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Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States

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ABSTRACT

Background/objectives: Familial hypercholesterolemia (FH) is a genetic disorder that leads to premature heart disease or stroke if untreated. Statins are effective for individuals with FH but less than 20% of actual cases are diagnosed in the US and many people are not adherent to treatment. Using new knowledge regarding mutations responsible for FH, some European countries have developed genetic FH screening strategies, many of which have been shown to be cost-effective. This study evaluates the cost-effectiveness of genetic screening and lipid-based screening with statin adherence measures compared to lipid-based screening alone in the US.

Methods: A decision tree was used to estimate disease detection with the three screening strategies, while a Markov model was used to model disease progression until death, quality-adjusted life years (QALYs) and costs from a US societal perspective.

Results: The results showed that Genetic Screening cost $15,594 for 18.29 QALYs per person and Lipid Screening with adherence measures cost $16,385 for 18.77 QALYs compared with $10,396 for 18.28 QALYs for Lipid Screening alone. The incremental cost-effectiveness ratio (ICER) of Genetic Screening versus Lipid Screening was $519,813/QALY and that of Lipid Screening with adherence measures versus Lipid Screening alone was $12,223/QALY. At a US willingness-to-pay threshold of $150,000/QALY Genetic Screening is not cost-effective compared with Lipid Screening. Sensitivity analyses showed that results were robust to reasonable variations in model parameters.

Conclusions: Although genetic screening is currently not a cost-effective option in the US, health outcomes for FH individuals could benefit from adherence measures encouraging statin use.

1. Introduction

Heterozygous familial hypercholesterolemia (FH) is a genetic disorder that affects about 1 in 500 Caucasians in the US [1]. While the exact pathways of this disease are still unknown, recent research has focused on mutations of the low-density lipoprotein (LDL) receptor gene (*LDLR*) and the gene for apolipoprotein B (*APOB*) as indicators for genetic FH diagnosis [2]. In individuals with FH, mutations in the genes responsible for plasma low-density lipoprotein cholesterol (LDL-C) clearance cause abnormal accumulation of cholesterol in the blood and premature coronary heart disease (CHD) and stroke. According to estimates of CHD risk from the Health Technology Assessment program in the UK, untreated Caucasian heterozygous FH individuals are up to four times more likely to develop CHD by the age of 60 than the non-FH population [3]. Treatment and outcomes for homozygous FH are different than those for the heterozygous form, and not the topic of this study [1].

Together, the economic and quality-of-life consequences of premature CHD present a huge burden in the US. The American Heart Association (AHA) estimates that in the US CHD and stroke cost $108.9 billion and $53.9 billion each year, respectively, including both direct and indirect costs [4]. In addition, it is estimated that for up to one-third of CHD patients, their first disease symptom is sudden cardiac death (SCD), and health-related quality-of-life for survivors decreases 30–50% following a major event, such as an acute myocardial infarction (AMI), angina, or stroke [5,6].

Abbreviations: FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; AMI, acute myocardial infarction; SCD, sudden cardiac death; CVD, cardiovascular disease; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; HDL-C, high-density lipoprotein cholesterol; PSA, probabilistic sensitivity analysis.

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Currently, the 2013 American College of Cardiology (ACC) and AHA cholesterol guidelines encourage more widespread use of statins in potential cardiovascular disease (CVD) patients, such as people with LDL-C levels ≥ 190 mg/dL, which includes FH individuals [7]. However, it is estimated that less than 20% of actual FH cases are diagnosed in the US and, according to the Centers for Disease Control and Prevention (CDC), less than 50% of adults with high cholesterol are getting treatment [8,9]. To address low levels of diagnosis and treatment, many European countries have established guidelines encouraging genetic testing for FH. For instance, the UK's National Institute for Health and Clinical Excellence (NICE) recommends using cascade screening with genetic testing to detect new FH cases for immediate lipid-lowering treatment. Cascade screening involves identifying index cases with a previous diagnosis of FH and screening first, second, and, possibly, third degree relatives for FH as soon as possible. Recently, a few European analyses have used both economic modeling and data from country-specific cohorts to demonstrate the cost-effectiveness of these newer genetic cascade screening strategies in improving treatment rates and health outcomes for the FH population [1,10–13].

