Clinical Implications from Recent Lipid Guideline for High-risk Patients

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Keimyung University Dongsan Medical Center
• I have nothing to disclosure for this presentation.
• The view expressed herein represents those of the speaker and not necessarily those of the MSD Korea.
1. Benefits of combination therapy aligned with recent update guidelines
   - Recent update guideline and Implications
   - Benefits of ezetimibe/statin combination therapy for LDL-C reduction

2. New considering point of view for preventing Atherosclerosis
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy
1. Benefits of combination therapy aligned with recent update guidelines
   - Recent update guideline and Implications
   - Benefits of ezetimibe/statin combination therapy for LDL-C reduction
Relationship Between LDL-C on Treatment and Clinical Event Rates in Major Trial

Atv = atorvastatin; Pra = pravastatin; Sim = simvastatin; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

LDL-C Goals for High-Risk Patients Have Become More Intensive

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time.

### Definition of high-risk / highest-risk or very high patient:

- ATP I: definite CHD or 2 other CHD risk factors
- ATP II: existing CHD or other atherosclerotic disease
- ATP III and the 2004 update: CHD or CHD risk equivalents
- 2° AHA/ACC 2006: established coronary and other atherosclerotic disease
- ADA 2010: overt CVD
- ESC/EAS 2011: CVD (MI, ACS, revascularization), ischemic stroke, type 2 DM, moderate to severe CKD, or SCORE ≥10%


Very high risk in updated ATPIII

- Established CVD plus
  - Multiple major risk factors (especially DM)
  - Severe and poorly controlled risk factors (especially continued smoking)
  - Multiple risk factors of MetS (especially Tg ≥ 200, Non-HDL-c ≥ 130, and HDL-c < 40)
  - Acute coronary syndrome

→ LDL-c goal < 70mg/dL

- In high risk persons (10yr CHD risk > 20%), LDL-c goal < 100 mg/dL
  - if LDL-c ≥ 100mg/dL, LDL-c lowering drug is indicated
  - if LDL-c < 100mg/dL, LDL-c lowering drug is an option
  - When TG ≥ 200mg/dL, non-HDL-c is secondary target of therapy, with a goal 30mg/dL higher than LDL-c goal

When LDL-c lowering drugs are used, LDL-c levels should be reduced at least 30-40%
The following table reflects the status of each report and progress through the remaining stages of the review process before the guidelines are released.

<table>
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<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>In Progress</td>
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<td><strong>Risk Assessment</strong></td>
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<td>Completed</td>
<td>Completed</td>
<td>In Progress</td>
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<tr>
<td><strong>Cholesterol</strong></td>
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<td>Completed</td>
<td>Completed</td>
<td>In Progress</td>
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<tr>
<td><strong>Blood Pressure</strong></td>
<td>In Progress</td>
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<tr>
<td><strong>Obesity</strong></td>
<td>In Progress</td>
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</tbody>
</table>

- **Draft Completed**: Expert panelists have completed a full draft of the systematic review and recommendations.
- **Federal Review**: Federal agency representatives of the NHLBI's National Program to Reduce Cardiovascular Risk (NPRCR) coordinating committee provide review and comment.
- **Expert Review**: External peer reviewers with expertise in the relevant risk factors provide review and comment.
- **Advisory Council**: The National Heart, Lung, and Blood Advisory Council provides review and comment and recommends approval.
- **Public Comment**: The draft is offered publicly for review and comment.
- **HHS Clearance**: The U.S. Department of Health and Human Services provides editorial review, comment, and approval.

http://www.nhlbi.nih.gov/guidelines/indevelop.htm#status
ESC/EAS 2011 Guidelines
: Very High– and High CV Risk Level Classification

Very High Risk includes subjects with any of the following:
- Documented CVD, previous MI, ACS, coronary revascularization, other revascularization procedure, ischemic stroke, PAD
- Type 2 diabetes or type 1 diabetes with target organ damage (such as microalbuminuria)
- Moderate to severe CKD (GFR <60 mL/min/1.73 m²)
- A calculated 10-year risk SCORE ≥10%

High Risk includes subjects with any of the following:
- Markedly elevated single-risk factors (eg, familial dyslipidemias or severe hypertension)
- A calculated 10-year risk SCORE ≥5% and <10% for fatal CVD

Patients with VERY HIGH or HIGH total CV risk need active management of all risk factors.

For all other people, the use of a risk estimation system such as SCORE is recommended to estimated total CV risk.

CVD = cardiovascular disease; MI = myocardial infarction; ACS = acute coronary syndrome; PAD = peripheral artery disease; CKD = chronic kidney disease; GFR = glomerular filtration rate; SCORE = Systematic Coronary Risk Estimation.

# ESC/EAS 2011 Guidelines: Lipid Targets

More aggressive target for high-risk patients

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Target</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td>&lt;1.8 mmol/L (≈70 mg/dL)</td>
<td>&lt;2.6 mmol/L (≈100 mg/dL)</td>
</tr>
<tr>
<td>And/or ≥50% reduction from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>&lt;2.5 mmol/L (≈100 mg/dL)</td>
<td>&lt;3.3 mmol/L (≈130 mg/dL)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&lt;3.0 mmol/L (≈115 mg/dL)</td>
<td>&lt;3.8 mmol/L (≈145 mg/dL)</td>
</tr>
</tbody>
</table>

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; apo = apolipoprotein; CVD = cardiovascular disease; MI = myocardial infarction; ACS = acute coronary syndromes; PAD = peripheral artery disease; CKD = chronic kidney disease; SCORE = Systematic Coronary Risk Estimation.


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**Very high risk**

Documented CVD, previous MI, ACS, coronary or other arterial revascularization, ischemic stroke, PAD, type 2 diabetes or type 1 diabetes with target organ damage, moderate to severe CKD, or a calculated 10 year risk SCORE ≥10%

**High risk**

Markedly elevated single risk factors such as familial dyslipidemia and severe hypertension, or a calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD

**Moderate risk**

SCORE is ≥1% and <5% at 10 years
ESC/EAS 2011 Guidelines:
Management of Dyslipidemia in Acute Coronary Syndrome

- High dose statin therapy be initiated during the first 1–4 days of hospitalization for the index ACS; if basal LDL-C values are known, the dose should aim at reaching the LDL-C target of <1.8 mmol/L (less than ~70 mg/dL).

- The use of lower intensity statin therapy should be considered in patients at increased risk of side effects with high doses of statin (e.g. the elderly, hepatic impairment, renal impairment, or potential for interaction with essential concomitant therapy).

- Lipids should be re-evaluated 4–6 weeks after the ACS to determine whether target levels have been reached and regarding safety issues; the statin dose can then be adapted accordingly.

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

Statins should be given to all patients with acute myocardial infarction, irrespective of cholesterol concentration.

The use of lower-intensity statin therapy should be considered in patients at increased risk of side-effects from statins.

- e.g. the elderly, patients with hepatic or renal impairment, with previous side-effects of statins or the potential for interaction with essential concomitant therapy

In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered
Statins are recommended for elderly patients with established CVD in the same way as for younger patients [Class I, Level B].

Since elderly patients often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to target lipid levels, which are the same as in younger subjects [Class I, Level C].

Statin therapy may be considered in elderly subjects without CVD, particularly in the presence of at least 1 other CV risk factor aside from age [Class IIb, Level B].
VYTORIN (ezetimibe/simvastatin): Dual Action in Cholesterol Metabolism

Intestine: EZETIMIBE

- 33% Dietary chol
- Cholesterol Pool (Micelles)
- Fecal sterols

Liver: STATIN

- Acetyl CoA
- Chol
- Bile Acids
- Remnant receptors
- LDLR

Atheroma

Blood

Peripheral Tissues

Ezetimibe add-on vs. Statin doubling in LDL-C lowering

Based on 3 Separate Clinical Studies, More Dosing Options of VYTORIN (ezetimibe/simvastatin) Provided ≥50% Mean LDL-C Reduction vs Other Selected LDL-C–Lowering Drugs

- The above comparisons do not establish that the products have the same indications, safety profiles, or dosing regimens.

