IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients
Michael O'Riordan | November 21, 2014

CHICAGO, IL (updated) — More than 9 years since the IMPROVE-IT study was launched, physicians now have their answer when it comes to using ezetimibe (Zetia, Merck/Schering-Plough) in clinical practice. The large-scale, long-delayed, and controversial study of ezetimibe in post–acute-coronary-syndrome (ACS) patients showed a "modest" benefit in reducing cardiovascular events when ezetimibe was added to simvastatin in this population.

Over a period of 7 years, the addition of ezetimibe to simvastatin 40 mg reduced the primary end point—a composite of cardiovascular death, MI, unstable angina requiring rehospitalization, coronary revascularization, or stroke—by 6.4% when compared with patients who received simvastatin alone ($P=0.016$). The absolute reduction in risk over 7 years was 2.0%, with 32.7% in the ezetimibe/simvastatin arm experiencing a primary end point compared with 34.7% in the simvastatin arm.

In terms of individual components of the primary end point, the reduction was driven by a statistically significant reduction in the risk of MI and ischemic stroke. Overall, there was a significant 10% reduction in the risk of cardiovascular death, nonfatal MI, or nonfatal stroke. All-cause mortality was not affected by treatment.

Dr Christopher Cannon (Brigham and Women's Hospital, Boston, MA), one of the lead investigators, said this is the "first trial demonstrating an incremental clinical benefit when adding a nonstatin, cholesterol-lowering agent to a statin."

The study, however, also supports the "lower–is-better" cholesterol premise, said Cannon. At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9 mg/dL at 1 year. The addition of ezetimibe 10 mg to simvastatin further lowered LDL-cholesterol levels, to 53.2 mg/dL at 1 year. Over 7 years, there remained a significant difference between the two treatments in the achieved LDL-cholesterol levels.

"Even lower was even better," said Cannon, noting that incremental benefit was achieved in patients treated well below the previously recommended threshold of 70 mg/dL. "More broadly, these findings in very well-treated patients, by going even further than we have in the past, reaffirm the LDL hypothesis, that reducing LDL cholesterol prevents cardiovascular disease," he added.

IMPROVE-IT: Results At Long Last

The results of IMPROVE-IT were presented this week at the American Heart Association (AHA) 2014 Scientific Sessions during the late-breaking clinical-trials session. The study included more than 18 000 patients from 39 countries who were stable following ACS (<10 days). Patients were randomized to one of two treatment strategies: simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg. They were followed for a minimum of 2.5 years or until the study investigators accrued 5250 clinical events.

Overall, the study was positive, with investigators reporting a statistically significant reduction in the primary end point as well as in three specified secondary end points (which were based on different combinations of the individual end points). The largest relative reduction was observed in the combined end point of coronary heart disease death, MI, and urgent coronary revascularization (18.9% event rate in the simvastatin arm vs 17.5% in the ezetimibe/simvastatin arm; $P=0.016$). For the primary end point, the number-needed-to-treat to prevent one event was 50 when measured over a median time of 7 years.

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Simvastatin, n=9077 (%)</th>
<th>Ezetimibe/Simvastatin, n=9067 (%)</th>
<th>$P$</th>
</tr>
</thead>
</table>

**IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients**

**Dr Christopher Cannon**

[Brigham and Women's Hospital, Boston, MA], one of the lead investigators, said this is the "first trial demonstrating an incremental clinical benefit when adding a nonstatin, cholesterol-lowering agent to a statin."

The study, however, also supports the "lower–is-better" cholesterol premise, said Cannon. At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9 mg/dL at 1 year. The addition of ezetimibe 10 mg to simvastatin further lowered LDL-cholesterol levels, to 53.2 mg/dL at 1 year. Over 7 years, there remained a significant difference between the two treatments in the achieved LDL-cholesterol levels.

"Even lower was even better," said Cannon, noting that incremental benefit was achieved in patients treated well below the previously recommended threshold of 70 mg/dL. "More broadly, these findings in very well-treated patients, by going even further than we have in the past, reaffirm the LDL hypothesis, that reducing LDL cholesterol prevents cardiovascular disease," he added.

**IMPROVE-IT: Results At Long Last**

The results of IMPROVE-IT were presented this week at the American Heart Association (AHA) 2014 Scientific Sessions during the late-breaking clinical-trials session. The study included more than 18 000 patients from 39 countries who were stable following ACS (<10 days). Patients were randomized to one of two treatment strategies: simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg. They were followed for a minimum of 2.5 years or until the study investigators accrued 5250 clinical events.

