On-Treatment Analysis of the IMPROVE-IT Study

DISCUSSION

JEFFREY L ANDERSON, MD, FACC, FAHA, MACP
Intermountain Heart Institute
Intermountain Medical Center
Murray, Utah

Disclosures: No relevant RWI and no trial involvement; Intermountain was an IMPROVE-IT site
New Perspective on LDL–C & Non-HDL–C Goals

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
- Quantitative comparison of statin benefits with statin risk
- Nonstatin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy
IMPROVE-IT Design and Trial Challenges and ITT Primary Results

Challenges to a positive study result:

• Moderate incremental LDL lowering (20-25%, 15mg/dL)
• Low event rates at low initial LDL; flattening of efficacy vs. LDL lowering relationship at low levels?
• Given long f/u (6y), high drug discontinuation rate?
• Negative publicity (SEAS: ↑cancer?; ENHANCE: ↓efficacy?; 80mg muscle toxicity): impact on recruitment, maintenance

Primary endpoint - ITT

<table>
<thead>
<tr>
<th></th>
<th>Event Rate</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>34.7%</td>
<td>0.936</td>
<td>(0.887, 0.988)</td>
<td>0.016</td>
</tr>
<tr>
<td>Eze/Simva</td>
<td>32.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular Death, MI, documented Unstable Angina requiring rehospitalization, coronary revascularization (>30 days) or stroke
Positive and Negative Arguments for On-Treatment Analyses

• Excluding non-compliers and drop-outs has substantial potential to introduce bias, which may be due to:
  • Baseline imbalances, drug-related AEs, drug-inefficacy, loss of motivation.

• However, if patient characteristics are balanced, drug efficacy is similar, and safety/tolerability is good and similar in both groups, on-treatment analysis may provide a better estimate of pharmacological treatment effect and potential drug efficacy with compliance.
  • (On-treatment analysis is preferred with non-inferiority designs, as ITT may mask true differences.)

IMPRESS-IT On-Treatment Results

- Patient characteristics and lipid metrics/response similar for on-treatment (OT) and off-treatment populations.
- Safety similar for ezetimibe/simvastatin and simvastatin groups.
- OT results directionally similar to, ~20% better than, mITT (NNT 38 vs 50; treatment effect 7.6% vs 6.4%; 33% time off-Rx in mITT avoided).

**Primary and 3 Prespecified Secondary Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary - ITT OT</td>
<td>34.7</td>
<td>32.7</td>
<td>0.936</td>
</tr>
<tr>
<td>2ndary #1 - ITT OT</td>
<td>40.3</td>
<td>38.7</td>
<td>0.948</td>
</tr>
<tr>
<td>2ndary #2 - ITT OT</td>
<td>18.9</td>
<td>17.7</td>
<td>0.912</td>
</tr>
<tr>
<td>2ndary #3 - ITT OT</td>
<td>36.2</td>
<td>34.5</td>
<td>0.945</td>
</tr>
</tbody>
</table>

*7 year event rates

**No statistically significant differences in muscle or gallbladder related events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva* (n=8855)</th>
<th>EZ/Simva* (n=8851)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystectomy</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0.948</td>
</tr>
<tr>
<td>Gallbladder related AE's</td>
<td>2.4%</td>
<td>2.8%</td>
<td>0.068</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.369</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.316</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.704</td>
</tr>
</tbody>
</table>

1 = All cause death, major coronary event, or stroke post randomization
2 = CV Death, non fatal MI, documented UA requiring rehospitalization, all revascularization (>30 days) after randomization or non fatal stroke
3 = CHD Death, non fatal MI, or urgent CABG or PCI (>30 days) after randomization

**Total patient years on clinical follow up ≥ 72 months**

[Image of Intermountain Heart Institute and Intermountain Medical Center logos]
Statin-Treated Individuals
Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - **Clinical** ASCVD <75 years of age
    - Baseline LDL–C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age

- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred
IMPROVE-IT On-Treatment Conclusions

- IMPROVE-IT has shown that incremental lipid (LDL) lowering with ezetimibe, on top of statin therapy, provides an incremental outcomes benefit.
- Ezetimibe, added to simvastatin, is safe and well-tolerated.
- While actually taking ezetimibe, patients have modestly greater MACE reductions, defining its potential for incremental benefit.
- However, strictly interpreted, results apply only to patients already on at moderate intensity statin therapy at low baseline LDL levels. Extrapolation is required to ezetimibe-only, and ezetimibe low-dose statin combination therapies, and to therapy with statins at higher baseline LDL levels.
- Nevertheless, overall results may be seen as supporting an additional lipid-lowering mechanism that beneficially impacts outcomes.