistics Registry. Cox proportional hazard regression analysis was used to assess the association of risk factors to hard cardiovascular outcomes in univariate and multivariate analyses.

Results: A total of 446 patients were identified as having "definite" FH based upon the DLCNC with 116 (26%) patients having hard evidence of CVD. There were 197 males, of which 35% developed CVD, and 249 females, of which 19% developed CVD. The mean age of onset of CVD was 49.5 in males and 56.5 in females. In the "extreme" subgroup comparison, 51 people were identified as "CVD susceptible" 72 people were identified as "CVD resistant". Male sex, smoking, family history of premature CVD, diabetes mellitus, low HDL-C and high Lp(a) proved to be significant, independent risk factors for CVD in the entire FH cohort. The same risk factors remained significant when comparing FH patients susceptible to CVD to those resistant to CVD. Of note, LDL-C and hypertension were not important risk factors for CVD in this cohort likely due to drug treatment. In men, family history, diabetes and low levels of HDL-C were significant risk factors for CVD while in women smoking, diabetes mellitus, low levels of HDL-C and high Lp(a) were significant risk factors for CVD. There were minimal detectable differences in risk factors between ethnicities.

Conclusion: In our ethnically diverse cohort with extensively documented risk factors, the significant and independent risk factors for CVD in decreasing order of importance were, male sex, diabetes, high Lp(a), smoking, family history of premature CVD, and low HDL-C in both the entire group as well as in the most susceptible subgroup. Men and women with FH differed in the impact of the risk factors on the presence of CVD.