IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome
## Trial Leadership

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Lowering LDL cholesterol (LDL-C) has been a mainstay of cardiovascular prevention.

- Evidence mostly from statin trials which show reduction in morbidity and mortality
  - High-dose statins further reduce non-fatal CV events

- To date, no lipid-modifying therapy added to statins has been demonstrated to provide a clinical benefit
  - Fibrates, niacin, CETP inhibitors

- Recent ACC/AHA Guidelines have emphasized use of statin therapy

- Despite current therapies, patients remain at high risk
Ezetimibe: Background

➢ Ezetimibe inhibits Niemann-Pick C1-like 1 (NPC1L1) protein
  – located primarily on the epithelial brush border of the GI tract
  – resulting in reduced cholesterol absorption

➢ When added to statin, produces ~20% further reduction in LDL-C

➢ Two recent human genetic analyses have correlated polymorphisms in NPC1L1 with lower levels of LDL-C and lower risk of CV events*

*MI Genetics Consortium Investigators NEJM 2014; online Nov 12; Ference BA et al AHA 2014
Goals

**IMPROVE-IT**: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

- Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
- “Is (Even) Lower (Even) Better?” (estimated mean LDL-C ~50 vs. 65mg/dL)
- Safety of ezetimibe

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
Patient Population

Inclusion Criteria:
- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:
- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease
Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
# Study Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Simva (N=9077)</th>
<th>EZ/Simva (N=9067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptitration to Simva 80mg, %</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Premature study drug D/C, %</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Median follow-up, yrs</td>
<td>6.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Withdraw consent w/o vital status, %/yr</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Lost to follow-up, %/yr</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Follow up for primary endpoint, %</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>Follow up for survival, %</td>
<td>97</td>
<td>97</td>
</tr>
</tbody>
</table>

- Total primary endpoint events = 5314
- Total patient-years clinical follow-up = 97,822
- Total patient-years follow-up for survival = 104,135
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (N=9077)</th>
<th>EZ/Simva (N=9067)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td><strong>MI prior to index ACS</strong></td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td><strong>STEMI / NSTEMI / UA</strong></td>
<td>29 / 47 / 24</td>
<td>29 / 47 / 24</td>
</tr>
<tr>
<td><strong>Days post ACS to rand (IQR)</strong></td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td><strong>Cath / PCI for ACS event</strong></td>
<td>88 / 70</td>
<td>88 / 70</td>
</tr>
<tr>
<td><strong>Prior lipid Rx</strong></td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td><strong>LDL-C at ACS event (mg/dL, IQR)</strong></td>
<td>95 (79, 110)</td>
<td>95 (79, 110)</td>
</tr>
</tbody>
</table>
## LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
<td></td>
</tr>
</tbody>
</table>

Median Time avg 69.5 vs. 53.7 mg/dL

Number at risk:

| EZ/Simva | 8990 | 8889 | 8230 | 7701 | 7264 | 6864 | 6583 | 6256 | 5734 | 5354 | 4508 | 3484 | 2608 | 1078 |
| Simva    | 9009 | 8921 | 8306 | 7843 | 7289 | 6939 | 6607 | 6192 | 5684 | 5267 | 4395 | 3387 | 2569 | 1068 |
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT= 50

7-year event rates
Primary and 3 Prespecified Secondary Endpoints — ITT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Simva* EZ/Simva* p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0.936</td>
</tr>
<tr>
<td>Secondary #1</td>
<td>0.948</td>
</tr>
<tr>
<td>Secondary #2</td>
<td>0.912</td>
</tr>
<tr>
<td>Secondary #3</td>
<td>0.945</td>
</tr>
</tbody>
</table>

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)
Individual Cardiovascular Endpoints and CVD/MI/Stroke

**HR** | **Simva** | **EZ/Simva** | **p-value**
--- | --- | --- | ---
All-cause death | 0.99 | 15.3 | 15.4 | 0.782
CVD | 1.00 | 6.8 | 6.9 | 0.997
CHD | 0.96 | 5.8 | 5.7 | 0.499
MI | 0.87 | 14.8 | 13.1 | 0.002
Stroke | 0.86 | 4.8 | 4.2 | 0.052
Ischemic stroke | 0.79 | 4.1 | 3.4 | 0.008
Cor revasc ≥ 30d | 0.95 | 23.4 | 21.8 | 0.107
UA | 1.06 | 1.9 | 2.1 | 0.618
CVD/MI/stroke | 0.90 | 22.2 | 20.4 | 0.003

*7-year event rates (%)

**Ezetimibe/Simva Better** | **Simva Better**
CV Death, Non-fatal MI, or Non-fatal Stroke

7-year event rates

Event Rate (%) vs. Time since randomization (years)

- **Simva — 22.2%**
  - 1704 events
  - HR 0.90 CI (0.84, 0.97)
  - p=0.003
  - NNT= 56

- **EZ/Simva — 20.4%**
  - 1544 events
Major Pre-specified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Simva†</th>
<th>EZ/Simva†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34.9</td>
<td>33.3</td>
</tr>
<tr>
<td>Female</td>
<td>34.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>30.8</td>
<td>29.9</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>39.9</td>
<td>36.4</td>
</tr>
<tr>
<td>No diabetes</td>
<td>30.8</td>
<td>30.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Prior LLT</td>
<td>43.4</td>
<td>40.7</td>
</tr>
<tr>
<td>No prior LLT</td>
<td>30.0</td>
<td>28.6</td>
</tr>
<tr>
<td>LDL-C &gt; 95 mg/dl</td>
<td>31.2</td>
<td>29.6</td>
</tr>
<tr>
<td>LDL-C ≤ 95 mg/dl</td>
<td>38.4</td>
<td>36.0</td>
</tr>
</tbody>
</table>

*p-interaction = 0.023, otherwise > 0.05
IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

CTT Collaboration.
Lancet 2005; 366:1267-78;

Proportional reduction in event rate (SE)

Reduction in LDL cholesterol (mmol/L)
No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva n=9077 %</th>
<th>EZ/Simva n=9067 %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST≥3x ULN</td>
<td>2.3</td>
<td>2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5</td>
<td>1.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5</td>
<td>3.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6</td>
<td>0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* (7-yr KM %)</td>
<td>10.2</td>
<td>10.2</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee % = n/N for the trial duration
Conclusions

**IMPROVE-IT**: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES**: *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES**: Even Lower is Even Better  
  (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES**: Confirms ezetimibe safety profile

- **Reaffirms the LDL hypothesis**, that reducing LDL-C prevents cardiovascular events
- **Results could be considered for future guidelines**