In hypercholesterolemia patients, VYTORIN 10/20mg provided ≥50% reduction in LDL-C. In a clinical study of patients with hypercholesterolemia and type 2 DM (VYTAL study), VYTORIN 10/20mg (n=238) and Atorvastatin 20mg (n=240) showed the following mean percent change from baseline at 6 weeks (%):

- **LDL-C**: -54% (P<0.001), -50%
- **TC**: -38% (P<0.001), -33%
- **HDL-C**: 8%, 5%
- **TG**: -26%, -26%
- **non-HDL-C**: -41%
- **hs-CRP**: -23%

HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides

#: median

Statin treated, but Not at LDL-C goal,

**Switching** to VYTORIN 10/20mg provided ≥ 25% reduction in LDL-C¹

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VYTORIN 10/20mg (n=301-305)</th>
<th>Rosuvastatin 10mg (n=292-297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-28% (P≤0.001)</td>
<td>-18% (P≤0.001)</td>
</tr>
<tr>
<td>TC</td>
<td>-18% (P≤0.001)</td>
<td>-10% (P≤0.001)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-11% (P≤0.001)</td>
<td>-14% (P≤0.001)</td>
</tr>
<tr>
<td>TG</td>
<td>-23% (P≤0.001)</td>
<td>-18% (P≤0.001)</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>-18% (P≤0.001)</td>
<td>-10% (P≤0.001)</td>
</tr>
<tr>
<td>ApoB</td>
<td>0%</td>
<td>-8%</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

Apo: apolipoprotein, HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides

# median

**VYTORIN** was Generally Well Tolerated\(^1,2\)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Statin untreated (^1)</th>
<th>Statin treated, not at goal (^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All VYTORIN 10/20, 10/40mg/day (n=485-494)</td>
<td>All atorvastatin 10, 20, 40mg/day (n=723-732)</td>
</tr>
<tr>
<td>≥1 Clinical event</td>
<td>19.8%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Drug-related clinical event</td>
<td>4.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Discontinuation due to drug-related clinical event</td>
<td>0.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>ALT and/or AST ≥3 × ULN (consecutive)</td>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>CK ≥ 10X ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CK ≥ 5X ULN</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; CK = creatine kinase.

Adapted from Goldberg RB, et al and Farnier M, et al.

60 admitted AMI patients were randomized to simvastatin 40 mg, VYTORIN (ezetimibe/simvastatin) 10/40mg or NLLD and had their lipid levels assessed 2, 4 and 7 days later.

AMI= acute myocardial infarction; NLLD= no lipid-lowering drugs; LDL-C= low density lipoprotein-cholesterol.

Benefit of Early Start of VYTORIN

Rapid LDL-C target goal achievement with VYTORIN in AMI patients.

45% target goal reached on the 4th day!

Percentage of patients achieving a goal LDL-C level of < 70 mg dL−1 during treatment with NLLD (n=20), simvastatin 40 mg/day (n=20), or ezetimibe 10 mg/day co-administered with simvastatin 40 mg/day (EZE/SIMVA, n=20) after an AMI.

AMI = acute myocardial infarction; NLLD = no lipid-lowering drugs; LDL-C = low density lipoprotein-cholesterol.

Ezetimibe add-on to any statin provided additional 25-31% reduction of LDL-C in diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in LDL-C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASE (n=3030)</td>
<td>-26%</td>
</tr>
<tr>
<td>Gagné (n=769)</td>
<td>-25%</td>
</tr>
<tr>
<td>Farnier (n=372)</td>
<td>-25%</td>
</tr>
<tr>
<td>Brohet (n=418)</td>
<td>-27%</td>
</tr>
<tr>
<td>Cruz-Fernández (n=450)</td>
<td>-31%</td>
</tr>
</tbody>
</table>

LDL-C lowering with initial statin dose Ezetimibe/Statin vs. monostatin

<table>
<thead>
<tr>
<th>Study type or sub category</th>
<th>N</th>
<th>Ezetimibe-statins(SD)</th>
<th>N</th>
<th>Statin% (SD)</th>
<th>Odds ratio 95% CI</th>
<th>Weight %</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td><strong>Goal (1st treatment period or study endpoint)</strong></td>
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<tr>
<td>Dobs, 2003</td>
<td>66</td>
<td>-24.50(1.50)</td>
<td>34</td>
<td>-11.10(2.00)</td>
<td>5.45 (-13.40(-20.26, -6.45))</td>
<td>11.58</td>
<td>-14.20(-16.94, -11.46)</td>
</tr>
<tr>
<td>Stein, 2004a</td>
<td>293</td>
<td>-22.80(0.70)</td>
<td>303</td>
<td>-8.60(0.70)</td>
<td>9.47 (-15.00(-18.92, -11.08))</td>
<td>3.99</td>
<td>-27.00(-35.62, -18.38)</td>
</tr>
<tr>
<td>Feldman, 2004</td>
<td>108</td>
<td>-53.00(1.20)</td>
<td>246</td>
<td>-38.00(0.80)</td>
<td>3.50 (-15.28(-24.69, -5.87))</td>
<td>12.88</td>
<td>-14.00(-16.00, -12.00)</td>
</tr>
<tr>
<td>Masana, 2005</td>
<td>355</td>
<td>-23.70(1.80)</td>
<td>78</td>
<td>3.30(2.60)</td>
<td>3.50 (-15.28(-24.69, -5.87))</td>
<td>12.88</td>
<td>-14.00(-16.00, -12.00)</td>
</tr>
<tr>
<td>Strony, 2008</td>
<td>87</td>
<td>-44.40(1.52)</td>
<td>22</td>
<td>-29.12(3.28)</td>
<td>12.88 (-14.00(-16.00, -12.00))</td>
<td>3.50</td>
<td>-15.28(-24.69, -5.87)</td>
</tr>
<tr>
<td>Zieve, 2010</td>
<td>515</td>
<td>-27.00(1.02)</td>
<td>515</td>
<td>-13.00(1.02)</td>
<td>12.88 (-14.00(-16.00, -12.00))</td>
<td>3.50</td>
<td>-15.28(-24.69, -5.87)</td>
</tr>
<tr>
<td><strong>Test for heterogeneity I-squared=41.5%, p=0.19</strong></td>
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<tr>
<td><strong>Single treatment period (endpoint)</strong></td>
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<tr>
<td>Leiter, 2008</td>
<td>277</td>
<td>-27.00(1.20)</td>
<td>279</td>
<td>-11.00(1.02)</td>
<td>11.12 (-16.00(-19.00, -13.00))</td>
<td>7.74</td>
<td>-20.00(-25.00, -15.00)</td>
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<tr>
<td>Conard, 2008</td>
<td>92</td>
<td>-31.00</td>
<td>92</td>
<td>-11.00(2.04)</td>
<td>18.86 (-17.48(-21.26, -13.69))</td>
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<tr>
<td><strong>Test for heterogeneity I-squared=44.7%, p=0.179</strong></td>
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<tr>
<td><strong>Forced titration (1st treatment period, endpoint b, or 2nd treatment period)</strong></td>
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<tr>
<td>Ballantyne, 2004</td>
<td>263</td>
<td>-50.30(0.80)</td>
<td>262</td>
<td>-37.20(0.80)</td>
<td>10.87 (-13.10(-16.24, -9.96))</td>
<td></td>
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<tr>
<td>Ballantyne, 2004</td>
<td>45</td>
<td>-48.40(1.33)</td>
<td>201</td>
<td>-38.60(1.85)</td>
<td>6.12 (-9.80(-16.03, -3.57))</td>
<td></td>
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<tr>
<td>Barrios, 2005</td>
<td>221</td>
<td>-32.80(1.20)</td>
<td>214</td>
<td>-20.30(1.20)</td>
<td>10.87 (-12.50(-15.64, -9.36))</td>
<td></td>
<td></td>
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<tr>
<td>McKenney, 2007</td>
<td>73</td>
<td>-53.00(1.53)</td>
<td>72</td>
<td>-50.00(1.53)</td>
<td>6.40 (-3.00(-9.00, 3.00))</td>
<td></td>
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</tr>
<tr>
<td><strong>Test for heterogeneity=68.0%, p=0.001</strong></td>
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<tr>
<td>Total</td>
<td>2395</td>
<td>-35.90</td>
<td>2318</td>
<td>-21.8</td>
<td>100.00 (-14.11(-16.13, -12.10))</td>
<td></td>
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</tr>
</tbody>
</table>

