Volume 13 • Number 6 • 2010
VALUE IN HEALTH

Projected Cost-Effectiveness of Ezetimibe/Simvastatin Compared with Doubling the Statin Dose in the United Kingdom: Findings from the INFORCE Study

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ABSTRACT

Objective: To evaluate the incremental cost-effectiveness ratio (ICER) of switching to ezetimibe/simvastatin (Eze/Simva) compared with doubling the submaximal statin doses, in patients with acute coronary syndrome (ACS) events in the INFORCE study.

Methods: Lifetime treatment costs and benefits were computed using a Markov model. Model inputs included each patient's cardiovascular risk factor profile and actual lipid values at baseline and 12 weeks (endpoint). Cardiovascular event and drug costs were discounted at 3.5%. Age-specific utilities were based on UK literature values and non–coronary heart disease mortality rates on the Office of National Statistics data. In the INFORCE study, 384 patients taking statins at stable doses for ≥6 weeks before hospital admission were stratified by statin dose/potency (low, medium, and high) and then randomized to doubling the statin dose or switching to Eze/Simva 10/40 mg for 12 weeks.

Results: The Eze/Simva group ($n = 195$) had a higher mean baseline total cholesterol than the double-statin group ($n = 189$). Analyses were adjusted for baseline characteristics. In the INFORCE study, Eze/Simva reduced low-density lipoprotein cholesterol (LDL-C) by ~30% (vs. 4% with doubling statin doses) and significantly enhanced LDL-C goal attainment. In the cost-effectiveness analysis, Eze/Simva conferred 0.218 incremental discounted quality-adjusted life year (QALY) at a discounted incremental cost of £2524, for an ICER of £11,571/QALY (95% confidence interval = £8181–£18,600/QALY). The ICER was £13,552/QALY, £11,930/QALY, and £10,148/QALY in the low-, medium-, and high-potency strata, respectively.

Conclusions: Switching to Eze/Simva 10/40 mg is projected to be a cost-effective treatment (vs. double-statin) in UK patients with ACS.

Keywords: coronary disease, cost-effectiveness, drug therapy, ezetimibe, hydroxymethylglutaryl CoA reductase inhibitors (statins), hypercholesterolemia, prevention and control.

Introduction

Cardiovascular disease is the leading modifiable cause of mortality in the western industrialized world. In the United States, 37 of every 100 deaths (>900,000) each year are ascribed to cardiovascular disease as an underlying cause [1]. By one estimate, 56% of ischemic heart disease worldwide can be ascribed to elevated total cholesterol (TC) [2]. In the United Kingdom, cardiovascular disease is also the main cause of death, accounting for nearly 200,000 fatalities, or 30% of premature deaths in men and 22% in women annually [3]. Each year, up to 146,000 British adults experience myocardial infarctions (MIs), and the total annual cost of coronary heart disease (CHD)–related disease burdens in the United Kingdom is approximately £7 billion [4,5]. Cardiovascular disease costs Europe €190 billion each year (2006) [6].

Hyperlipidemia, which includes elevations in low-density lipoprotein cholesterol (LDL-C), represents a pivotal modifiable risk factor to prevent cardiovascular disease [7–9]. For every 1% decrease in LDL-C, the cardiovascular event rate declines by approximately 1% [10]. Statin therapy reduced the 5-year incidence of major vascular (coronary) events by 21% (and of ischemic stroke by 19%) per 1-mmol/l reduction in LDL-C (largely irrespective of baseline cholesterol) [11]. Randomized controlled trials have demonstrated that the magnitude of reduction in absolute coronary risk in patients with CHD (or at advanced CHD risk [12,13]) is directly proportional to the absolute reduction in LDL-C on treatment. The landmark UK Heart Protection Study (HPS) documented significant reductions in cardiovascular events and mortality after simvastatin treatment [14–16]. The Scandinavian Simvastatin Survival Study (4S) also demonstrated significant cardioprotective benefits of daily simvastatin 10–40 mg, which significantly reduced the relative risk of all-cause mortality by 30% versus placebo ($P = 0.0003$) over 5.4 years in patients with a history of acute MI or angina pectoris [17].

