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PCSK9 Inhibitors Show Value for Patients and the US Health Care Systemt

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ABSTRACT

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were approved by the US Food and Drug Administration (FDA) as cholesterol-lowering therapies for patients with familial hypercholesterolemia or atherosclerotic cardiovascular disease. **Objectives:** To estimate the long-term health and economic value of PCSK9 inhibitors for Americans (51 years and older). **Methods:** We conducted simulations using the Future Elderly Model, an established dynamic microsimulation model to project the lifetime outcomes for the US population aged 51 years and older. Health effects estimates and confidence intervals from published meta-analysis studies were used to project changes in life expectancy, quality-adjusted life-years, and lifetime medical spending resulting from the use of PCSK9 inhibitors. We considered two treatment scenarios: 1) current FDA eligibility and 2) an extended eligibility scenario that includes patients with no pre-existing cardiovascular disease but at high risk. We assumed that the price of PCSK9 inhibitors was discounted by 35% in the first 12 years and by 57% thereafter, with gradual uptake of the drug in eligible populations. **Results:** Use of PCSK9 inhibitors by individuals covered by current FDA approval would extend life expectancy at the age of 51 years by an estimated 1.1 years and would yield a lifetime net value of $5800 per person. If use was extended to those at high risk for cardiovascular disease, PCSK9 inhibitors would generate a lifetime net benefit of $14,100 per person. **Conclusions:** Expanded access to PCSK9 inhibitors would offer positive long-term net value for patients and the US health care system at the current discounted prices.

Keywords: alirocumab, cardiovascular disease, cholesterol, evolocumab, familial hypercholesterolemia, microsimulation, PCSK9.

Introduction

Despite advances in medical technologies, cardiovascular disease (CVD) remains the leading cause of death—nearly 7.2 million deaths annually—and a major cause of disability in the United States [1,2]. From 2011 to 2012, the estimated annual direct and indirect costs of CVD and stroke were more than $310 billion [3], with annual costs projected to nearly triple from 2010 to 2030, from $273 billion to $818 billion [4,5]. Additional interventions are needed for people at risk of CVD, focusing on both patient lifestyle changes and managing modifiable cardiovascular risk factors successfully.

A large body of evidence demonstrates that low-density lipoprotein cholesterol (LDL-C) is a principal driver of atherosclerotic cardiovascular disease (ASCVD)—the underlying cause of most clinical manifestations of CVD—and thus the primary target for CVD risk reduction interventions [6–9]. For more than a decade, guidelines have indicated that patients with elevated LDL should use 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, adjunct to diet to reduce cholesterol. Despite the use of statins, previous research has shown that a substantial proportion of treated high-risk patients fail to achieve target LDL-C levels [10,11]. Moreover, statin intolerance is a common concern in clinical practice, with wide variation in individual lipid-lowering and risk reduction [12–15]. A substantial proportion of patients not meeting conventional LDL-C goals—more than 73 million US adults (32%) experience elevated LDL-C levels [16]—suggests substantial benefits in reducing the burden of hypercholesterolemia.

Recently, the Food and Drug Administration (FDA) approved two monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), alirocumab and evolocumab, which are novel lipid-lowering approaches that inhibit the binding of PCSK9 to the LDL receptor, resulting in powerful LDL-C–lowering potency [17–19]. Both agents are administered via subcutaneous injection and have been approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with familial hypercholesterolemia (FH) or clinical ASCVD who require additional lowering of LDL-C [20].

Preliminary phase III clinical trials, although not powered to assess long-term cardiovascular outcomes because of the short study windows, showed approximately a 50% risk reduction in

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cardiovascular events and all-cause mortality while maintaining a favorable safety profile [21–23]. If clinical benefits observed in trials are sustained long-term, PCSK9 inhibitors could become an important option for patients at high risk of ASCVD and potentially create substantial health benefit by preventing CVD events.

Despite health benefits suggested by the literature, payers and policymakers are concerned that this new class of expensive specialty medications poses a substantial economic burden given the drugs' current prices, which range from $14,100 to $14,600 per patient per year. A recent study suggested that even if the drug price of PCSK9 inhibitors could be covered by an annual $245 billion savings in prevented CVD events, the high price of PCSK9 inhibitors still poses a substantial economic burden to the US health care system if accounting only for direct medical costs from avoided CVD [24]. Another study suggested that these agents may not be cost-effective in patients with FH or ASCVD at current US prices [25]. Answers are needed about whether PCSK9 inhibitors will significantly improve mortality and reduce CVD events in Americans beyond currently available diet-statin therapy and prove cost-effective over time [26]. Given uncertainty in long-term efficacy, the FDA approved use of PCSK9 inhibitors under strict criteria, and because of the drugs' high prices, payers have suggested that PCSK9 inhibitors should be targeted to a narrow population [20,27,28]. Nevertheless, a larger population with elevated LDL-C levels could benefit from PCSK9 inhibitors because clinical trials have shown substantial LDL-C–lowering effects in persons who failed to receive adequate health benefits from statins regardless of their history of ASCVD [29–31]. Therefore, it is essential to evaluate the value of PCSK9 inhibitors under broader indications.