**Test for heterogeneity I-squared=68.5%, p=0.001**

**Test for overall effect Z statistic=13.71, p<0.001**

### LDL-C lowering with initial dose failure Ezetimibe add on vs. doubling statin

<table>
<thead>
<tr>
<th>Study type</th>
<th>Sub category</th>
<th>N</th>
<th>(Ez + St) - (St (P1)(SD))</th>
<th>N</th>
<th>St - (Ez + St) (P2)(SD)</th>
<th>WMD95% CI</th>
<th>Weight %</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple treatment periods</td>
<td>Zieve, 2010&lt;sup&gt;44&lt;/sup&gt;</td>
<td>516</td>
<td>-14.00 (1.79)</td>
<td>509</td>
<td>-9.00 (2.19)</td>
<td>-5.00 (-12.81, 2.81)</td>
<td>12.63</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>Ballantyne, 2004&lt;sup&gt;45&lt;/sup&gt;</td>
<td>263</td>
<td>-13.10 (1.25)</td>
<td>262</td>
<td>-3.10 (1.33)</td>
<td>-10.00 (-15.04, -4.96)</td>
<td>18.01</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>Masana, 2005&lt;sup&gt;36&lt;/sup&gt;</td>
<td>355</td>
<td>-27.00 (3.43)</td>
<td>78</td>
<td>-0.70 (3.43)</td>
<td>-26.30 (-39.75, -12.85)</td>
<td>6.29</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 72.30\%$, $p=0.027$

| Single treatment period | Conard, 2008<sup>41</sup> | 92 | -31.00 (2.04) | 92 | -11.00 (2.04) | -20.00 (-25.00, -15.00) | 18.11 | 100.00 |
| | Leiter, 2008<sup>42</sup> | 277 | -27.00 (1.28) | 279 | -11.00 (1.02) | -16.00 (-19.00, -13.00) | 212.42 | 100.00 |
| | Roeters van Lennep, 2008<sup>38</sup> | 178 | -29.10 (1.40) | 189 | -11.50 (1.50) | -17.60 (-20.54, -14.66) | 22.54 | 100.00 |

Test for heterogeneity: $I^2 = 0.00\%$, $p=0.390$

Total | 1681 | -24.05 | 1409 | 8.79 | -15.3% | -15.26 (-19.14, -11.38) | 100.00 | 100.00 |

Test for heterogeneity: $I^2 = 72.50\%$, $p=0.002$

Test for overall effect Z statistic = 7.71, $p<0.001$

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**LDL-C goal attainment with initial statin dose Ezetimibe/Statin vs. monostatin**

Eze/Simva combination therapy was better than mono statin in achieving LDL-C goal attainment

<table>
<thead>
<tr>
<th>Study type or sub category</th>
<th>N Ezetimibe-statin%</th>
<th>N Statin%</th>
<th>Odds ratio 95% CI</th>
<th>Weight %</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal (1st treatment period)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobs, 2003(^{33})</td>
<td>66</td>
<td>27.27</td>
<td>34</td>
<td>2.94</td>
<td>1.15</td>
</tr>
<tr>
<td>Stein, 2004(^{43})</td>
<td>293</td>
<td>12.00</td>
<td>303</td>
<td>2.00</td>
<td>5.19</td>
</tr>
<tr>
<td>Feldman, 2004(^{35})</td>
<td>108</td>
<td>83.00</td>
<td>246</td>
<td>46.00</td>
<td>14.83</td>
</tr>
<tr>
<td>Masana, 2005(^{56})</td>
<td>355</td>
<td>59.60</td>
<td>53</td>
<td>22.60</td>
<td>7.84</td>
</tr>
<tr>
<td>Zieve, 2010(^{64})</td>
<td>515</td>
<td>47.40</td>
<td>515</td>
<td>17.90</td>
<td>17.69</td>
</tr>
</tbody>
</table>

**Test for heterogeneity: I-squared = 72.30%, p=0.027**

| **Single treatment period** | | |
|------------------------------|---------------------|-----------|-------------------|----------|---------------------|
| Leiter, 2008\(^{82}\)       | 277                 | 74.00     | 279               | 32.00    | 16.70              | 2.32 (1.72, 3.13)  |
| Conard, 2008\(^{81}\)       | 92                  | 84.00     | 92                | 49.00    | 6.27               | 2.90 (1.34, 6.29)  |
| Roeters van Lennep, 2008\(^{38}\) | 178               | 67.00     | 189               | 26.00    | 13.85              | 2.58 (1.74, 3.81)  |

**Test for heterogeneity: I-squared = 0.00%, p=0.390**

| **Single treatment period** | | |
|------------------------------|---------------------|-----------|-------------------|----------|---------------------|
| Barrios, 2005\(^{46}\)      | 221                 | 78.00     | 214               | 52.00    | 16.47              | 1.50 (1.10, 2.04)  |

**Total**                    | 2215                | 66.05     | 1925              | 32.42    | 100.00             | 2.38 (1.89, 2.98)  |

**Test for heterogeneity: I-squared = 72.50%, p=0.002**

**Test for overall effect Z statistic = 7.71, p<0.001**
## LDL-C goal attainment with initial dose failure Ezetimibe add on vs. doubling statin

<table>
<thead>
<tr>
<th>Study type or subcategory</th>
<th>N</th>
<th>Ezetimibe-statin%</th>
<th>N</th>
<th>Statin%</th>
<th>Odds ratio 95% CI</th>
<th>Weight %</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple treatment periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zieve, 2010⁴⁴</td>
<td>277</td>
<td>74.00</td>
<td>279</td>
<td>32.00</td>
<td></td>
<td>57.60</td>
<td>2.32 (1.72, 3.13)</td>
</tr>
<tr>
<td>Ballantyne, 2004⁴⁵</td>
<td>92</td>
<td>84.00</td>
<td>92</td>
<td>49.00</td>
<td></td>
<td>8.59</td>
<td>2.90 (1.34, 6.29)</td>
</tr>
<tr>
<td>Masana, 2005³⁶</td>
<td>178</td>
<td>67.00</td>
<td>189</td>
<td>26.00</td>
<td></td>
<td>33.80</td>
<td>2.58 (1.74, 3.81)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: I-squared = 72.30%, p=0.027

Total: 547 72.49 560 31.43

Test for heterogeneity: I-squared = 72.50%, p=0.002

Test for overall effect Z statistic = 7.71, p<0.001

2. New considering point of view for preventing Atherosclerosis
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy
Atherosclerosis is the Most Common Pathologic Condition Leading to Cardiovascular Disease

- A dynamic disease process clinically characterized by narrowing of the arterial lumen due to accumulation of atherogenic lipoproteins
- Mainly due to a complex interaction of lipoproteins, inflammation, and the arterial wall

Prolonged retention leads to ApoB modification

- Interaction between lipoproteins and subendothelial matrix molecules promotes retention¹
- Prolonged retention leads to LDL modification (e.g., oxidation, lipolysis, aggregation)²

---

ApoB = apolipoprotein B.