Research findings such as these [18–20] have provided the foundation for an overall treatment strategy of "lower (LDL-C) is better," particularly in patients with CHD (e.g., acute coronary syndrome [ACS]). For these patients, US and European consensus panels have recommended consideration of more stringent LDL-C targets, on the order of <1.8 mmol/l (<70 mg/dl) to <2.0 mmol/l (<80 mg/dl) "if feasible." (For a comprehensive review, see Catapano [21].) Despite these increasingly aggressive cholesterol treatment targets, numerous recent studies have demonstrated that most patients with CHD or elevated cardiovascular risk do not achieve even less stringent guideline targets [22–27]. Regimens in many of these studies comprised statin monotherapy at low- to medium-dose potency, with infrequent adjustment of doses despite suboptimal goal achievement and infrequent prescription of combination regimens.

Given that cardiovascular mortality in the United Kingdom is among the highest of all countries in Western Europe, the government has resolved to lower the mortality rate from CHD and stroke in people ages <75 years by 40% by 2010 (the target has already been met), saving approximately 200,000 lives in total

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10.1111/j.1524-4733.2010.00742.x

[28,29]. UK guidelines have recommended the use of statins in all patients with a 10-year cardiovascular risk of ≥20% [8]. The General Medical Services contract [30] requires general practitioners to increase efforts to use lipid-lowering treatments in secondary prevention and offers financial incentives. Nevertheless, reports from the Health Survey for England have documented improved, yet still decidedly suboptimal, treatment and control rates for lipids between 1998 and 2003 [31]. A 2002 survey revealed that nearly 70% of adults had TC ≥5 mmol/l, and the mean TC level was 5.47 mmol/l (212 mg/dl) in men and 5.59 mmol/l (216 mg/dl) in women [32].

In light of these trends, novel clinical strategies are warranted to achieve increasingly aggressive consensus treatment targets. Combination therapies with potentially complementary mechanisms of action include 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins) with niacin (nicotinic acid), or with a fibric-acid (fibrate) derivative. A third option for adjunctive therapy to enhance lipid effects and cholesterol goal attainment is dual cholesterol inhibition, including a statin, such as simvastatin (Simva), to inhibit the rate-limiting enzyme in hepatic cholesterol biosynthesis (HMG-CoA reductase) and ezetimibe (Eze; Ezetrol, Zetia; Merck, Whitehouse Station, NJ) to inhibit intestinal absorption of cholesterol [33,34].

Treatment with Eze/Simva (Inegy, Vytorin; Merck) is associated with significant improvements in lipid levels and LDL-C goal achievement and is well tolerated (vs. up-titrating statin doses [35–38]). In a recent European study involving patients with CHD and/or type 2 diabetes mellitus, individuals whose treatments were switched from atorvastatin 10 mg to Eze/Simva 10/20 mg were ~6 times more likely to achieve LDL-C treatment targets (vs. doubling the atorvastatin dose; [odds ratio = 5.7; 95% confidence interval [CI] = 3.7–9.0; $P < 0.0001$] [37]). Other clinical studies have demonstrated that Eze/Simva treatment is associated with significantly enhanced LDL-C–lowering (and LDL-C goal-achieving) effects (vs. statin monotherapy) across a broad spectrum of patient populations [35,37,39–41].

