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Ezetimibe Plus Moderate-dose Simvastatin After Acute Coronary Syndrome: What Are We IMPROVEing On?

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ABSTRACT

The recent IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is the first study to demonstrate a significant benefit of another medication (ezetimibe) on top of statin therapy in patients who have recently experienced an acute coronary syndrome. Despite the fact that ezetimibe led to positive results on the primary endpoint, the clinical benefit translated to real-life practice is only modest at best. However, this is the first major trial to demonstrate a significant benefit of a lipid medication in addition to statins. We explore the strengths and weaknesses of IMPROVE-IT in the context of current-day acute coronary syndrome practice, where high-dose statins now are prescribed widely.
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KEYWORDS: Acute coronary syndrome; Ezetimibe; Simvastatin; Statin

Increased low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol are independent risk factors of coronary artery disease and increased mortality.[1] Additionally, intensive lowering of low-density lipoprotein cholesterol has been shown to result in improved outcomes.[2] While different medications lower low-density lipoprotein cholesterol or increase high-density lipoprotein cholesterol, only certain therapies have been found to stabilize atherosclerotic plaque, prevent further progression of atherosclerosis, and decrease the risk of cardiovascular events. Although a handful of lipid-modifying agents, such as niacin, antioxidants, fibrates, and cholesteryl ester transfer protein inhibitors are available, none have been found to provide incremental cardiovascular event reduction when prescribed on top of statin therapy. Moreover, compared with less intensive statin therapy, more intense statin therapy has been found to improve clinical outcomes in both the primary and secondary prevention setting.[3] This has provided cardiovascular societies—including the American College of Cardiology/American Heart Association (ACC/AHA)—to recommended initiating and continuing high-intensity statin therapy in acute coronary syndrome patients unless there is a contraindication.[4,5]

Unfortunately, a significant proportion of patients remain at high risk even with the use of high-dose statin therapy. Thus, current clinical practice still awaits answers to 2 main questions:

1. Which medications targeting other aspects of the lipid profile—such as high-density lipoprotein cholesterol—provide benefit?
2. Are there other medications that can be added on top of statin therapy that will provide cardiovascular benefit?

While statins lower low-density lipoprotein cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is the rate-determining step in cholesterol biosynthesis, ezetimibe inhibits an enterocyte cholesterol transporter Niemann-Pick C1-like 1 protein—further lowering low-density

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lipoprotein cholesterol by up to 23% when used in adjunct with statins.[6] Although ezetimibe has been on the market since its inception, there was never an outcomes trial to prove cardiovascular benefit (alone or in addition to statin therapy) until IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) investigators presented the findings in an AHA meeting on November 17, 2014.[7] Subsequently, enormous interest and buzz has occurred around the cardiovascular community regarding the results of this long-awaited study, particularly since the findings of the ENHANCE study,[8] which had cast a shadow over ezetimibe by showing that despite significant improvements in low-density lipoprotein cholesterol, there was not even a trend for benefit on carotid intimal media thickness—a surrogate marker of questionable predictive value for major cardiovascular disease and cardiovascular events. Nonetheless, the ENHANCE results and subsequent debate among experts following its publication led to a marked decline in prescriptions for both Vytorin (simvastatin and ezetimibe in combination; Merck & Co., Kenilworth, NJ) and ezetimibe (Zetia; Merck & Co.) by approximately one-half.[9,10]

CLINICAL SIGNIFICANCE

- The IMPROVE-IT study is the first trial showing that another lipid-lowering agent on top of a statin therapy benefits the primary endpoint in acute coronary syndrome patients.
- The clinical relevance of this finding is hindered by the fact that ezetimibe was not given on top of a high-dose potent statin.