¹ Results from prospective clinical trials do not show a benefit of antioxidants in treating atherosclerosis.³
Modified ApoB triggers a series of maladaptive inflammatory response

- Attracts circulating monocytes, which differentiate into macrophages
- Inhibits macrophage egress and enhances macrophage uptake of ApoB lipoproteins
- Causes endothelial activation

Lipoprotein retention accelerates maladaptive inflammatory response

- Macrophages ingesting modified lipoproteins and forming foam cells\(^1\)
- Other immune cells entering lesion\(^1\)
- Release of growth factors and cytokines from foam cells\(^2\)

SMC = smooth muscle cell

Lesion progresses give rise to necrotic areas

- Immune cells further contribute to inflammatory response
- SMCs migrate into intima
- Fibrous cap forms
- Macrophages begin to die and give rise to necrotic areas

SMC = smooth muscle cell.

hs-CRP lowering was related to LDL-C lowering

Plot of Change in CRP by change in LDL

\[ r = 0.80 \]
\[ p < 0.001 \]

Strong efficacy of VYTORIN in hs-CRP reduction

hs-CRP lowering was related to LDL-C lowering

Strong efficacy in hs-CRP reduction

- Effect of baseline hs-CRP levels at clinically meaningful strata on the hs-CRP response to treatment with simvastatin monotherapy (pooled across doses), and ezetimibe 10mg+simvastatin (pooled across doses).

**Infammatory markers were significantly improved by VYTORIN**

- **Arms:** 10 mg/d of ezetimibe, 20 mg/d of simvastatin, 40 mg/d of simvastatin and 10 mg/d of ezetimibe
- **Duration:** 12 wks
- **Pts:** 178 pts with hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ezetimibe(10 mg)</th>
<th>Simvastatin(40 mg)</th>
<th>Ezetimibe + simvastatin(10/40 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-sensitivity C-reactive protein (mg L⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.2 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>3.3 ± 0.3(3)</td>
<td>2.8 ± 0.3(-18)</td>
<td>2.5 ± 0.2(-22)</td>
<td>2.0 ± 0.4(-43)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>3.4 ± 0.5(6)</td>
<td>2.7 ± 0.4(-19)</td>
<td>1.9 ± 0.2(-42)</td>
<td>1.1 ± 0.2(-69)</td>
</tr>
<tr>
<td><strong>Intercellular adhesion molecule 1 (ng mL⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>302 ± 32</td>
<td>305 ± 46</td>
<td>307 ± 31</td>
<td>299 ± 35</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>306 ± 24(1)</td>
<td>253 ± 31(-17)</td>
<td>236 ± 18(-23)</td>
<td>202 ± 24(-32)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>308 ± 26(2)</td>
<td>247 ± 23(-19)</td>
<td>196 ± 15(-36)</td>
<td>147 ± 16(-51)</td>
</tr>
<tr>
<td><strong>TNF-α release (ng mL⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>348 ± 31</td>
<td>361 ± 26</td>
<td>364 ± 34</td>
<td>359 ± 38</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>361 ± 33(4)</td>
<td>305 ± 28(-16)</td>
<td>280 ± 25(-23)</td>
<td>241 ± 22(-33)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>365 ± 31(5)</td>
<td>298 ± 32(-17)</td>
<td>220 ± 21(-40)</td>
<td>175 ± 23(-51)</td>
</tr>
<tr>
<td><strong>IFN-γ release (ng mL⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>53.2 ± 6.0</td>
<td>54.2 ± 7.1</td>
<td>54.4 ± 5.2</td>
<td>52.9 ± 6.4</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>52.8 ± 7.4(-1)</td>
<td>45.6 ± 3.7(-16)</td>
<td>41.6 ± 3.5(-24)</td>
<td>36.7 ± 5.1(-31)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>52.4 ± 4.4(-2)</td>
<td>44.5 ± 4.5(-18)</td>
<td>32.7 ± 3.2(-40)</td>
<td>24.8 ± 2.2(-53)</td>
</tr>
<tr>
<td><strong>IL-2 release (ng mL⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.5 ± 0.6</td>
<td>5.6 ± 0.6</td>
<td>5.8 ± 0.5</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>After 4 weeks</td>
<td>5.5 ± 0.5(0)</td>
<td>4.6 ± 0.5(-18)</td>
<td>4.5 ± 0.3(-22)</td>
<td>3.9 ± 0.4(-32)</td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>5.7 ± 0.5(4)</td>
<td>4.5 ± 0.5(-19)</td>
<td>3.7 ± 0.2(-36)</td>
<td>2.9 ± 0.3(-49)</td>
</tr>
</tbody>
</table>

Data represent the mean ± SD. Values in parentheses represent percentage changes from baseline values. aP<0.05, bP<0.01, cP<0.001 vs. control group. dP<0.05, eP<0.01, fP<0.001 vs. pretreatment values. gP<0.05, hP<.001, iP<0.001 vs. ezetimibe-treated patients. jP<0.05, kP<0.001 vs. simvastatin-treated patients. lP<0.05, mP<0.01, nP<0.001 vs. the effect after 4 weeks of treatment.

Only data from subjects who completed the study were included in the final analyses.

2. **New considering point of view for preventing Atherosclerosis**
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy
Cholesterol homeostasis

ApoB-containing lipoproteins are atherogenic

- ApoB-containing lipoproteins (chylomicron, chylomicron remnants, VLDL, VLDL remnants, IDL, large buoyant LDL, and small, dense LDL) are atherogenic.\(^3\)

Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; TG = triglyceride; C = cholesterol.

\(^a\)Except in the presence of insulin resistance and/or metabolic syndrome.\(^5\)

ApoB concentration is in positive correlation with CVD
Fewer numbers of ApoB 48-containing particles are retained within the intima relative to ApoB 100-containing particles (Approximately 10-fold less)

In human, ApoB 48-containing chylomicron remnants contain approximately 40 times more cholesterol per particle than do ApoB 100-containing LDL particles.

ApoB 48-containing lipoprotein, Possible significant atherogenic risk factor

Chylomicron (apoB48) occupied significantly larger area of human carotid atherosclerotic plaques, compared to hepatic apoB100

- **Objective**: To evaluate relative quantification of apoB100 and apoB48 in plaque.
- **Design**: DS-IF for apoB100 and apoB48 was performed on 4 human carotid plaques from the lesion and proximal and distal regions.
- **Results**: Compared to apoB100, ApoB48-positive area was significantly larger in proximal, mid and distal sections (70% vs 5%, 53.4% vs 16.2% and 55% vs 9.3%, respectively; p<0.001 for all)

Macrophage change to foam cell formation by CM remnant

- Lipid taken up from CMRs, regardless of their oxidative state, is not readily cleared from the cells by efflux (cholesterol) or metabolism (TAG).
- This may be due to the sequestration of the lipid in lysosomes after their uptake by the cells.
- This resistance of the lipid to removal from macrophages, therefore, is another factor which is likely to contribute to the atherogenicity of CMRs.

- The bottom left panel shows the cells only, the top left shows the Dil fluorescence, the top right the FITC fluorescence and the bottom right the Dil and FITC fluorescence merged. The yellow color indicates co-localization of LAMP-1 and CRLP-derived lipid.


CRLPs : Chylomicron remnant lipoproteins
LAMP-2 : lysosomal associated membrane protein-1
Both hepatic apoB100 and intestinal apoB48 co-localize with macrophages in human carotid atherosclerotic plaques

- **Objective**: To evaluate co-localization of apoB48 and apoB100 with macrophages.
- **Design**: In 3 patients undergoing carotid endarterectomy (CEA), plaques were stained for apoB100/CD68 and apoB48/CD68 dual stain (DS)-IF
- **Results**: (A,D) Both apoB100 and apoB48 are present in plaques. (C,F) while CD68 staining is present throughout the plaque and in areas independent of apoB100 and apoB48, both apoB100 and apoB48 are always co-localized with CD68.

