Cardiovascular Disease Risk Associated With Familial Hypercholesterolemia: A Systematic Review of the Literature

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ABSTRACT

Purpose: The goal of this study was to determine cardiovascular disease (CVD) risk associated with familial hypercholesterolemia (FH).

Methods: A systematic review of the published literature was conducted. All publications describing FH risk from PubMed ("cardiovascular disease risk + familial hypercholesterolaemia," 2004–2015), Internet and Medline search of FH registries, and associated references were screened for FH-related CVD risk in titles, abstracts, and study methods. CVD risk expressed as rates, odds, or ratios of mortality and morbidity were extracted. Each article was reviewed for bias by 2 reviewers within 17 items in 7 categories; a modified Newcastle-Ottawa assessment scale was used for nonrandomized studies.

Findings: The complete literature search identified 712 potential publications: 549 from PubMed (Medline), 150 from registries, and 13 from references. Fourteen articles met the inclusion criteria: 8 from registries in the United Kingdom, the Netherlands, Norway, and Spain; 5 from single hospitals or families in Japan, Denmark, the Netherlands, and the United Kingdom; and a population survey in Denmark. Across studies, attrition bias was low in 22 (80%) of 28 items. Risk of selection bias was high in 35 (63%) of 56 items. Selection bias risk was due to low representativeness and lack of a non-FH comparator group within the same study; detection bias risk was due to variable definitions of CVD outcomes/measurement; and performance bias risk was due to long-term, intensive treatment, the most common limitations for registries. Studies from single hospitals and families lacked generalizability. In contrast, the Danish study revealed a low bias in each of the 4 selection bias criteria and 2 attrition risk criteria. Fatal and nonfatal CVD events were collected in the study. Comparing patients with FH versus non-FH patients, the odds ratios for coronary artery disease were 10.3 (95% CI, 7.8–13.8) and 13.2 (95% CI, 10.0–17.4) in subjects treated and not treated with lipid-lowering therapy, respectively. These ratios fall within the ranges of ratios reported in other studies but are generally higher than the ratios from registries and clinics, in which intensive specialized management is available.

Implications: There is a lack of available data describing CVD risk in patients with FH, and many of the existing studies have biases in their design that could affect their risk estimates. A Danish study had the highest quality based on a predefined quality check list, providing the most credible estimates of the increase in CVD risk in patients with FH. The CVD risk due to FH is high and represents unmet medical need for patients with FH. Further research is warranted to validate the magnitude of risk. (*Clin Ther.* 2016;38:1696–1709) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bias, cardiovascular disease, familial hypercholesterolemia, lipid-modifying therapy, risk.

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INTRODUCTION

Familial hypercholesterolaemia (FH) is a genetic disorder characterized by autosomal inheritance in genes related to LDL-C metabolism, which results in lifelong elevation of LDL-C. More than 1500 mutations have been identified in the LDL receptor gene (*LDLR*), as well as mutations in other genes leading the clinical FH phenotype.[1]

The major clinical manifestation of FH results from the prolonged exposure of the vasculature to high levels of LDL-C, which leads to the development of atherosclerotic lesions in the heart, brain, and peripheral arteries.[2] These lesions in the arterial wall gradually progress in size, occupying an increasing proportion of the arterial lumen over time. This scenario in turn results in restriction of blood flow, with clinical symptoms of ischemia, such as angina, developing when $\geq 70\%$ obstruction occurs.[3] However, most acute complications, such as myocardial infarction (MI) and sudden cardiac death, occur in lesions that are not severely obstructed, and the first manifestation of coronary disease is often sudden death or nonfatal MI in one half of men and women. These events occur at a higher frequency and at an earlier age in patients with FH than in patients without FH or patients with polygenetic causes of elevated LDL-C.[4]

The risk of cardiovascular disease (CVD) is affected by additional risk factors, including obesity, diabetes, smoking, hypertension, male sex, and age, as well as risk factors that are in addition to the risk associated with increased LDL-C in both FH patients and non-FH patients.[1] The interaction of these additional risk factors in FH compared with non-FH patients is not well understood or studied.

The genetic mutation leading to FH is present at birth with the increased level of LDL-C being asymptomatic until the occurrence of end-organ damage. Hence, patients can come to the attention of the health care system through the development of end-organ damage, the serendipitous performance of a LDL-C measurement, or an active screening program, in which individuals are generally targeted for screening because of a family association or a general population-level screening program.[5] Early management and primary CVD prevention, with aggressive treatment of LDL-C levels with lipid-modifying therapy and modification of other risk factors, have been found to be effective.[6] The effectiveness of primary prevention has led to the introduction of screening programs in some countries and a call for increased awareness by the European Society of Cardiology.[7] Screening uses clinical criteria for FH, and no genetic mutations are identified in many patients who have a clinical phenotype of FH.[8]

Estimating the absolute increase in cardiovascular risk resulting from FH is complicated. Case ascertainment is likely to be biased toward patients experiencing symptoms and cardiovascular events. When FH is identified, modification of risk factors, particularly LDL-C, will reduce the risk of cardiovascular events. Recent evidence has also demonstrated an increased risk of raised concentrations of the LDL-like particle plasma lipoprotein(a).[9] Comparison populations will likely be diluted by unidentified patients with FH, leading to an overestimation of cardiovascular risk in the comparison group. Prevalence of risk factors such as smoking, obesity, and hypertension, as well as their management and impact, will also likely differ between patients with FH and the general population, adding further complexity to calculating the absolute risk of CVD due to FH.[10]

The rate of increase in cardiovascular risk associated with FH is important in determining the likely adoption of screening and primary prevention programs for the management of FH, as well as new therapies recently approved to better manage patients with FH and their CV risk.[11]

With these complexities in mind, the goal of the present study was to examine the literature systematically and to quantify, if possible, the excess risk of cardiovascular disease in FH, assessing the adequacy and availability of the evidence according to a study quality checklist to support health technology assessment decision-making.

MATERIALS AND METHODS

A systematic search of the literature was undertaken to identify studies that examined the risk of cardiovascular disease in FH. A Medline search using the search string "((((Cardiovascular Disease Risk + Familial Hypercholesterolaemia) NOT Nursing) AND English [Language]) NOT randomized controlled trials) NOT reviews [Publication Type]" was performed for articles published between January 1, 2004, and December 31, 2015. An additional targeted