IMPROVE-IT started nearly a decade ago with its intention to establish the clinical benefit and safety of Vytorin vs simvastatin monotherapy in high-risk subjects presenting with acute coronary syndrome.[7] It was a multicenter, double-blind, randomized control trial among 18,144 high-risk patients within 10 days of acute coronary syndrome. These patients had low-density lipoprotein cholesterol levels of 50-125 mg/dL or 50-100 mg/dL if on a prior cholesterol-lowering drug. The patients were allocated to either ezetimibe 10 mg + simvastatin 40 mg or simvastatin 40 mg + placebo, and followed for an average of 6 years. The trial ended after there were 5250 primary endpoint events (cardiovascular death, myocardial infarction, hospital admission for unstable angina, coronary revascularization $\geq$30 days after randomization, or stroke). Primary endpoint events occurred in 34.7% of the control group vs 32.7% of the treatment group, representing a 6.4% reduction in risk (hazard ratio 0.936, 95% confidence interval 0.887-0.988, $P = .016$). The investigators calculated that 50 patients would need to be treated for 7 years to prevent one event over 7 years.[7] There was no difference between the groups in overall deaths, coronary artery disease deaths, or cardiovascular deaths, but there were significant reductions in myocardial infarction (13%, $P = .002$) and ischemic stroke (21%, $P = .008$). The effect was significant across subgroups, except for diabetics, who had a considerably larger benefit than nondiabetics.

Some have argued that IMPROVE-IT emphatically strengthens the postulate that lowering low-density lipoprotein cholesterol prevents cardiovascular events (median low-density lipoprotein cholesterol levels were 69.9 mg/dL in the control group vs 53.2 mg/dL in the treatment group) and generates a new debate: "the lower low-density lipoprotein cholesterol the better: but how low?" However, we have shown that when ezetimibe is added to simvastatin, there are also marked improvements in several markers of platelet reactivity compared with simvastatin alone.[11] Thus, IMPROVE-IT does not prove that lowering low-density lipoprotein cholesterol caused the overall positive results, as these results may be specific for ezetimibe. Nevertheless, the results of IMPROVE-IT have several important implications, as it was the first randomized control trial to add a medication on top of a statin showing added benefits in long-term cardiovascular outcomes among acute coronary syndrome patients. Moreover, the results of this long-awaited study could have the potential to influence the fate of several new drugs awaiting US Food and Drug Administration approval (eg, Proprotein convertase subtilisin/kexin type 9 inhibitors).

IMPROVE-IT has some major limitations that should be taken into consideration. One limitation is the choice of statin to be used (ie, simvastatin) and at a moderate dose (ie, 40 mg) in the acute coronary syndrome setting—when clinical practice and consensus guidelines favor higher-intensity statin therapy such as generic atorvastatin, and at a high dose (ie, 80 mg),[12,13] respectively (the current guidelines from AHA/ACC specifically define high-intensity statin as rosuvastatin 20 and 40 mg and atorvastatin 40 and 80 mg, although only atorvastatin 80 mg has major clinical trial evidence).[4,14] From different trials it has become a well-established fact that the cardiovascular risk-reduction benefits from an intensive statin therapy overshadows small increased risk in adverse events, especially for patients at high risk of cardiovascular events. The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL), which compared the effects of high-dose (atorvastatin 80 mg/d) vs usual-dose (simvastatin 20 and 40 mg/d) statin therapy on the incidence of major coronary artery disease events in 8888 patients with a history of myocardial infarction, showed that intensive statin therapy leads to a reduction in nonfatal myocardial infarction (17%) and major adverse cardiovascular events (13%).[15] In contrast, usual statin dose is corroborated by meta-analyses indicating that higher-dose statin therapy reduces myocardial infarction by 16% and strokes by 18% in patients with coronary artery disease.[16] As ezetimibe (on top of moderate-dose statin) reduced myocardial infarction by 13% and strokes by 14%, it is possible that simply using a higher-dose statin (atorvastatin 80 mg) vs simvastatin 40 mg, rather than adding ezetimibe, might have led to similar if not

greater benefits. Indeed, the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) study enrolled 4162 participants with a recent acute coronary syndrome (within the last 10 days—similar to IMPROVE-IT), which clearly showed that intensive statin therapy (atorvastatin 80 mg) compared with moderate statin therapy (pravastatin 40 mg) significantly reduced the primary endpoint (death, myocardial infarction, unstable angina requiring rehospitalization, stroke, or revascularization) by 16%.[17] Supporting the PROVE-IT TIMI 22 trial results is the Study Assessing Goals in the Elderly (SAGE) trial, which randomized 893 ambulatory elderly coronary artery disease patients to either atorvastatin 80 mg/d or pravastatin 40 mg/d, and found a significant reduction in all-cause mortality with higher-dose statin therapy after 12 months of follow-up.[18] These results question the clinical relevance of the IMPROVE-IT trial, where ezetimibe was prescribed on top of a moderate-dose statin instead of a high-dose statin. In essence, IMPROVE-IT never really improved on PROVE-IT.