Single stain immunofluorescence (SS-IF) demonstrates the distribution of intestinal apoB48; Hepatic-apoB100(red)(A, D) and macrophages-CD68(blue)(B, E); Dual stain immunofluorescence (DS-IF) showing co-localization of apoB48 and apoB100 with macrophages(purple) in human carotid artery(C, F)

1. Vazquez-Figueroa E542 JACC 2012;59
Chylomicron remnants have multiple direct effects on three major cell types of the arterial wall which are likely to promote the development of atherosclerotic lesions.

These effects may be modulated by various lipids carried by the particles, including the type of fat (saturated or unsaturated or oxidized fat).

**CM may be the most atherogenic lipoproteins in human physiology and therefore CMR accumulation should be considered a relevant factor contributing to CV risk.**

THP-1 macrophages were incubated with or without oxLDL, CRLPs or oxCRLPs (30mg cholesterol/ml) for 48 h and the cholesterol (C), cholesteryl ester (CE), triacylglycerol (TG) and total lipid (TL = C + CE + TG) content of the cells was determined. (P<0.01 three lipoprotein types vs. control cells)

LDL, low density lipoprotein, CV, cardiovascular.

Ezetimibe/statin reduced migration of macrophage

Beneficial effects of ezetimibe
1. atherosclerosis progression
2. depletion of plaque lipid and macrophages & contributing to the plaque stabilization

Immunolocalization of monocyte chemoattractant protein-1 (MCP-1) on femoral arteries from normolipidemic diet (ND, A), untreated (B), ezetimibe-treated (Eze, C), simvastatin-treated (Simva, D) and ezetimibe + simvastatin-treated (Eze + Simva, E) rabbits. *P < 0.05 versus untreated rabbits.

SANDS (Stop Atherosclerosis in Native Diabetics Study)

499 men and women with diabetes and no CVD
- 40 yrs old
- SBP>130, LDL>100

Standard Targets
LDL-C <100; SBP <130
non-HDL-C <130
N=247

Aggressive Targets
LDL-C <70; SBP <115
non-HDL-C <100
N=252

Measure CVD using carotid and cardiac ECHO at baseline
18 months and after 3 yrs intervention
Primary outcome—change in CIMT

SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

- Study population:
  - Native Americans (>40 years of age) with type 2 diabetes (N=499)
  - Lipid lowering therapy at enrollment:
    - 37% - 44% on statins
    - 4% - 7% on fibrates
    - 0 – 2% on niacin
    - 0 – 2% on fish oil
- Treatment duration: 3 years
- Primary endpoint: mean change in cIMT

<table>
<thead>
<tr>
<th>Tx arm</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Endpoint LDL-C (mg/dL)</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care</td>
<td>102</td>
<td>103</td>
<td>+ 0.9</td>
</tr>
<tr>
<td>Aggressive Tx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin only</td>
<td>101</td>
<td>68</td>
<td>− 32</td>
</tr>
<tr>
<td>EZE + statin</td>
<td>108</td>
<td>78</td>
<td>− 31</td>
</tr>
</tbody>
</table>

*P-value for change in cIMT for both active treatment arms vs usual care group

SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

Mean cIMT

VYCTOR (VYTORIN on cIMT and Overall Arterial Rigidity) Study

- Population:
  - Mexican patients 40 – 72 years of age with 10-year absolute risk for CD or MI >20% (N=90)
  - Majority of patients on prior low-dose statins
  - No prior use of ezetimibe
- Treatment Duration: 12 months
- Primary endpoint: change in mean cIMT

<table>
<thead>
<tr>
<th>Tx arm</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Endpoint LDL-C (mg/dL)</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin 40 mg ± EZE 10 mg</td>
<td>128</td>
<td>48</td>
<td>-62</td>
</tr>
<tr>
<td>Simvastatin 40 mg or 80 mg</td>
<td>130</td>
<td>45</td>
<td>-65</td>
</tr>
<tr>
<td>Simvastatin 20 mg or 40 mg + EZE</td>
<td>131</td>
<td>48</td>
<td>-63</td>
</tr>
</tbody>
</table>

A: EZE added in month 2 if goal was not attained
B: Simva titrated to 80mg in month 2 if goal was not attained
C: EZE/Simva titrated to 10/40mg in month 2 if goal was not attained

Mean cIMT

CD = Coronary death; MI = Myocardial infarction
*P-value for intragroup analysis for 12 month vs baseline cIMT for all groups

P<0.01* vs baseline

Same cIMT regression, but low discontinuation

<table>
<thead>
<tr>
<th>Group</th>
<th>No Goal Attainment</th>
<th>Raise of CPK</th>
<th>Abandonment</th>
<th>Rash</th>
<th>Myalgia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin 40 ± Ezetimibe 10mg</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Simvastatin 40 or 80mg</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>VYTORIN 10/20 or 10/40mg</td>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>2</td>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

CPK, creatine phosphokinase, 5 times higher than normal reference values. All secondary effects in group B occurred with 80 mg of simvastatin.

a. Pravastatin 40 mg + ezetimibe 10 mg.
b. Simvastatin 80 mg.
c. Simvastatin 40 mg.
d. Simvastatin + ezetimibe 40/10 mg.
e. Simvastatin + ezetimibe 20/10 mg.

2. New considering point of view for preventing Atherosclerosis
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy
In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, combined ezetimibe (10 mg) and simvastatin (40 mg) decreased low-density lipoprotein cholesterol levels by 50% and ischemic cardiovascular event (ICE) risk by 22% compared to placebo.

In JV tertiles 1 (baseline mean JV=2.5m/s) and 2 (3.1m/s), ICE risk decreased by 47% and 36%, respectively, was reasonably well predicted by all LCs, and was consistent with findings from meta-regression analyses in other populations. (JV tertiles 3: 3.7m/s)
SHARP: Eligibility and Key outcome

- The effects of lowering LDL cholesterol with Simvastatin plus Ezetimibe in patients with chronic kidney disease (Study of Heart And Renal Protection : SHARP)

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis

- No history of myocardial infarction or coronary revascularization

**Key outcome**

Composite of major atherosclerotic events including
- Coronary death,
- Non-fatal MI
- Non-haemorrhagic stroke
- Any revascularization
### SHARP: Study of Heart And Renal Protection

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin + ezetimibe (n=4,650)</th>
<th>Placebo (n=4,620)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous vascular disease*</td>
<td>711 (15%)</td>
<td>682 (15%)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>1,054 (23%)</td>
<td>1,040 (23%)</td>
</tr>
<tr>
<td>Men</td>
<td>2,915 (63%)</td>
<td>2,885 (62%)</td>
</tr>
<tr>
<td>Age at randomisation (years)*</td>
<td>62 (12)</td>
<td>62 (12)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.88 (1.20)</td>
<td>189 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.90 (1.17)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.77 (0.88)</td>
<td>107 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.78 (0.87)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.12 (0.35)</td>
<td>43 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.11 (0.34)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.31 (1.76)</td>
<td>204 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.34 (1.68)</td>
</tr>
<tr>
<td>Renal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On dialysis</td>
<td>1,533 (33%)</td>
<td>1,490 (32%)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>1,275 (27%)</td>
<td>1,252 (27%)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>258 (6%)</td>
<td>238 (5%)</td>
</tr>
<tr>
<td>Not on dialysis†</td>
<td>3,117 (67%)</td>
<td>3,130 (68%)</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or median (IQR). MDRD=Modifi ed Diet in Renal Disease.17 GFR=glomerular fi ltration rate. *Variables updated at 1 year for patients originally allocated simvastatin only who were rerandomised to simvastatin plus ezetimibe or placebo. †Five versus fi ve patients received a transplant before rerandomisation.

coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization

2.1% Absolute Risk Reduction

13.4%
11.3%

Number at risk

Placebo 4620 4204 3849 3469 2566 1269
Simvastatin plus ezetimibe 4650 4271 3939 3469 2655 1265