However, no recent cost-effectiveness analyses (CEAs) have been conducted from a US perspective. Further, the current cost of genetic sequencing and mutation detection tests can be thousands of US dollars, yet the sensitivity of these tests is variable because hundreds of biomarkers could potentially be linked to FH [1]. FH genetic testing kits validated in European countries have not been validated in the US where the common population mutations may vary from those identified in European patient populations. In addition to genetic screening, another possible option to improve outcomes for FH individuals in the US is the use of statin adherence programs, many of which have been demonstrated to improve adherence and heart disease outcomes in randomized trials [14]. Because the treatment and disease consequences of FH are clinically identical to those due to high cholesterol from other reasons, such a program would not only benefit FH individuals but also high cholesterol individuals with no FH gene mutations. By using the information available between Europe and the US, this study is the first to attempt a complete cost-effectiveness model for the US FH population, which considers the effect of statin adherence and includes modeling of both disease diagnosis and progression.

1.1. Objectives

The objective of this study is to evaluate the cost-effectiveness of two FH screening and treatment strategies not currently used in the US, compared with the lipid cascade screening strategy currently recommended for individuals with high cholesterol and a family history of FH or heart disease (Lipid Screening) [7,15]. The two new strategies will include genetic cascade screening of at-risk relatives from an index case (Genetic Screening) and an enhanced lipid cascade screening strategy that includes a statin adherence program (Lipid Screening + AD). This study will evaluate the incremental cost-effectiveness ratios (ICERs) between the three screening arms, Lipid Screening, Genetic Screening and Lipid Screening + AD, in 2013 US dollars per quality-adjusted life year (QALY). The results of this study will add to the limited cost-effectiveness literature regarding FH in the US and provide insight into where current screening and treatment pathways can be best improved.

2. Methods

2.1. The model

The analysis was conducted with a US societal perspective and lifetime time horizon. An initial cohort of 1000 Caucasian male adults with a family history of FH and high-risk baseline cholesterol levels of 46 mg/dL high-density lipoprotein cholesterol (HDL-C), 224 mg/dL LDL-C, and 305 mg/dL total cholesterol were followed in a Markov model simulation using Microsoft Excel. Because females have different baseline health-state utilities and risk profiles for heart disease, the model focuses on male patients. The baseline levels were adapted from the study population for the UK's Simon Broome Register of Familial Hyperlipidaemia, where genetic testing and FH data is most available [16]. Average systolic blood pressure by age group was obtained from a report based on the Framingham Heart Study, as the Simon Broome Register data did not include blood pressure by age [17]. Parameters for transition probabilities, health-state utilities, and costs were derived from peer-reviewed literature and publically available databases. All costs and QALYs were discounted using an annual discount rate of 3% [18].

