Trends in Use of Ezetimibe After the ENHANCE Trial, 2007 Through 2010

Joseph S. Ross, MD, MHS; Sharon G. Frazee, PhD, MPH; Susan B. Garavaglia, PhD, MBA; Rebecca Levin, MPH; Haik Novshadian, BS; Cynthia A. Jackevicius, PharmD, MSc; Glen Stettin, MD; Harlan M. Krumholz, MD, SM

**IMPORTANCE** Results from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, announced in January 2008, demonstrated that ezetimibe use lowered cholesterol levels but did not slow the progression of atherosclerosis.

**OBJECTIVE** To examine the association of this announcement with national patterns of ezetimibe prescribing, including medication initiation and discontinuation, as well as predictors of use.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective analysis of a national sample of adults 18 years or older who were continuously enrolled in plans of a large US pharmacy benefit manager from 2007 to 2010.

**MAIN OUTCOMES AND MEASURES** Lipid-lowering therapy prescription claims were categorized as ezetimibe-containing treatments or any other lipid-lowering agent. Initiation was defined as an ezetimibe claim without another in the prior 180 days; discontinuation, as an ezetimibe claim without another in the subsequent 180 days.

**RESULTS** From 2007 to 2010, 29.1% of the 10,597,296 continuously eligible adults obtained at least 1 lipid-lowering agent prescription. Among these adults, 17.8% were prescribed ezetimibe and 95.3% another lipid-lowering agent, predominantly statins. Ezetimibe use peaked in January 2008, when 2.5% of all adults were ezetimibe users, but declined to 1.8% by December 2010. The ENHANCE trial announcement was associated with a nonsignificant 0.16% fewer monthly ezetimibe users (P = .11) but a significant 0.14% more monthly ezetimibe monotherapy users and 0.30% fewer users of ezetimibe concomitant with other lipid-lowering agents (both P = .01). The ENHANCE trial was also associated with 0.44% fewer monthly ezetimibe initiations (P = .002) and 10.4% more monthly ezetimibe discontinuations (P < .001), particularly of ezetimibe monotherapy for both. More than half of adults who initiated ezetimibe use did so without first being prescribed another lipid-lowering agent, both before (50%-60%) and after (60%-70%) the trial. Those aged 50 to 64 years and those living in the East South Central US Census division were both more likely to initiate and less likely to discontinue ezetimibe after the ENHANCE trial.

**CONCLUSIONS AND RELEVANCE** After announcement of the results of the ENHANCE trial, nearly 2% of all continuously enrolled adult beneficiaries within a large US pharmacy benefit manager used ezetimibe, although ezetimibe initiations declined and discontinuations increased.

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In 2002, the Food and Drug Administration approved ezetimibe on the basis of its effectiveness at lowering serum low-density lipoprotein (LDL) cholesterol levels. Ezetimibe quickly became a blockbuster drug with worldwide sales of $4 billion by 2008.1 Whereas professional clinical practice guidelines emphasized the use of statins to lower lipid levels as part of primary and secondary prevention of cardiovascular disease, the use of other medications to lower lipid levels, such as ezetimibe, was encouraged in order to reach target LDL cholesterol thresholds.2-4 However, in January 2008, the results were announced from the first large-scale efficacy study, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, which compared the effects of use of simvastatin alone against simvastatin plus ezetimibe among patients with familial hypercholesterolemia.4-5 The trial, published in April 2008, showed that ezetimibe therapy effectively reduced LDL cholesterol levels but did not slow the progression of atherosclerosis, as measured by the carotid intima-media thickness.6 These findings raised questions about ezetimibe’s effect on clinical outcomes despite the drug’s effectiveness for lowering of LDL cholesterol levels.7

In the 6 months immediately following the release of the ENHANCE trial results, sales of ezetimibe declined sharply,8,9 particularly in the United States.10 While ezetimibe users stopped refilling their medications, only a small proportion switched to appropriate alternative lipid-lowering therapies, such as statins.11 However, this decline in ezetimibe sales was short-lived. In the ensuing years, ezetimibe sales rebounded and now again exceed $1 billion per year,12,13 despite several additional clinical trials having been published that similarly showed that while the drug effectively lowered LDL cholesterol levels, it failed to have a beneficial effect on clinical outcomes.14-16