Rate reduction 17% (95% CI 6-26%)
Log-rank p=0.0021

SHARP: Major Atherosclerotic Events composite endpoint

<table>
<thead>
<tr>
<th>Coronary events</th>
<th>Simvastatin plus ezetimibe (n=4,650)</th>
<th>Placebo (n=4,620)</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>134 (2.9%)</td>
<td>159 (3.4%)</td>
<td>0.84 (0.66-1.05)</td>
<td>159 (3.4%)</td>
</tr>
<tr>
<td>CHD death</td>
<td>91 (2.0%)</td>
<td>90 (1.9%)</td>
<td>1.01 (0.75-1.35)</td>
<td>90 (1.9%)</td>
</tr>
<tr>
<td>Subtotal: hemorrhagic event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>0.92 (0.76-1.11)</td>
<td>230 (5.0%)</td>
</tr>
</tbody>
</table>

Non-hemorrhaging stroke

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin plus ezetimibe (n=4,650)</th>
<th>Placebo (n=4,620)</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>114 (2.5%)</td>
<td>157 (3.4%)</td>
<td>0.72 (0.57-0.92)</td>
<td>157 (3.4%)</td>
</tr>
<tr>
<td>Unknown type</td>
<td>18 (0.4%)</td>
<td>19 (0.4%)</td>
<td>0.94 (0.49-1.79)</td>
<td>19 (0.4%)</td>
</tr>
<tr>
<td>Subtotal: any non-hemorrhagic</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td>0.75 (0.60-0.94)</td>
<td>174 (3.8%)</td>
</tr>
</tbody>
</table>

Revascularisation procedures

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin plus ezetimibe (n=4,650)</th>
<th>Placebo (n=4,620)</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>149 (3.2%)</td>
<td>203 (4.4%)</td>
<td>0.73 (0.59-0.90)</td>
<td>203 (4.4%)</td>
</tr>
<tr>
<td>Non-coronary</td>
<td>154 (3.3%)</td>
<td>169 (3.7%)</td>
<td>0.90 (0.73-1.12)</td>
<td>169 (3.7%)</td>
</tr>
<tr>
<td>Subtotal: any revascularisation</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td>0.79 (0.68-0.93)</td>
<td>352 (7.6%)</td>
</tr>
<tr>
<td>Total: any major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>0.83 (0.74-0.94)</td>
<td>619 (13.4%)</td>
</tr>
</tbody>
</table>

↓28% ↓21%

Ezetimibe/Simvasatin better → Placebo better
SHARP: Safety

Myopathy

- CK >40 x ULN
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

- CK >5 x but ≤40 x ULN
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

Hepatitis

- Hepatitis
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

- Pancreatitis without gallstones
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

- Other hospitalization for gallstones
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

- Complications of gallstones
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)

- Persistently elevated ALT/AST >3x ULN
  - Simvastatin+Ezetimibe (n=4,650)
  - Placebo (n=4,620)
Event reduction based upon the level of LDL-C reduction of ezetimibe/statin and the Cholesterol Treatment Trialists’
IMPROVE-IT: IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

Patients stabilized post-ACS ≤ 10 days
LDL-C ≤ 125mg/dL (or ≤ 100mg/dL if prior statin)

Double-blind

ASA+ Standard Medical Therapy

Simvastatin 40 mg*

Ezetimibe/Simvastatin 10/40mg*

Follow-up visit day 30, every 4 months

Duration: Minimum 2 ½ year follow-up (5,250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, Revascularization (>30 days after randomization), or Stroke

LDL-C, low density lipoprotein-cholesterol; CV, cardiovascular; MI, Myocardial infarction; UA, unstable angina

Ezetimibe and Statin Fixed dose combination might be smart option for managing dyslipidemia in high risk patients

1. Ezetimibe/Statin therapy may be useful for lowering LDL-C level, irrespective of baseline levels of cholesterol absorption and synthesis marker\(^1\)

2. ESC/ESA 2011 recommends more aggressive lipid target for very high-risk patients \([< 1.8 \text{ mmol/L} (\sim 70 \text{ mg/dL}) \text{ And/or } \geq 50\% \text{ reduction from baseline}]\)^2

3. Combined ezetimibe (10mg) and simvastatin(40 mg) decreased LDL-C by 50% and ischemic cardiovascular event(ICE) risk by 22% compared to placebo\(^3\)

---

STAR VYTORIN

STrong, sAfe, Rapid

on target
MSD does not recommend the use of any product in any different manner than as described in the approved Prescribing information. Physicians are advised to consult the prescribing information issued by the manufacturers before prescribing any drug discussed or described at this meeting.
바이토린 정(에제티미브/심바스타틴) 10/10, 10/20, 10/40, 10/80 mg

[효능 효과] 원발성 고콜레스테롤혈증(이형접합 가족형 및 비가족형) 및 혼합형 고지혈증 환자의 상승된 총 콜레스테롤(total-C), LDL-콜레스테롤(LDL-C), 아포 B 단백(Apo B) 및 트리글리세라이드(TG)을 감소시키고, HDL-콜레스테롤(HDL-C)을 증가시키기 위한 식이요법의 보조제로서 투여합니다. 동형접합 가족형 고콜레스테롤혈증(HoFH) 환자의 상승된 총콜레스테롤 및 LDL-콜레스테롤을 감소시키기 위한 다른 지질저하 치료(예, LDL Apheresis)의 보조제로서, 또는 다른 지질 저하 치료가 유용하지 않은 경우 투여합니다.

[용법 용량] 바이토린을 투여전 및 투여중인 환자는 표준 콜레스테롤 저하식을 해야 하며, 투여량은 환자의 LDL-콜레스테롤의 기저치, 권장되는 치료목표치 및 환자의 반응에 따라 조절되어야 합니다. 바이토린은 식사와 관계없이 1일 1회 저녁에 투여합니다. 일반적으로 권장되는 초회용량은 1일 10/20mg이고, LDL-콜레스테롤 감소의 필요성이 적은 환자인 경우 1일 10/10mg으로 시작할 수 있습니다. 바이토린의 투여를 시작 후 또는 용량 적정 후, 4주 이상의 간격을 두고 혈중 지질치를 확인한 후 용량을 조절합니다. 심바스타틴 80 mg 용량은 저용량 및 다른 스타틴계 약물에 비해 근육염증의 위험이 높기 때문에 10/80mg 용량은 중증의 고콜레스테롤혈증 환자 및 심혈관계 합병증의 위험성이 높은 환자 중 지용량에서 치료목표에 이르지 못하고, 약물사용의 유익성이 잠재적인 위험성을 상회하는 경우에 한하여 제한적으로 투여합니다. 경증의 신장애(추정 사구체여과율(GFR) ≥ 60mL/min/1.73㎡) 환자의 경우 용량 조절이 필요하지 않습니다. 만성 신장 질환을 동반하고 추정 사구체 여과율 <60mL/min/1.73㎡인 환자의 경우, 바이토린10/20mg을 1일 1회 저녁에 투여합니다. 이러한 환자에게 더 높은 용량으로 투여할 때에는 신중히 투여하여야 하며 세심히 모니터링 해야 합니다. 경증의 간장애환자의 경우 용량 조절이 필요하지 않으나, 중등도 또는 중증의 간장애 환자의 경우 바이토린의 투여가 권장되지 않습니다.

[금기] 바이토린의 성분에 과민증인 환자 / 활동성 간질환 환자 또는 혈청 아미노전이효소 수치가 원인불명으로 지속적으로 높은 환자 / 임부 및 수유부 / 강력한 CYP3A4 억제제를 투여 중인 환자 / 젠피브로질, 사이클로스포린 또는 다나졸을 투여 중인 환자 / 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 혼수장애(glucose-galactose malabsorption)등의 유전적인 문제가 있는 환자
[경고]
1) 근육병증/횡문근융해: 근육병증/횡문근융해의 위험성은 심바스타틴 용량과 관련이 있습니다. 바이토린의 투여를 시작하는 모든 환자, 또는 용량을 증량한 모든 환자에게 근육병증의 위험성을 알려야 하며 설명되지 않는 근육통, 압통 또는 근육약화가 생기면 즉시 의사에게 보고해야 합니다. 만일 근육병증이 진단되거나 의심되면, 바이토린의 투여를 즉시 중지해야 합니다. 근육병증을 유발하는 요소로는 65세 이상의 고령자, 여성, 조절되지 않는 갑상선기능 저하와 신기능 손상 등이 있습니다.