Overall, the study was positive, with investigators reporting a statistically significant reduction in the primary end point as well as in three specified secondary end points (which were based on different combinations of the individual end points). The largest relative reduction was observed in the combined end point of coronary heart disease death, MI, and urgent coronary revascularization (18.9% event rate in the simvastatin arm vs 17.5% in the ezetimibe/simvastatin arm; $P=0.016$). For the primary end point, the number-needed-to-treat to prevent one event was 50 when measured over a median time of 7 years,
<table>
<thead>
<tr>
<th>Primary end point (Cardiovascular death, MI, unstable angina, coronary revascularization, or stroke)</th>
<th>34.7</th>
<th>32.7</th>
<th>0.016</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>15.3</td>
<td>15.4</td>
<td>0.782</td>
</tr>
<tr>
<td>MI</td>
<td>14.8</td>
<td>13.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8</td>
<td>4.2</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.1</td>
<td>3.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.9</td>
<td>2.1</td>
<td>0.618</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>23.4</td>
<td>21.8</td>
<td>0.107</td>
</tr>
</tbody>
</table>

In a separate session the day after the main IMPROVE-IT presentation, Dr Michael Blazing (Duke Clinical Research Institute, Durham, NC) presented the results of the on-treatment analysis. This analysis excluded patients documented not to have taken ezetimibe or who stopped taking the drug during the course of the trial, which left 10 573 who completed the study on treatment. These patients were equally distributed among the two randomized treatment arms, said Blazing. When looking at the trial in this light, ezetimibe fared a little better. For the primary end point, adding ezetimibe to simvastatin resulted in a statistically significant 7.6% relative reduction in the primary end point. Also, the number-needed-to-treat to prevent one event was 38 over 7 years.

To heartwire, Dr Sanjay Kaul (Cedars Sinai Medical Center, Los Angeles, CA), who was not affiliated with the study, said the IMPROVE-IT trial “technically” won on the primary end point, but he questions the clinical significance of the findings, noting the overall treatment effect was modest. He also points out that the difference in the composite primary end point “was elevated to the lofty pedestal of statistical significance simply due to the large sample size, a classic example of a disconnect between statistical significance and clinical importance.”

“Are we to applaud and celebrate a 6% relative risk reduction in a quintuplet end point that is primarily driven by reductions in nonfatal end points?” asked Kaul. He added that it is not clear which type of MIs, spontaneous or periprocedural, were reduced with treatment.

For Cannon, however, as well as others involved in the trial, the lack of benefit on mortality is something they did not anticipate with ezetimibe. Cannon said clinical end points such as MI and stroke are valid because they are meaningful to patients. In IMPROVE-IT, there was a relative 13% relative reduction in the risk of MI and a 21% relative reduction in the risk of ischemic stroke.

**The Back Story With Ezetimibe and ENHANCE**

Ezetimibe has been a controversial drug almost since the moment it was approved. The controversy, however, largely stems from a surrogate-end-point study presented in 2008. With ENHANCE, which measured subclinical atherosclerosis using carotid intima-media thickness in patients with familial hypercholesterolemia (FH), investigators did not observe a reduction in atherosclerosis when patients received ezetimibe on top of statin therapy.

This led many in the cardiology community to question whether the drug had any clinical benefit aside from lowering LDL-cholesterol levels. On top of the neutral ENHANCE results, the trial attracted criticisms because there was a significant 18-month delay between when the trial was completed and when it published. The trial even attracted the attention of US legislators, who launched a congressional investigation into the study's many delays. Given the lack of benefit on atherosclerosis in ENHANCE, critics said Merck/Schering-Plough needed to prove the drug was effective beyond LDL lowering. "All we said was that they had an obligation to demonstrate that this method of LDL lowering would produce a clinical benefit," Dr Steven Nissen (Cleveland Clinic, OH) told heartwire at the AHA meeting this.
And they did, albeit it's a very small treatment effect after a very long treatment exposure."

Nissen believes IMPROVE-IT is a positive trial, and despite flaws, it is a statistically valid result. He pointed out that the treatment effect was observed in a very high-risk patient population, so this does not mean LDL lowering with ezetimibe should be widely used elsewhere. "It doesn't mean that everybody ought to get ezetimibe, and it doesn't mean that primary-prevention patients ought to get it," said Nissen. "It does mean that this method of LDL lowering is a clinically beneficial approach."

Dr Harlan Krumholz (Yale University School of Medicine, New Haven, CT) told heartwire the clinical community had hoped the results from IMPROVE-IT would be positive, especially since it has been used in so many patients since it was approved. "In this case, the drug shaves off a small amount of risk, and some physicians might find it clinically meaningful. We now have some evidence to inform patient choice for a drug that we've already spent billions and billions of dollars on."