To date, we have lacked a more granular understanding of prescribing patterns for ezetimibe. Guidelines and experts have emphasized that the drug should not be used as a first-line agent,17 although how often it is used in this way is not clear. Moreover, patterns of use, initiation, and discontinuation after announcement of the ENHANCE trial results may offer insights into whether evidence from an eagerly anticipated, robust clinical trial can influence practice, as well as whether physicians were reluctant to discontinue ezetimibe therapy among current users but willing to stop prescribing it as new therapy. Accordingly, using national data from the largest pharmacy benefit manager in the United States, our objective was to examine the association of this announcement with national patterns of ezetimibe prescribing, including medication use, initiation, and discontinuation, as well as predictors of use, for ezetimibe overall and stratified by ezetimibe monotherapy and ezetimibe therapy concomitant with other lipid-lowering therapy. We also determined how often ezetimibe use was initiated without prior use of any other lipid-lowering therapy and discontinued without subsequent use of any other lipid-lowering therapy.

Methods

Study Design and Data Sources

This retrospective analysis used deidentified data collected by a large pharmacy benefit manager, Express Scripts Inc, for adults 18 years of age or older who were continuously enrolled in an Express Scripts-managed pharmacy benefit plan from January 2007 through December 2010. Express Scripts administers prescription drug benefits for employers, government agencies, managed care organizations, and union-sponsored benefit plans, serving tens of millions of members. The Express Scripts data warehouse contains claims for all prescriptions filled and submitted for coverage by beneficiaries through retail, mail-order, and long-term care pharmacies in the United States, allowing examination of prescription-filling behavior among a large number of patients in ambulatory medical practice. Given that we analyzed aggregate trends in medication use and did not have access to personal health information from which any subject could be identified, this study was exempted from full review by the Yale Human Research Protection Program and did not require informed consent.

Ezetimibe and Other Lipid-Lowering Treatment Use

We identified all lipid-lowering therapy prescription claims for adult beneficiaries. We then categorized prescriptions as ezetimibe-containing treatments (hereafter referred to as ezetimibe), which included both ezetimibe alone (Zetia) and ezetimibe in combination with simvastatin (Vytorin). Other lipid-lowering treatments included 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (known as statins), either alone or in combination with other treatments, bile acid sequestrants, fibrates, and other agents such as niacin.

For ezetimibe users within our study period, we identified those who were new initiators and those who discontinued therapy, capturing the month and year of either event. New initiation was defined as any ezetimibe prescription claim without another ezetimibe claim in the prior 180 days; thus, ezetimibe new initiation could only be identified from July 2007 onward because the period from January to June 2007 was required to ensure that no other ezetimibe prescription was obtained during the prior 180 days. Medication discontinuation was defined as any ezetimibe prescription claim without another ezetimibe claim in the subsequent 180 days after the last day of supply on hand is exhausted; thus, ezetimibe discontinuation could only be identified prior to June 2010 because the period from July to December 2010 was required to ensure that no other ezetimibe prescription was obtained during the subsequent 180 days.

Other Variables

For each beneficiary, we determined the following: beneficiary age, sex, geographic location, and concomitant use of other medications for angina and/or coronary artery disease or diabetes mellitus, determined using clinically derived medication rules developed at Express Scripts that link particular medications with the conditions that they are most commonly used to treat. We categorized geographic locations according to the beneficiaries’ home addresses.

Statistical Analysis

We used descriptive analyses to characterize national patterns of ezetimibe use in the periods before (January to December 2007) and after (January 2008 to December 2010) the announcement of results from the ENHANCE trial. Using ret-
rospective data sets, we determined per-beneficiary ezetimibe use and other lipid-lowering therapy use, ezetimibe use without prior use of any other lipid-lowering therapy, ezetimibe initiations and discontinuations, and regional variation in ezetimibe use.