심바스타틴을 투여한 41,413 환자의 임상시험 테이터베이스 중 평균 추적조사 기간 4년 이상인 24,747명의 환자(약 60%)에서, 심바스타틴 20mg, 40mg, 80mg/일을 투여하였을 때 근육병증의 발현율은 각각 약 0.03%, 0.08% 및 0.61%였습니다. 이 임상시험들에서 환자는 주의깊게 모니터링 되었으며, 약물상호작용이 있는 몇몇 의약품들은 제외되었습니다.

심근경색증의 병력을 가진 환자에게 심바스타틴 80mg/일을 투여한 임상시험에서(평균 6.7년 동안 추적조사) 근육병증 발현율이 20mg 투여군에서 0.02%인 것에 비해, 80mg 투여군에서는 약 0.9%였습니다. 근육병증의 위험성은 유사한 LDL-콜레스테롤 감소 효능을 가진 다른 스타틴계 약물 치료에 비해 심바스타틴 80mg를 복용하는 환자군에서 더 높았습니다. 따라서 바이토린 10/80mg 용량은 심혈관계 병합증의 위험성이 높은 환자 중 저혈당증에서 치료목표에 이르지 못하고, 약물사용의 유익성이 잠재적인 위험성을 상회하는 경우에 한하여 제한적으로 투여합니다. 바이토린 10/80mg를 복용하는 환자가 바이토린과 상호작용하는 약물을 복용해야 하는 경우, 저혈당의 심바스타틴을 투여하거나 이 약 또는 약물 상호작용 가능성이 보다 낮은 다른 스타틴-에테티미브 요법을 투여해야 합니다.

다음 약과의 병용투여시 근육병증/횡문근융해의 위험성이 증가됩니다:
- 바이토린의 용량은 아미오다론, 베라파밀 또는 헤피브로질을 병용투여하고 있는 환자에서 1일 10/20mg를 초과해서는 안 됩니다. 또한, 암로디린을 병용투여하고 있는 환자에서 1일 10/40mg를 초과해서는 안 됩니다.
- 바이토린과 CYP3A4에 대한 중간 정도의 억제 효과를 가지는 것으로 알려져 있는 약물의 복용량을 증가시켜야 하는 경우, 근육병증의 위험성이 증가할 수 있습니다.
- 바이토린은 깨피브로질과 병용 투여하지 않습니다. 바이토린과 피브레이트계 약물과의 병용투여는 피해야 합니다.
- 바이토린과 췌독산을 병용투여하는 환자는 주의깊게 모니터링 되어야 하며, 바이토린의 임시적인 투여 중단을 고려할 수 있습니다.
- 심바스타틴과 지질저하 용량(1일 1g 이상)의 니코틴산을 복용 투여하였을 때 근육병증/횡문근융해가 관찰되었습니다. 바이토린과 니코틴산 병용투여시 근육병증에 대한 위험성이 증가할 수 있으므로, 1일 10/20mg 을 초과하는 용량과 지질저하 용량(1일 1g 이상)의 니코틴산을 복용 투여하지 않도록 합니다.
2) 간기능 이상환자: 3개의 위약대조, 12주 임상시험 결과, 혈청 아미노전이효소(transaminase) 수치의 지속적 상승(정상상한치의 3배 이상)의 발현율은 바이토린을 투여한 전체 환자에서 1.7%였으나, 10/80mg를 투여한 환자에서는 2.6%로 용량과 관련 있게 나타났습니다. 바이토린을 투여 전 및 투여시작 후 임상적으로 필요한 시기에 간기능 검사를 실시하는 것이 바람직합니다. 바이토린 10/80mg으로 증량한 환자는 증량하기 전과 증량하고 3개월 후, 이후 치료의 첫 1년간 주기적인(예, 년2회) 간기능 검사를 추가 실시합니다. 혈청 아미노전이효소 수치가 상승된 환자의 경우 간기능검사를 다시 하여 모니터링 하며, 정상치로 돌아 올 때까지 간기능검사를 자주 실시해야 합니다. 만약, 혈청 아미노전이효소(ALT 또는 AST)의 수치가 정상상한치의 3배 이상 상승할 경우 바이토린의 투여를 중지하는 것이 바람직합니다. 바이토린을 투여하는 동안 임상적 증상 및/또는 고릴리루빈혈증을 동반한 심각한 간손상이나 황달이 나타날 경우, 즉각 투여를 중단합니다. 다른 병인이 확인되지 않을 경우, 바이토린을 재투여하지 않습니다.

[이상반응] 바이토린 (또는 바이토린과 동등한 에제티미브와 심바스타틴의 병용투여)에 대한 안전성은 임상시험에 참여한 10,189명 이상의 환자에서 평가되었습니다. 바이토린은 일반적으로 내약성이 우수하였습니다. 유사하게 실시된 3개의 위약대조 임상시험(n=1,420)에서 투여약과의 관련성을 고려하지 않고 바이토린을 투여한 환자의 2% 이상에서 보고되었으며, 위약군에서의 발현율보다 높은 비율로 보고된 임상적 이상반응은 두통, 설사, 인플루엔자, 상기도 감염, 근육통 사지통 이었습니다.

[임부/수유부에 대한 투여] 임부에게 투여해서는 안 되며, 임신이 확인되면 즉시 투여를 중지해야 합니다.

[소아에 대한 투여] 소아 환자에 대한 안전성 및 유효성 자료는 불충분합니다.

[고령자에 대한 투여] 임상시험에서, 바이토린을 투여한 환자 중 792명이 65세 이상이었고(176명의 환자는 75세이상이었음) 안전성은 고령자 환자와 젊은 환자간에 유사하였으나, 일부 고령자 환자에서 보다 민감한 반응이 나타날 수 있음을 배제할 수 없습니다.

개정년월일 2012년 9월 18일

처방하시기 전에 각 항목에 대한 자세한 내용은 제품설명서 전문을 참조하시기 바랍니다.
Visual Comparison of the retention of LDL (red) and Chylomicron remnants (yellow) in carotid arteries from normal rabbits and WHHL rabbits

- Using 3D confocal microscopy to quantitatively determine arterial retention of ApoB 100 and ApoB48 lipoprotein
- Watanabe Heritable HyperLipidemic strain is primary model of human familial hypercholesterolemia. WHHL rabbits have mutation in the gene that encodes the ApoB100/ApoE LDL receptor

⇒ The arterial retention of cholesterol derived from apoB48 and apoB100 lipoproteins was investigated in a rabbit carotid perfusion model under physiological conditions. We found that the intimal retention of cholesterol derived from apoB48 lipoproteins was greater in WHHRs compared with controls despite evidence that up to 90% of apoB48 lipoprotein internalization is mediated via the LDL receptor

Normal rabbits

WHHL rabbits = watanabe heritable hyperlipidemic rabbits

Ezetimibe/statin reduced migration of macrophage

Immunolocalization of monocyte chemoattractant protein-1 (MCP-1)
Ezetimibe/statin might improves plaque stabilization (in rabbit model)

- Arms: ezetimibe, simvastatin, E/S
- Duration: 6 weeks
- Animal model: 34 Rabbits of accelerated atherosclerosis

Normal lipid diet (-) vs. untreated rabbits:

- **Femoral arteries**
  - **ND**, **Untreated**, **Eze**, **Simva**, **Eze+Simva**

**Graph**

- **ND**: normolipidemic diet (ND, B), untreated (C), ezetimibe-treated (Eze, D), simvastatin-treated (Simva, E) and ezetimibe + simvastatin-treated (Eze + Simva, F) rabbits.
  - *p < 0.05 versus untreated rabbits.