Another interesting question is: Would reloading a high-dose statin (with an additional dose of statin) provide greater (and faster) clinical benefit than adding ezetimibe on top of a moderate statin dose? This notion is supported by the ARMYDA RECAPTURE trial, which showed that if atorvastatin 40 mg is reloaded—on top of atorvastatin 80 mg in myocardial infarction patients undergoing percutaneous intervention—there is a reduction in major adverse cardiovascular endpoints in just 30 days.[19] It reiterates the fact that using ezetimibe on top of moderate-dose simvastatin (which provides only moderate benefit after 7 years of therapy) may not be the best strategy, especially when there would likely be a significant reduction in major adverse cardiac endpoints by simply using high-dose atorvastatin—particularly if reloaded with another 40 mg before percutaneous intervention.

However, this prior evidence does not totally negate the benefits found in IMPROVE-IT, but it should temper them. Unfortunately, despite the use of both ezetimibe and simvastatin (acting via 2 different pathways) leading to significant decrease in low-density lipoprotein cholesterol level (16.7 mg/dL greater reduction in low-density lipoprotein cholesterol with ezetimibe + simvastatin vs simvastatin + placebo arm), this only translates into a 2% absolute and 6.4% relative risk reduction in the primary outcome over 7 years. The question we propose is: Does this provide a "confirmation of the low-density lipoprotein cholesterol theory"? Whether replacing moderate-dose simvastatin with high-dose atorvastatin would improve outcomes is certainly a matter of debate, but the overall evidence in the literature indicates that this scenario is highly probable. Although, the IMPROVE-IT investigators have claimed that the number needed to treat was 50, which occurred over 7 years, making the yearly number needed to treat 350.

Likely the major implication of IMPROVE-IT is that ezetimibe as an adjunct to statin therapy—even in patients with very low-density lipoprotein cholesterol levels—still leads to clinical benefit (although a rather modest benefit, and greater benefits would be anticipated in patients with much higher levels of low-density lipoprotein cholesterol) and provides confidence in the safety of ezetimibe (although no cardiovascular trial is powered for safety). Future research could be directed toward testing whether adding ezetimibe to a more potent statin would provide incremental cardiovascular benefit, as many patients in clinical practice continue to have quite high levels of low-density lipoprotein cholesterol despite high doses of statins. Also, despite the current AHA/ACC Guidelines not recommending specific lipid targets, substantial evidence[13,20]—somewhat supported by PROVE-IT—does suggest to many clinicians that "Lower is Better."

There is hope that the success of IMPROVE-IT will prove that low-density lipoprotein cholesterol is the most important surrogate marker for predicting cardiovascular outcomes. There is a fair possibility that new lipid-modifying drugs, such as Proprotein convertase subtilisin/kexin type 9 inhibitors, could be more likely to be accepted by the US Food and Drug Administration based on benefiting this surrogate marker.[21] Although low-density lipoprotein cholesterol could be an important surrogate marker for cardiovascular outcomes, it is certainly not the only one. Indeed, low levels of high-density lipoprotein cholesterol and high levels of triglycerides also pose as growing problems in coronary artery disease patients, as the prevalence of diabetes mellitus, obesity, and metabolic syndrome increases.[22] Moreover, patients still remain at cardiovascular risk even when intensive low-density lipoprotein cholesterol-lowering agents are administered. Thus, other medications targeting different aspects of the cardiovascular profile need to be addressed adequately in the future to mitigate the residual risk. Quite possibly, prior studies with extended-release nicotinic acid[20] and fenofibrate[23] (both generic agents) may have been more positive if

Table 1 Strengths of IMPROVE-IT

Large patient population
Long duration of follow-up
Positive results for the primary endpoint
Good side effect profile with addition of ezetimibe + statin

IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial.

Table 2 Limitations of IMPROVE-IT

Use of moderate dose statin in acute coronary syndrome patients vs high dose statin (ie, questionable clinical relevance in a typical acute coronary syndrome population)
Moderate benefit shown for the primary endpoint
High yearly Number Needed to Treat

IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial.

their studies were many times larger, as was IMPROVE-IT, and patients were followed for close to 7 years (instead of 3-5 years). **Tables 1** and **2** provide the strengths and weaknesses of the IMPROVE-IT trial, respectively.

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