In addition, we examined the impact of the announcement of results from the ENHANCE trial using interrupted time-series regression analysis. This method is commonly used for evaluating effects of an interruption that occurs at a specific point in a time series—in this case, January 2008, the date that the ENHANCE trial results were announced via the first press reports.4,5 We created a monthly time-series view of the data for total ezetimibe use (percentage of ezetimibe users from among the total beneficiary population), new ezetimibe initiators (percentage of new ezetimibe users from among the total beneficiary population using ezetimibe), and ezetimibe discontinuers (percentage of ezetimibe users discontinuing the medication from among the total beneficiary population using ezetimibe). We built these time-series models using a lagged dependent variable (as appropriate), a dummy variable representing the pre-ENHANCE and post-ENHANCE regimens, and a linear and quadratic time trend to estimate the effect of the release of the ENHANCE trial results on ezetimibe use, initiation, and discontinuation. Next, we conducted counterfactual analysis for each of these models, which involves estimating the expected rates of use, initiation, and discontinuation after January 2008 had the ENHANCE trial results not been announced, using the pretrial prescribing trends (January through December 2007). We compared the predicted use as of January 2008 with the observed use. Finally, all time-series analyses were repeated, stratifying by ezetimibe monotherapy and ezetimibe therapy concomitant with other lipid-lowering therapy.

We then used multivariable logistic regression to identify beneficiary predictors of ezetimibe initiation and ezetimibe discontinuation after announcement of the ENHANCE trial results, taking into account beneficiary age, sex, Census division, and concomitant use of other medications for angina and/or coronary artery disease or for diabetes mellitus. Data on beneficiary age and sex were missing for fewer than 0.1% of adults, and Census division, for 1.6%; these beneficiaries were excluded from multivariable analyses. All analyses were conducted using SAS software, version 9.3 (SAS Institute).

Results

The study population included 10,597,296 adults who were continuously enrolled in an Express Scripts–managed pharmacy benefit plan from January 2007 through December 2010. Within this cohort, we identified 3,086,906 beneficiaries (29.1%) who obtained at least 1 prescription for a lipid-lowering agent during the study period. Among these beneficiaries, 548,688 (17.8%) obtained at least 1 prescription for an ezetimibe agent and 2,941,794 (95.3%) obtained at least 1 prescription for any other (non–ezetimibe-containing) lipid-lowering agent during the
study period. Among beneficiaries who obtained at least 1 prescription for an ezetimibe agent, 403,576 (73.6%) also obtained at least 1 prescription for another (non–ezetimibe-containing) lipid-lowering agent during the study period. Beneficiaries receiving ezetimibe were broadly similar to beneficiaries receiving other lipid-lowering agents (Table 1), although ezetimibe users were slightly more likely to be 50 years or older and to be concomitant users of other medications for angina and/or coronary artery disease and for diabetes mellitus.

**Ezetimibe Use and the ENHANCE Trial**

Ezetimibe use peaked in January 2008, when 266,244 adult beneficiaries were ezetimibe users (2.5% of all continuously enrolled beneficiaries). By December 2010, there had been a slight decline in use such that 186,272 adult beneficiaries were ezetimibe users (1.8% of all continuously enrolled beneficiaries) (Figure 1A). In fact, throughout the study period, ezetimibe use persisted at a rate of nearly 2% among all adult beneficiaries. As of December 2010, announcement of
the ENHANCE trial results was associated with a nonsignificant 0.16% fewer monthly ezetimibe users among all continuously enrolled beneficiaries \( (P = .11) \). However, patterns in ezetimibe monotherapy use differed from those in ezetimibe use concomitant with other lipid-lowering agents. Throughout the study period, ezetimibe monotherapy use persisted at a rate between 0.3% and 0.7% among all adult beneficiaries and the ENHANCE trial announcement was associated with a significant 0.14% more monthly monotherapy users \( (P = .01) \). In contrast, ezetimibe use concomitant with other lipid-lowering agents ranged between 0.9% and 1.9% among all adult beneficiaries during the study period and the ENHANCE trial announcement was associated with a significant 0.30% fewer monthly concomitant users \( (P = .01) \).