The INFORCE trial (lipid-altering efficacy of Inegy compared with doubling the statin dose [i.e., double-statin group]) in adults admitted to the hospital for suspected (and later proven) ACS events was a phase IV, randomized, open-label study conducted from January 2005 through June 2007 at 48 sites in 14 countries [36]. It evaluated the effects on LDL-C of switching to Eze/Simva 10/40 mg compared with doubling the existing statin dose (i.e., double-statin group). The study demonstrated that switching to Eze/Simva 10/40 mg was associated with significantly reduced LDL-C, TC, apolipoprotein B (apoB), non–high-density lipoprotein cholesterol (non–HDL-C), and both TC : HDL-C and LDL-C : HDL-C ratios compared with doubling the statin dose ($P \leq 0.001$ for each between-group difference) [36]. Further, patients whose regimens were switched to Eze/Simva were about twice as likely to achieve aggressive LDL-C treatment targets as their counterparts in the double-statin group ($P \leq 0.001$ for each between-group difference). Moreover, whether the patients were previously on a low-, medium-, or high-potency statin, Eze/Simva consistently produced greater improvements in lipids with a similar safety profile compared with doubling the dose of statins [35]. The purpose of the present analysis was to estimate the incremental cost-effectiveness ratio (ICER) for patients in the INFORCE trial (all patients and per statin dose strata) of switching to Eze/Simva (vs. doubling a submaximal statin dose) by translating improvements in lipids (observed TC : HDL-C ratio) into projected lifetime costs and benefits.

Methods

Data Source: The INFORCE Study [36]

The design/timeline of the INFORCE study (Merck/Schering-Plough Protocol 808; NCT00132717; http://clinicaltrials.gov/archive/NCT00132717/2009_04_13) has been previously described [36]. Study subjects were hospitalized for suspected (and later proven) ACS events and had been using a stable (submaximal) dose of a statin for ≥6 weeks before admission. After being discharged, patients were stratified into 3 levels of statin doses of approximately equal mg : mg LDL-C–lowering potencies. These included stratum 1, low-potency (fluvastatin 40 mg; pravastatin 10 and 20 mg; Simva 10 mg); stratum 2, medium-potency (atorvastatin 10 mg; Simva 20 mg); and stratum 3, higher-potency (atorvastatin 20 and 40 mg; rosuvastatin 10 and 20 mg; and Simva 40 mg). Patients were randomized in a 1:1 ratio to either switch to Eze/Simva 10/40 mg or to double the statin dose, with treatment for 12 weeks. At the 12-week visit, Eze/Simva 10/40 mg lowered LDL-C by 27.0% compared with 4.2% in the double-statin group, for an incremental reduction of 22.8%.

Cost-Effectiveness Model Structure

A Markov decision-analytic model was used to project lifetime benefits and costs of lipid-lowering therapy [42]. This model was applied to estimate the costs and benefits for each patient of different lipid-lowering therapies. According to the model, Eze potentiates the LDL-C–lowering capacity of statin therapy by a further 23.2% (vs. statin monotherapy). On the other hand, doubling the dose of statin therapy or switching to an alternative statin is associated with further decrements in LDL-C concentrations of approximately 6% and 8%, respectively [43,44]. The model compared the cost-effectiveness of switching treatment to Eze/Simva 10/40 mg with remaining on a statin and doubling its dose.

Costs and health outcomes of lipid-lowering treatment were captured in a Markov process with a cycle length of 1 year. Five health states were included: no event, MI, angina pectoris, CHD death, or non–CHD death (Fig. 1) [42]. Stroke was not included in the analysis. Each health state was assigned an expected cost. The probability of moving from one health state to another during a given year depends on current health status and cardiovascular risk factor profiles. These risk profiles were used to compute the annual risks of fatal and nonfatal CHD events according to risk equations derived from the Framingham Heart Study [45,46] as well as the annual risk of non–CHD death using UK-specific mortality data [47]. The model took a payor (UK Department of Health) perspective.

Model Inputs: INFORCE Patient Data

To estimate the ICER of switching to Eze/Simva 10/40 mg compared with doubling the statin dose, differences in treatment costs and benefits for each individual were estimated from the baseline and 12-week follow-up lipid measures. Patients from the INFORCE study were considered eligible for the economic analysis if they were included in the primary efficacy analysis.

The comparative effects of switching to Eze/Simva or doubling the statin dose were reflected in observed alterations in each respondent's actual lipid levels at baseline and endpoint in the INFORCE trial [36]. The effects of different treatments, including Eze/Simva 10/40 mg and statins at various potencies and doses, on changes from baseline to endpoint in lipids were entered into the Markov model on a per-patient basis, with treatment costs and benefits being computed for each patient at