This study's primary objective was to estimate the health benefits of PCSK9 inhibitors in the US population with FH or CVD and to quantify the value of these gains while taking into account the uncertainty surrounding the drugs' clinical effectiveness. The secondary objective was to estimate the long-term value of PCSK9 inhibitors if their use was extended to persons with no pre-existing CVD but with high CVD risks.

Methods

The Future Elderly Model

We estimated potential health benefits and costs by using the Future Elderly Model (FEM), a dynamic microsimulation model that tracks cohorts older than 50 years to project their health and economic outcomes. Rather than aggregating health characteristics of a cohort, the FEM follows the evolution of individual-level health trajectories in a microsimulation framework. Initially, the FEM was developed to forecast long-term health and health care costs under different scenarios for medical technology and utilization [32]. In recent years, the FEM has been used to estimate the value of statin therapy in the obese population [33], the value of aspirin [34], and the value of delayed biological aging [35,36]. The FEM has also been used to estimate the impacts of other health policy changes, such as the introduction of dietary sodium reduction policies [37], tobacco control policies [38], and US pharmaceutical policies [39]. We describe the model and methods briefly here; complete technical information is available in the FEM technical document in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.014.

The FEM simulates the lives of older Americans on the basis of the Health and Retirement Survey (HRS), a nationally representative biennial survey of Americans aged 51 years and older. The FEM has three core components. The first is the health transition module, which consists of a series of health and functional status transition equations and mortality equations to model the health of this population over their lifetimes. Health is described by the presence of certain chronic conditions, and functional status is measured by limitations in activities of daily living, instrumental activities of daily living, and nursing home residency, reported by the HRS data. All health conditions, functional states, and risk factors were modeled with first-order Markov processes that controlled for a set of baseline variables, including age, sex, education, race, body mass index, smoking status, and health at the time of entry into the study.

For the purpose of this study, we added biomarkers (specifically cholesterol and glycated hemoglobin levels), blood pressure measurements, and treatment status (including respondents' current therapies for cholesterol, blood pressure control, and diabetes) in the health transition module. These variables were added to better identify the target population eligible for PCSK9 inhibitors and their CVD risk as the model moves forward. These variables were obtained from the HRS biomarker data available from 2006 to 2012. We added biomarker and blood pressure levels to the list of covariates predicting CVD. In the simulations, biomarker and blood pressure transitions were modeled as a function of respondents' social demographic characteristics, health status, and treatment status.

We computed quality-adjusted life-year (QALY) measures on the basis of the EuroQol five-dimensional questionnaire, a standardized health-related quality-of-life instrument measuring a respondent's general health status on five dimensions: mobility, daily activities, self-care, anxiety/depression, and pain [40]. The EuroQol five-dimensional questionnaire scores are estimated with an ordinary least squares regression as a function of the chronic conditions and FEM-specified functional status, using Medical Expenditure Panel Survey data.

The second FEM component is the policy outcomes module, which examines fiscal outcomes, including the costs of health entitlement programs—specifically federal and state spending for Medicare and Medicaid. The FEM predicts expected enrollment for Medicare and Medicaid, as well as expenditures for both entitlement programs and private medical expenditures, given a set of health, economic, and demographic states and characteristics. The predictions are based on the Medical Expenditure Panel Survey data before the age of 65 years and the Medicare Current Beneficiary Survey after the age of 65 years.

The third component is a replenishing cohort module, which introduces new cohorts of 51-year-olds in each simulated year as the model progresses. The FEM predicts the demographic and health characteristics for these younger populations on the basis of data from the National Health Interview Survey, the Current Population Survey, and the National Health Nutrition and Examination Survey.

Simulations

First, we conducted "cohort simulations," tracking a 2016 cohort of Americans aged 51 to 52 years until their death under alternative PCSK9 inhibitor scenarios. In addition, we conducted "population simulations" to investigate the population-wide trends implied by observing a representative cross section of the older US population in each period. We used the full FEM population to project outcomes (including the replenishing cohort) for the entire population of Americans aged 51 years and older from year 2016 to year 2056. Population health outcomes were calculated for each time period by aggregating individual health measures.

Scenarios

We considered three scenarios—one representing the status quo and the other two representing scenarios introducing the use of