**Ezetimibe Initiation and the ENHANCE Trial**

Announcement of the ENHANCE trial results was associated with significant changes in ezetimibe initiation (Figure 1B). From July 2007 to January 2008, among continuously enrolled adult beneficiaries using ezetimibe, between 11,000 and 14,000 initiated ezetimibe use each month \( (0.11\%-0.13\%) \), but after the ENHANCE trial, ezetimibe initiation steeply declined such that by 2010, fewer than 1500 beneficiaries \( (0.2\%) \) initiated ezetimibe use monthly. As of December 2010, the ENHANCE trial announcement was associated with 0.44% fewer monthly ezetimibe initiations \( (P = .002) \). Patterns in ezetimibe monotherapy initiation and ezetimibe initiation concomitant with other lipid-lowering agents were somewhat similar, as the ENHANCE trial was associated with a significant 0.02% fewer monthly monotherapy initiations \( (P < .001) \) but...
a nonsignificant 0.01% fewer monthly concomitant initiations ($P = .14$). Of note, among the adults who initiated ezetimibe use, the proportion who initiated therapy without first being prescribed another lipid-lowering agent, including statins, was approximately 55% in July 2007 (Figure 2). However, after the ENHANCE trial, between 60% and 70% of adults who initiated ezetimibe did so without first being prescribed any other lipid-lowering therapy.

**Ezetimibe Discontinuation and the ENHANCE Trial**

Similarly, announcement of the ENHANCE trial results was associated with significant changes in ezetimibe therapy discontinuation (Figure 1C). Before January 2008, among continuously enrolled adult beneficiaries using ezetimibe, the proportion discontinuing therapy each month increased slowly from 3.6% to 8.0%, but from January to April 2008, the number of beneficiaries discontinuing ezetimibe use monthly exceeded 16,500 (18.3%-20.6%). As of December 2010, the ENHANCE trial announcement was associated with 10.4% more monthly ezetimibe therapy discontinuations ($P < .001$). However, patterns in ezetimibe monotherapy discontinuation differed from those in discontinuation of ezetimibe when used concomitantly with other lipid-lowering agents, as the ENHANCE trial was associated with a significant 12.5% more monthly monotherapy discontinuations ($P < .001$) and a nonsignificant 0.86% fewer monthly concomitant discontinuations ($P = .47$). Of note, among the 305,949 adults who discontinued ezetimibe therapy during the study period, 159,999 (52.3%) switched lipid-lowering therapy and began using statins, 27,346 (8.9%) switched lipid-lowering therapy and began using either fibrates or niacin, and 118,604 (38.8%) completely discontinued lipid-lowering therapy.

**Predictors of Ezetimibe Initiation and Discontinuation**

After announcement of the ENHANCE trial results, several beneficiary characteristics were associated with the likelihood of ezetimibe therapy initiation and discontinuation. Adults between the ages of 50 and 64 years were more likely to newly initiate ezetimibe use after the ENHANCE trial when compared with older groups of adults (Table 2), as were adults concomitantly using other medications for angina and/or coronary artery disease (odds ratio [OR], 1.28 [95% CI, 1.23-1.34]) and diabetes mellitus (OR, 1.45 [95% CI, 1.40-1.50]), whereas men were less likely to newly initiate ezetimibe when compared with women (OR, 0.82 [95% CI, 0.80-0.85]). In addition, adults living in the South Atlantic, East South Central, and West South Central Census divisions were all more likely to newly initiate ezetimibe use after the ENHANCE trial when compared with adults living in the Middle Atlantic Census division. Predictors of ezetimibe monotherapy initiation and ezetimibe initiation concomitant with other lipid-lowering agents were broadly similar (eTable 1 in the Supplement).

Adults living in the East North Central, West North Central, East South Central, Mountain, and Pacific Census divisions were all less likely to discontinue ezetimibe therapy after the ENHANCE trial when compared with adults living in the Middle Atlantic Census division. Concomitant use of other medications for angina and/or coronary artery disease or diabetes mellitus was not associated with likelihood of discontinuing ezetimibe use. Predictors of ezetimibe monotherapy discontinuation and discontinuation of use of ezetimibe concomitant with other lipid-lowering agents were broadly similar (eTable 2 in the Supplement).

