Implications for Ezetimibe Therapy Use Based on IMPROVE-IT Criteria

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ABSTRACT

PURPOSE: In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), simvastatin/ezetimibe combination was associated with a 6% relative risk reduction in the combined cardiovascular outcome compared with simvastatin alone in patients with acute coronary syndrome. Given strict inclusion criteria (low-density lipoprotein cholesterol 50-125 mg/dL and no use of statins more potent than simvastatin 40 mg), the implications of this important trial in routine acute coronary syndrome care are unknown.

METHODS: We identified patients with acute coronary syndrome from the Veterans Affairs health care system over a 5-year period and determined what proportion would be candidates for ezetimibe on the basis of IMPROVE-IT criteria. We then evaluated what proportion could potentially see an increase in ezetimibe use if IMPROVE-IT criteria are not strictly followed.

RESULTS: Of 219,625 patients with acute coronary syndrome, 69,508 (31.6%) would qualify for ezetimibe on the basis of strict criteria. Among those who did not meet IMPROVE-IT criteria (n = 150,117), ezetimibe could potentially be prescribed by clinicians in a further 28% of patients (n = 61,635) using statins more potent than simvastatin 40 mg, 7.1% of patients (15,527) with a documented statin intolerance, and 10.4% of patients (22,758) with low-density lipoprotein cholesterol >125 mg/dL.

CONCLUSIONS: Our results provide a first look at the implications of this trial in a large health care system. Although 31.6% of patients would qualify for ezetimibe, there is a large potential for an increase in ezetimibe use in acute coronary syndrome outside of the strict trial inclusions. These findings call for a discussion on ezetimibe’s role in patients with acute coronary syndrome already taking high-intensity statins or those with statin intolerance.

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The results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) were recently presented. IMPROVE-IT was a multicenter randomized study to establish the clinical benefit and safety of VYTORIN (Merck & Co, Inc, Whitehouse Station, NJ) (ezetimibe/simvastatin) versus simvastatin monotherapy in patients presenting with acute coronary syndrome. The IMPROVE-IT randomized 9077 patients to simvastatin...
alone versus 9067 patients to simvastatin/ezetimibe. The use of the simvastatin/ezetimibe combination was associated with a 6% relative (2% absolute) risk reduction for the combined cardiovascular outcome compared with simvastatin alone over 7 years of follow-up, resulting in a number needed to treat of 50.

It is important to note that there were several exclusions for the IMPROVE-IT. Patients with low-density lipoprotein cholesterol (LDL-C) levels <50 mg/dL or >125 mg/dL (>100 mg/dL if taking lipid-lowering medications) at the time of the acute coronary syndrome were excluded. Patients who were taking statins more potent than simvastatin 40 mg at the time of the acute coronary syndrome also were excluded. Given these exclusions, the clinical implications of the IMPROVE-IT are unknown. In addition, it is possible that clinicians may opt to use ezetimibe therapy in patients who would not have been included in the IMPROVE-IT (those intolerant to statins, taking statins more potent than simvastatin 40 mg, or with persistently elevated levels of LDL-C despite maximum recommended or tolerated statin doses).

The purpose of our analysis was to evaluate the implications for the use of ezetimibe therapy in a large cohort of patients presenting with acute coronary syndrome in the Department of Veterans Affairs Health Care system on the basis of IMPROVE-IT criteria. We also evaluated what proportion of the patient population with acute coronary syndrome could potentially see an increase in ezetimibe use if IMPROVE-IT clinical trial criteria are not strictly followed in the routine clinical management of these patients.

**MATERIALS AND METHODS**

By using Veterans Affairs data sources, we identified patients with ischemic heart disease\(^2\) with a history of acute coronary syndrome (unstable angina, non-ST-segment myocardial infarction, and ST-segment elevation myocardial infarction) in the last 5 years. We excluded those with metastatic cancers or receiving hospice care (Figure). Among 220,846 patients with acute coronary syndrome, 1221 had a documented ezetimibe allergy, leaving a final study population of 219,625 patients.

We first evaluated what proportion of patients with acute coronary syndrome fit IMPROVE-IT criteria, including those with LDL-C between 50 and 125 mg/dL (50-100 mg/dL if taking a lipid-lowering medication) at the time of the acute coronary syndrome and not meeting any specified IMPROVE-IT exclusions\(^1\): patients taking statins more potent than simvastatin 40 mg at the time of acute coronary syndrome, patients who underwent coronary artery bypass grafting within 6 months of acute coronary syndrome, and patients with a history of chronic kidney disease (creatinine clearance <30 mL/min or undergoing dialysis) or liver disease.

Among patients remaining after exclusions, we evaluated what proportion were receiving ezetimibe therapy at the time of the acute coronary syndrome. Because some of these patients may have been administered moderate- to high-intensity statins after their acute coronary syndrome event, we also evaluated the proportion of these patients who would still qualify for ezetimibe therapy on the basis of their most recent statin dose in 2014 (ie, if their most recent statin dose was less potent than or equal to simvastatin 40 mg/d).

We also evaluated several subgroups of patients who did not fulfill the IMPROVE-IT inclusion criteria but in whom providers could use ezetimibe therapy. These included patients taking statins more potent than simvastatin 40 mg, patients with a documented statin allergy (an indirect marker of statin intolerance), and patients with LDL-C >125 mg/dL at the time of their acute coronary syndrome. Analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

**RESULTS**

Final analyses included 219,625 patients (67% with unstable angina and 33% with non-ST-segment myocardial infarction or ST-segment elevation myocardial infarction). The average age of patients was 65.5 years, 97% were male, and 77% were white. The mean LDL-C at the time of the acute coronary syndrome event was 95 mg/dL (standard deviation, 36).