Nissen said a lot of his criticism pertaining to ezetimibe stemmed from its marketing. When the drug was approved by the US Food and Drug Administration in 2002, a massive direct-to-consumer advertising campaign was launched without any hard clinical-outcomes data. "Until they got into trouble, they had no plans on doing an outcomes trial. And that was not in society's best interest," he said.

Ironically, now that physicians have data on ezetimibe, the drug will soon be off patent and likely available as a generic. Adding ezetimibe to the clinical armamentarium will likely have little impact on healthcare costs.

**Changing Treatments Since IMPROVE-IT Launched**

More important than cost, however, is that medicine has changed a great deal since IMPROVE-IT was designed, said Krumholz. Given this, the study raises more questions than it answers. Clinically speaking, simvastatin 40 mg, a moderate-intensity statin, is not used frequently in practice any more. In fact, the US guidelines recommend high-dose statin therapy with atorvastatin 80 mg or rosvuavastatin (Crestor, AstraZeneca) 40 mg for the high-risk post-ACS patient.

To be more useful in the present day, Krumholz said IMPROVE-IT would have benefited clinicians if it had an additional arm testing clinical outcomes in patients treated with atorvastatin 80 mg or rosvuavastatin 40 mg. With such a comparator, physicians would know how ezetimibe fared against high-intensity statin therapy, which is what the current guidelines recommend in post-ACS patients.

Dr Lori Mosca (Columbia University Medical Center, New York), who runs a specialty practice in preventive cardiology, has prescribed ezetimibe in recent years because her patients are considered very high risk and some are unable to get to goal with a high-dose statin or are intolerant of the medication class. As a result, she sees the IMPROVE-IT findings positively, although she stresses ezetimibe should still remain in limited rotation. "I came to [ezetimibe] because I really felt, for a long time, that it's LDL lowering that matters," said Mosca. "Unlike other nonstatin drugs that lower LDL, ezetimibe didn't really have a side-effect profile I was concerned about. Still, I don't want to give the message that this should be first-line treatment. I still don't believe that. The evidence base for statins is very strong."

Kaul said, given the modest treatment effect, one driven primarily by nonfatal end points, along with the added cost of treatment, that he will "not be rushing" to routinely add ezetimibe on top of statin post-ACS. But like Mosca and others, he said ezetimibe does provide a useful option.

"So this trial provides justification for maintaining the status quo for both camps—those who did not use ezetimibe routinely as first- or second-line therapy, as well for those who used the drug in combination with statins to optimize benefit/risk balance," Kaul told heartwire.

**IMPROVE-IT and the US Cholesterol Guidelines**

Dr Neil Stone (Northwestern University Feinberg School of Medicine, Chicago, IL), who cochaired the 2013 US American College of Cardiology (ACC)/American Heart Association guidelines for cholesterol treatment, said he believes IMPROVE-IT supports the newest cholesterol guidelines.
The guidelines, he stressed, already give physicians room to use other nonstatin medications to lower LDL cholesterol if a patient is unable to tolerate a statin or unable to achieve the recommended 50% reduction in risk. IMPROVE-IT, said Stone, affirms the central role of intensive LDL reduction for preventing recurrent cardiac events and expands the options for additional proven lipid-lowering therapy.

"The recent guidelines refuse to say 'lower is better.' They say 'lower is better with proven therapy, a therapy shown to provide incremental benefit that's safe.' " He also said these "data don't speak to the use of ezetimibe in low-risk primary-prevention patients."

During the media briefing, as well as during the late-breaking clinical-trials presentation, a question that arose was whether or not ezetimibe could be added to patients who are treated with a high-intensity statin. Cannon said he'd be willing to treat such patients in this way. He noted that high-risk familial hypercholesterolemia (FH) patients routinely receive ezetimibe on top of atorvastatin 80 mg or rosuvastatin 40 mg.

Stone, on the other hand, refused to wander down this hypothetical road. For him, there is no evidence supporting such a treatment because that's not what IMPROVE-IT tested. "My first principle: don't guess when you can know," said Stone. "It simply wasn't tested, not just in terms of efficacy, but also in terms of safety."

Merck/Schering-Plough sponsored the IMPROVE-IT trial. Cannon reports research grants from Accumetrics, Merck, Arisaph, AstraZeneca, GlaxoSmithKline, Janssen, Takeda, and Boehringer-Ingelheim and honoraria from Bristol-Myers Squibb, Pfizer, Takeda, Merck, GlaxoSmithKline, Essentialis, CSL, Lipimedix, Regeneron, and Sanofi.

See also: What I'm Telling Patients About Ezetimibe on Monday Morning

References