The model uses a decision tree to estimate first year screening costs and diagnosis probabilities, and a Markov model to simulate heart disease progression and cost outcomes for the initial cohort in each of the three screening arms. The decision tree for FH screening differentiates between the two lipid cascade screening strategies and the genetic cascade screening strategy. Fig. 1 outlines the different procedures. In Genetic Screening, index cases are individuals with a previous clinical diagnosis of FH based on cholesterol levels. Because common US FH gene mutations have not been identified and are possibly different from European mutations, gene sequencing is conducted in index cases to identify familial mutations in the *LDLR* or *APOB* genes and improve efficiency of genetic mutation detection [3]. Because of the large number of mutations linked to FH and possible high cholesterol due to non-genetic factors, approximately 3.4 index cases must be sequenced to reach one genetic diagnosis of FH and identify one familial FH mutation [1]. Index cases with a genetic diagnosis are assumed to provide an average of 2.5 relatives who are male adults, alive, at risk and agree to be screened [1]. These relatives will make up the initial cohort for the Markov model. Using the DNA mutation identified from a respective index case, relatives will be tested for FH using a site-specific DNA mutation detection test with an assumed sensitivity based on genetic testing strategies in the UK of 78.5% [1,2]. Given the accessibility, affordability, and effectiveness of statins, all positive FH cases from Genetic Screening will be prescribed statin therapy. Negative cases will be given an LDL-C test with a sensitivity of 91% to diagnose FH cases missed in genetic testing and to ensure that all high LDL-C cases are identified [1]. Because cholesterol levels are highly variable in an individual at any given time and LDL-C tests do not directly measure the amount of LDL particles, LDL-C tests cannot provide a 100% guarantee of FH diagnosis, but will help identify high cholesterol individuals who require statin therapy. Those who test positive will be prescribed statin therapy, while the remaining negative cases will continue to be tested with LDL-C tests every two years, as long as they adhere to the intervention.

The approach for lipid cascade screening, with or without a statin adherence program, does not involve extra testing of the index cases. At-risk relatives are identified from index cases and diagnosed for FH based on LDL-C levels. Again, all positive FH cases are treated with statins, plus an adherence program in the Lipid Screening + AD arm, while negative cases will continue to be tested for high LDL-C until everyone from the initial cohort with dyslipidemia is on statin therapy.

All individuals from these screening programs will enter the Markov model to simulate their health outcomes at 1-year intervals until death. The Markov model is shown in Fig. 2 and includes three health states: Pre-CVD, CVD Event/Stroke, and Death. All individuals start in the Pre-CVD state and enter the CVD Event/Stroke state following a first AMI, angina, or stroke event. While FH individuals are mainly at risk for AMI or angina, high cholesterol also increases the risk for cardiovascular events and stroke [1]. After an event individuals will transition to the Death state in the case of a CVD-related or non-CVD-related fatality. Individuals can also transition directly from the Pre-CVD state to Death due to either SCD, a CVD-related fatality or a non-CVD-related fatality. Approximately 22.7% of individuals who experience a first CVD or stroke event will die from SCD [5,19]. Similar models with pre-event, post-event and Death states have been used previously to simulate cardiovascular outcomes, although not specifically for an FH population [20–23]. Event incidences from the US were used to estimate the proportion of CHD individuals who had an AMI, angina, or stroke event in the CVD Event/Stroke state for health-state utility and cost calculations [19]. Different events were not modeled separately due to insufficient evidence regarding statin efficacy for specific events in a US FH setting. The final outcome of the Markov model is a calculation of life expectancy and discounted QALYs for individuals from the initial cohort of each screening arm. These values are used in cost and ICER calculations.

2.2. Transition probabilities

Transition probabilities between the health states in the Markov model depend on the risk of CVD and CVD-related death calculated with the Framingham Heart Study risk equations [24,25]. The main parameters are summarized in Table 1 with 95% confidence intervals, when available. Statin efficacy in all arms is based on a moderate daily dose of 10 mg atorvastatin to minimize possibility of medication-related side effects, but adherence decreases with time on statin treatment across arms and is increased with the statin adherence program in the Lipid Screening + AD arm only [26–31]. Individuals diagnosed with FH or high LDL-C in the Pre-CVD and CVD Event/Stroke state in this arm receive an annual lipid test and physician follow-up, monthly mailed educational pamphlets regarding CVD risk and statin therapy, monthly mailed refill reminders, and 10-minute monthly pharmacist counseling calls to discuss adherence. Here, a fairly comprehensive adherence program is described to ensure that all reasonable cost elements will be included in the model. The percent increase in statin adherence with a treatment adherence program was derived from a randomized controlled trial of a comprehensive pharmacy care program with similar components [31]. While not a long-term experiment, the study used