Of these 219,625 patients, 69,508 (31.64%) met IMPROVE-IT criteria. Of these patients, 275 (0.13%) were receiving ezetimibe therapy before their acute coronary syndrome event. Therefore, 69,233 patients (31.5%) potentially would have qualified for combination statin/ezetimibe therapy on the basis of IMPROVE-IT criteria. By evaluating the use of statin therapy in these patients at the time of their primary care visit in 2014, 52,304 patients (23.8% of the total population with acute coronary syndrome) would still have qualified for ezetimibe therapy on the basis of their history of acute coronary syndrome and the use of statins no more potent than 40 mg of simvastatin daily.

Among patients who would not have qualified on the basis of the IMPROVE-IT criteria (n = 150,117), we
evaluated several subgroups in whom ezetimibe could potentially be prescribed by providers (Figure). The largest subgroup among these patients were those taking statins more potent than simvastatin 40 mg/d at the time of their event (n = 61,635, 28% of the total population). Of the remaining patients, 15,527 (7.1%) had a documented allergy to statins and 22,758 (10.4%) had LDL-C > 125 mg/dL at the time of the acute coronary syndrome event, making them potential candidates for ezetimibe therapy.

**DISCUSSION**

In these analyses from a national cohort, we found that approximately 31.5% of patients would qualify for ezetimibe therapy at the time of their acute coronary syndrome event. Even when accounting for the fact that these patients could be treated with moderate- to high-intensity statins after their acute coronary syndrome event, 23.8% (~1 in 4) would still qualify for ezetimibe therapy.

Our results also show that there is a large potential for ezetimibe to be used outside of the IMPROVE-IT inclusion criteria. As expected, one of the largest exclusions was the use of statins more potent than simvastatin 40 mg. This was responsible for 28% of the population who would not qualify for ezetimibe therapy. On the other hand, it is possible that clinicians would use ezetimibe in patients with acute coronary syndrome who have an intolerance or allergy to statin therapy. Our results indicate that approximately 7.1% of the patients with acute coronary syndrome and a documented allergy or intolerance...
to statins could potentially receive ezetimibe therapy. It must be noted that IMPROVE-IT compared a combination of simvastatin/ezetimibe therapy with simvastatin alone; therefore, it is not known whether ezetimibe therapy alone in these patients would provide cardiovascular benefit.

Another group of patients who were not enrolled in IMPROVE-IT includes patients with LDL-C >125 mg/dL. It is possible that clinicians would use ezetimibe therapy in addition to statin therapy in these patients for further LDL-C reduction compared with a statin alone. Our results indicate that this would lead to a further 10.4% of patients receiving ezetimibe therapy. Taken together, these results indicate that a large proportion of patients with acute coronary syndrome would qualify for ezetimibe therapy. For example, by combining patients with acute coronary syndrome who fulfill strict IMPROVE-IT criteria on the basis of their most recent statin dose and patients with documented allergy to statins, approximately 31% of the patients with acute coronary syndrome (3/10) could potentially receive ezetimibe therapy. These results need to be put in the perspective of the IMPROVE-IT, which found that approximately 50 patients would need to be treated with a combination of ezetimibe and statin for approximately 7 years to prevent 1 cardiovascular event compared with statin therapy alone. On the other hand, given the excellent safety profile of ezetimibe in the IMPROVE-IT, even a modest 2% absolute risk reduction in this high-risk secondary prevention population seen in this trial could be acceptable to most patients and their health care providers.

Study Limitations
Our study has limitations that should be considered while interpreting these results. These results indicate the treatment patterns within the Department of Veterans Affairs, in which the dynamics of care may differ from other health care systems.

CONCLUSIONS
These results provide a first look at the implications of this important trial in a large health care system and show that although 23.4% of patients with acute coronary syndrome would qualify for ezetimibe on the basis of IMPROVE-IT criteria, there is a large potential for an increase in ezetimibe use in the routine clinical care of patients with acute coronary syndrome outside of the trial inclusions. Our findings thus call for a discussion on the role of ezetimibe in patients with acute coronary syndrome already taking high-intensity statins and in patients with statin intolerance.

References

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Conflict of Interest: VN is a national monitor for a study sponsored by Anthera; is on the regional advisory board of Sanofi Regeneron; and has a research collaboration with TomTec and a provisional patent: “Biomarkers to Improve Prediction of Heart Failure Risk” (Patent No. 61721475) filed by Baylor College of Medicine and Roche. CMB received grant and research support (all paid to the institution, not the individual) from Abbott Diagnostics, Amarin, Amgen, Eli Lilly, Esperion, Novartis, Otsuka, Pfizer, Regeneron, Roche Diagnostics, Sanofi-Synthelabo, National Institutes of Health, American Diabetes Association, and American Heart Association; is a consultant to Abbott Diagnostic, Amarin, Amgen, AstraZeneca, Eli Lilly, Esperion, Genzyme, Merck, Novartis, Pfizer, Regeneron, Roche, and Sanofi-Synthelabo; and has a provisional patent: “Biomarkers to Improve Prediction of Heart Failure Risk” (Patent No. 61721475) filed by Baylor College of Medicine and Roche.

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