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ORIGINAL ARTICLE

Cost-effectiveness of Simvastatin Plus Ezetimibe for Cardiovascular Prevention in Patients with a History of Acute Coronary Syndrome: Analysis of Results of the IMPROVE-IT Trial

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Background Simvastatin plus ezetimibe reduced the risk of cardiovascular events in the IMProved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) study. The aim of this study is to investigate the cost-effectiveness of adding ezetimibe to simvastatin treatment for patients with ACS based on the recently completed IMPROVE-IT trial.

Methods We constructed a Markov state-transition model to evaluate the costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness (ICER) associated with co-therapy compared with simvastatin alone from a health care perspective. We ran separate base-case analyses assuming a trial-length and longer term follow-up. One-way sensitivity analyses were used to explore uncertainty in model parameters.

Results In the trial-length model, the ICERs compared with simvastatin alone were $114,400 per QALY for the combination therapy. In 5- and 10-year time horizons, the ICERs remained above the cost-effectiveness threshold of $50,000 per QALY. In the lifetime horizon model, The ICER was $45,046 per QALY for combination treatment compared with simvastatin alone. The combination therapy is cost-effective at an 80% decrease in the current branded simvastatin and ezetimibe cost. Probabilistic sensitivity analysis suggested simvastatin and ezetimibe co-therapy would be a cost-effective alternative to simvastatin monotherapy 60.7% of the time.

Conclusions In our trial-length, 5-year, and 10-year models, the co-therapy was not a cost-effective alternative; however, as follow-up was extended to lifetime, the co-therapy became a cost-effective treatment compared with the simvastatin monotherapy in patients with histories of ACS.

Keywords Simvastatin • Ezetimibe • Acute coronary syndrome • Cost-effectiveness analysis

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Background

Cardiovascular disease (CVD) is an important health care issue because of its high prevalence, mortality, morbidity, and cost of care. Despite declines in death rates attributable to CVD since the 1960s, CVD remains the leading cause of death in the United States and accounts for more than 787,000 deaths annually [1]. It imposes a greater burden on society than any other class of diseases. The annual direct health care costs devoted to CVD amounted to $141 billion [2] and are estimated to double by 2030 [3].

The most common type of CVD is acute coronary syndrome (ACS), which is responsible for 50% of all CVD deaths [4]. In addition, ACS is associated with more than 2.5 million hospitalisations worldwide each year [5,6]. According to the Heart Disease and Stroke Statistics 2014 Update from the American Heart Association (AHA), there were over 625,000 hospital discharges due to ACS, and this number increased to 1,141,000 when adding secondary hospital discharges of ACS in 2010 [7].

The focus on prevention is now more critical than ever due to increases in both the prevalence of CVD and the cost of treatment. Elevated blood cholesterol has been identified as a major risk factor for developing CVD. According to data from the National Health and Nutrition Examination Surveys (NHANES), 2009–2010, an estimated 23.3% of US adults had had uncontrolled high LDL-C [8] defined as ≥160 mg/dL for low-risk groups, ≥130 mg/dL for intermediate-risk groups, and ≥100 mg/dL for high-risk groups [9].

Over the past few years, reducing high blood cholesterol has been an important goal of pharmacotherapy [10]. Current national CVD prevention guidelines strongly reflect this observation. In November 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) published a guideline for the treatment of high cholesterol to reduce the risk of CVD, which provides comprehensive recommendations for treating high cholesterol levels with statins. The guideline eliminated emphasis on LDL treatment targets. Instead, it focussed on intensiveness of LDL-lowering therapy based on a person's CVD risk level [11]. Adding a lipid-modifying agent such as ezetimibe to statin monotherapy is considered a good option to reach patients' lipid goals beyond those achieved with statin monotherapy [12–14].

Several high-profile, randomised, controlled trials (RCTs) and meta-analyses have shown that the combination of ezetimibe and simvastatin was superior to statins in lowering LDL cholesterol levels [15–18]. However, whether the addition of ezetimibe to statin therapy will lead to a reduction in cardiovascular (CV) events in patients with ACS has been controversial [19] until findings from a recently completed large clinical trial, Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), were published in 2015. The study showed that the combination of ezetimibe plus simvastatin has a clear effect on the overall reduction in the primary composite endpoint of CV death, nonfatal myocardial infarction (MI), unstable angina requiring hospitalisation, coronary revascularisation, or nonfatal stroke over a median six years of follow-up compared to simvastatin alone in patients with ACS [20].

Despite the positive findings of the simvastatin co-therapy with ezetimibe in reducing the CV events, it may not seem to be a cost-effective option, because the difference in drug costs between the two therapies is substantial ($8.7/day for the combination and $0.10/day for simvastatin monotherapy). However, it is expected that many more patients will undergo combination therapy for longer durations when the patent of the brand-name ezetimibe expires in 2017. Therefore, it is becoming increasingly important to consider long-term cost-effectiveness analysis to capture the full associated costs and effectiveness of combination treatment in those patients. Such analysis is crucial in supporting clinical decisions when outcome improvement and cost containment need to be rationalised. For this reason, we developed a Markov model using data from the IMPROVE-IT trial, to examine the lifetime costs and effectiveness of adding ezetimibe to simvastatin therapy in patients presenting with ACS, and to identify the main drivers of cost effectiveness.

Methods

Overview of the Clinical Trial

The target population of this analysis was similar to the IMPROVE-IT trial population. IMPROVE-IT was a large, multicentre, randomised, prospective study, the methodology and results of which are reported in detail elsewhere [20]. Briefly, between 26 October, 2005, and 8 July, 2010, 18,144 men and women, aged at least 50 years who had been hospitalised for an acute coronary syndrome (with a confirmed diagnosis of ST or non-ST segment elevation, MI, or high-risk unstable angina) within the preceding 10 days were randomised to receive, once daily, either a combination of simvastatin (40 mg) and ezetimibe (10 mg) (n = 9076) or simvastatin (40 mg) (n = 9077) for an average of six years.

Description of the Model

We constructed a Markov model replicating the course of treatment observed in the IMPROVE-IT trial and extending out for longer periods. Figure 1 shows a depiction of the model for IMPROVE-IT trial with the states and events associated with disease progression. In each prevention strategy (i.e., simvastatin monotherapy or simvastatin plus ezetimibe therapy), all individuals had the probabilities of moving among the seven health states in yearly cycles. The health states were myocardial infarction, ischaemic stroke, haemorrhagic stroke, coronary revascularisation, unstable angina, death, and no CV events.

If patients incurred a nonfatal CV event (i.e., we assume they developed a CV event and survived until the end of the cycle), they entered a post-event state. They entered the state death from CV cause if they developed a fatal CV event or death from non-CV causes. Because minor adverse events related to ezetimibe are uncommon, and according to the

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