**Discussion**

Using national data from the largest pharmacy benefit manager in the United States, we found that nearly 2% of all adults continuously enrolled in pharmacy benefit plans use ezetimibe, even after the results of the ENHANCE trial were announced that the drug did not slow the progression of atherosclerosis. However, although announcement of the ENHANCE trial results was not associated with a significant change in overall ezetimibe use, it was associated with slightly greater use of ezetimibe monotherapy and slightly decreased use of ezetimibe therapy concomitant with other lipid-lowering agents, perhaps masking the overall impact of the trial’s results. Moreover, announcement of the ENHANCE trial results was associated with both a decrease in ezetimibe therapy initiation and an increase in ezetimibe therapy discontinuation, particularly of ezetimibe monotherapy for both.

Because the ENHANCE trial was focused on carotid intima-media thickness, as opposed to a clinical outcome, the results were not expected to be definitive. However, they were eagerly awaited by the clinical community, as evidenced by the media attention that the trial received. Our findings suggest that physicians and patients were responsive either to the trial’s negative findings, and the growing awareness of the absence of evidence related to this drug, or to any of several other factors that were concurrent with announcement of the trial’s results. For instance, in response to the ENHANCE trial, the US Food and Drug Administration immediately issued a communication highlighting the trial’s negative findings and emphasizing the uncertainty of ezetimibe’s effect on clinical outcomes. In addition, there was substantial media and professional attention, partly because of concerns that results of the ENHANCE trial had been delayed by the sponsor because of unfavorable findings, both of which served to raise public and professional awareness about the uncertainty of ezetimibe’s clinical benefits.

Even after release of the ENHANCE trial, and several other clinical trials that have failed to demonstrate a beneficial effect of ezetimibe use on clinical outcomes, ezetimibe continues to be initiated as new therapy, both as monotherapy and as therapy concomitant with other lipid-lowering agents. And, in contrast to professional guidelines and expert recommendations that broadly reinforce first use of statins along with exercise and dietary modification to prevent cardiovascular disease, more than half of adults who newly initiate ezetimibe use the ENHANCE trial, and several other clinical trials that have failed to demonstrate a beneficial effect of ezetimibe use on clinical outcomes, ezetimibe continues to be initiated as new therapy, both as monotherapy and as therapy concomitant with other lipid-lowering agents. And, in contrast to professional guidelines and expert recommendations that broadly reinforce first use of statins along with exercise and dietary modification to prevent cardiovascular disease.
mibe therapy do so without prior use of another lipid-lowering agent, statins in particular.

Our findings question whether ezetimibe is truly being used only after maximizing statin therapy, as recommended by experts, or instead to intensify lipid management, perhaps in order to reach guideline recommendation target LDL levels. The latter possibility is supported by our finding that among beneficiaries who obtained at least 1 prescription for an ezetimibe agent during the study period, nearly three-quarters also obtained at least 1 prescription for another (non-ezetimibe-containing) lipid-lowering agent. In addition, concomitant use of other medications for angina and/or coronary artery disease and diabetes mellitus, conditions for which lower target LDL levels are commonly recommended by guidelines, were among several predictors of ezetimibe use and initiation. In contrast, if ezetimibe were being used only for patients who were currently receiving a high-dose statin or could not tolerate statin therapy but had not reached goal LDL levels, we would have expected nearly all adults to have used another lipid-lowering agent in the 6 months prior to initiating ezetimibe use, as opposed to only 30% to 40%.

Patterns of ezetimibe discontinuation also raise questions about the use of ezetimibe in our study population. Nearly 40% of adults who discontinued ezetimibe use did not initiate use of another lipid-lowering agent in the subsequent 6 months. Whereas some adults may be intolerant of other lipid-lowering agents, including statins, niacin, and fibrates, we would have expected most to switch to some other form of prescription therapy if the medication were truly indicated. However, we also cannot rule out the possibility that patients were simply intolerant of ezetimibe and discontinued use for that reason.

There are other reasons why patients and physicians may continue to use ezetimibe, the most likely being a general unawareness of the lack of clinical trial evidence demonstrating any beneficial effect of the medication on clinical outcomes. Whereas studies have demonstrated that robust positive trials, in which an intervention is found to be effective, have an impact on clinical practice,23 few studies have examined the impact of negative trials. Any lack of awareness of the trial's negative findings, or misunderstanding of ezetimibe's effect on clinical outcomes, may also have been influenced by marketing and promotional efforts by the manufacturer. In addition, thought leaders and other experts may have differed in their interpretation of the trial, which has been observed in the dissemination of other large negative studies,24 potentially explaining the differential geographic patterns of ezetimibe use, initiation, and discontinuation that we observed. Moreover, clinical trials have consistently found that ezetimibe therapy lowers LDL cholesterol levels and patients and physicians observe this effect in clinical practice settings, reinforcing decisions to use or prescribe the medication. Finally, perhaps physicians are reluctant to completely discontinue use of the medication while awaiting results from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [clinicaltrials.gov identifier: NCT00202878], anticipated in September 2014, before finalizing an opinion on the clinical benefit of ezetimibe therapy.

Several insurance companies have since taken steps to deter the use of ezetimibe, including both Zetia and Vytorin. For instance, in 2010, a large national health plan doubled patient co-payments for Zetia and Vytorin, and many other plans offer free prescription refills if patients switch from Vytorin to a generic statin.25 In addition, a large number of pharmacy benefit plans managed by Express Scripts now have benefit designs in which out-of-pocket costs or coverage protocols encourage clinicians to consider prescribing statins alone over ezetimibe alone or in combination with a statin. Future studies will be needed to determine the impact of these benefit changes.

There are several limitations to consider. First, although data collected by Express Scripts allow for examination of contemporaneous national patterns of prescribing, we were able to examine only prescription-filling behavior, not actual adherence to use of ezetimibe or any of the other lipid-lowering treatments. Second, we could not determine whether adults were using ezetimibe samples provided by a pharmaceutical company to physicians in their offices. Third, we cannot determine whether ezetimibe prescription patterns were motivated by patients, physicians, or health care plans. Neither could we determine cholesterol levels among patients using ezetimibe, whether ezetimibe was prescribed in response to patients' experience of myopathy or other adverse reaction to another lipid-lowering agent, or whether ezetimibe was prescribed for primary or secondary prevention of cardiovascular disease or for familial hypercholesterolemia. However, we were able to determine that 15% of ezetimibe users concomitantly used other medications for angina and/or coronary artery disease and 29% used other medications for diabetes mellitus, suggesting that these patients were using ezetimibe for secondary prevention, and our multivariable analyses examining likelihood of ezetimibe use, initiation, and discontinuation accounted for concomitant use of these medications. Finally, to focus on the impact of the ENHANCE trial results, we studied adults who were continuously enrolled in the same pharmacy benefit plan between 2007 and 2010. Prescriptions among adults who changed pharmacy benefit plans were not captured, and current rates of ezetimibe use were not estimated.

Conclusions

Even after the results of the ENHANCE trial were announced that the drug failed to demonstrate a beneficial effect on progression of atherosclerosis, nearly 2% of all continuously enrolled adult beneficiaries within a large US pharmacy benefit manager continued to use ezetimbe. However, announcement of the trial results was associated with slightly greater use of ezetimibe monotherapy and slightly decreased use of ezetimibe therapy concomitant with other lipid-lowering agents, as well as with both a decrease in ezetimibe therapy initiation and an increase in ezetimibe therapy discontinuation. In addition, we found that ezetimibe use was commonly initiated without prior use of another lipid-lowering agent, contrary to guideline recommendations.
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Frazee, Garavaglia, Novshadian.

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Study supervision: Frazee, Garavaglia, Levin, Novshadian, Stettin, Krumholz.

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