Endothelial function marker was related with LDL-C lowering

- Arms: Simvastatin 80mg vs. Ezitimibe/Simvastatin (E/S) 10/10mg
- Duration: 6 wks
- Pts: 39 T2DM or IGT pts

**Absolute changes in FMD**

**A**

E10/S10 at baseline

- **B**

E10/S10 at follow-up

**C**

S80 at baseline

**D**

S80 at follow-up

\[ P = 0.39 \]
ESC/EAS 2011 Guidelines:
Management of Dyslipidemia in Diabetes

- **Type 1 Diabetes**
  - In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (≥30%) with statins as the first choice is recommended irrespective of the basal LDL-C concentration [Class I, Level C]

- **Type 2 Diabetes**
  - In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with 1 or more CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (~70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL [Class I, Level B]
  - In all people with type 2 diabetes, LDL-C goal <2.5 mmol/L (~100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets. [Class I, Level B]

Class= Class of recommendation, Level= Level of evidence, CV= cardiovascular, ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

VYTORIN 10/20mg provided ≥50% LDL-C reduction in Type 2 Diabetes patients¹

In a clinical study of patients with hypercholesterolemia and type 2 DM (VYTAL study)

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>HDL-C</th>
<th>TG #</th>
<th>non-HDL-C</th>
<th>hs-CRP #</th>
</tr>
</thead>
<tbody>
<tr>
<td>VYTORIN 10/20mg (n=238)</td>
<td>-54%</td>
<td>-50%</td>
<td>5%</td>
<td>8%</td>
<td>-48%</td>
<td>-14%</td>
</tr>
<tr>
<td>Atorvastatin 20mg (n=240)</td>
<td>-45%</td>
<td>-41%</td>
<td>-23%</td>
<td>-23%</td>
<td>-41%</td>
<td>-23%</td>
</tr>
</tbody>
</table>

HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein,
LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides
#: median

In hypercholesterolemia with Metabolic syndrome patients

VYTORIN 10/20mg provided \( \geq 50\% \) reduction in LDL-C\(^1\)

In a clinical study of patients with hypercholesterolemia and Metabolic Syndrome (VYMET study)

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>TC(^\S)</th>
<th>HDL-C(^\P)</th>
<th>TG(^\S)</th>
<th>non-HDL-C(^\P)</th>
<th>hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7%</td>
<td>3%</td>
<td>6%</td>
<td>-17% -17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-27%</td>
<td>-28%</td>
<td>-23% -22%</td>
<td>-17% -17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-37%</td>
<td>-39%</td>
<td>-23% -22%</td>
<td>-17% -17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-50%</td>
<td>-34%</td>
<td>-28%</td>
<td>-22%</td>
</tr>
</tbody>
</table>

HDL-C= high-density lipoprotein cholesterol; hs-CRP= high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; TC= total cholesterol; TG= triglycerides.

\(^\S\) Number of patients 220 for E/S 20 mg, 216 for A 20 mg.

\(^\P\) Number of patients 216 for A 20 mg.

**VYTORIN 10/20mg: Greater improvements in key parameters than mono statin in elderly hyperlipidemia patients**

In a clinical study of hypercholesterolemia patients ≥ 65 years of age with or without cardiovascular disease (VYTELD study)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VYTORIN 10/20mg (n=232)</th>
<th>Atorvastatin 20mg (n=238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-54.2 (%)</td>
<td>-37.8 (%)</td>
</tr>
<tr>
<td>TC</td>
<td>-37.8 (%)</td>
<td>-33.3 (%)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-24.9 (%)</td>
<td>-21.3 (%)</td>
</tr>
<tr>
<td>TG #</td>
<td>-49.9 (%)</td>
<td>-43 (%)</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>-10.2 (%)</td>
<td>-46.6 (%)</td>
</tr>
<tr>
<td>hs-CRP *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides

#: Nonparametric results (medians) are presented for triglycerides

*: Longitudinal data analysis results are presented for high-sensitivity C-reactive protein.

* Foody JM, et al, Am J Cardiol 2010;106:1255–1263
**VYTORIN** was Generally Well Tolerated\(^1\)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All VYTORIN 10/20, 10/40mg/day (n=513)</th>
<th>All atorvastatin 10, 20, 40mg/day (n=771)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Clinical event</td>
<td>28.3%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Drug-related clinical event</td>
<td>4.1%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Discontinuation due to drug-related clinical event</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>ALT or AST ≥3 × ULN (consecutive)</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>CK ≥ 10 X ULN with muscle symptoms</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase.

Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and to thrombosis is the foremost cause of premature mortality and of disability-adjusted life years (DALYs).

The management of dyslipidemias as an essential and integral part of CVD prevention.

Dyslipidemias cover a broad spectrum of lipid abnormalities, some of which are of great importance in CVD prevention.
Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

The Framingham Study

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD.
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C.
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C.

1. Liu Am J Cardiol. 2006;98:1363-1368
Non-HDL-C concentration is in positive correlation with CVD

Non HDL-C: Secondary target of therapy

- Non-HDL-C = TC – HDL-C
- Apo B concentration represents total number of lipoprotein particles (LDL + IDL + VLDL + chylomicron)
- This may be called “non-HDL” cholesterol or “atherogenic cholesterol”
- If baseline triglycerides: ≥200 mg/dL,

Non-HDL cholesterol: Secondary target of therapy

The LOWER, The BETTER: Cholesterol Treatment Trialists

Significantly Greater % Reductions in CRP Were Achieved With Eze/Simva

- Significantly Greater % Reductions in CRP Were Achieved With Eze/Simva Compared With Each Corresponding Dose of Simva Monotherapy

\[ \text{Median \% Change (SEM)} \]

<table>
<thead>
<tr>
<th>PBO</th>
<th>EZE 10mg</th>
<th>Pooled SIMVA</th>
<th>Pooled EZE/SIMVA</th>
<th>SIMVA (mg)</th>
<th>EZE/SIMVA (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>10/10</td>
</tr>
<tr>
<td>7.4</td>
<td>-2.8 ns</td>
<td>-14.3</td>
<td>-16.2</td>
<td>-17.3</td>
<td>-19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>10/20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>10/40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>10/80</td>
</tr>
</tbody>
</table>

\[ *p<0.001 \text{ vs. corresponding dose of SIMVA} \]
\[ **p<0.01 \text{ vs. corresponding dose of SIMVA} \]
\[ ***p<0.001 \text{ vs. pooled SIMVA} \]

NS = not significant

Lower LDL-C levels were correlated with reduced CV risk

- In a meta-analysis of more than 169,000 patients in 26 clinical trials with statins.
- There were 87,903 (52%) participants with preexisting CHD, 32,210 (19%) with a history of diabetes, and 25,920 (15%) with other vascular disease.¹

For every 39 mg/dL (1.07mmol/L) reduction in LDL-C, there was a 22% relative reduction in the incidence of any major vascular event (p<0.0001)¹ and a 21% relative reduction in the incidence of ischemic stroke (p<0.0001)¹.

¹ Cholesterol Treatment Trialists’ (CTT) Collaboration. Lancet 2010; 376: 1670–81
2001 NCEP ATP III: LDL-C goal value

Non-coronary form of atherosclerotic dz. DM.
2+ risk factors with 10yr>20%

CHD or CHD equivalent

Yes | No

≥2 major CV risk factors

Major risk factors: age, hypertension, smoking, family history of premature CHD, HDL-c<40 mg/dL

10-year CHD risk: Framingham Score

≥20%

10-20%

<10%

<table>
<thead>
<tr>
<th>Risk</th>
<th>High</th>
<th>Moderately high</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-c goal</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Medication start</td>
<td>≥130 (100-129: optional)</td>
<td>≥130</td>
<td>≥160</td>
<td>≥190 (160-189: optional)</td>
</tr>
</tbody>
</table>

1. NCEP ATP III. JAMA. 2001;285:2486–2497
Cholesterol homeostasis

- 33% Dietary chol
- 67% Biliary chol
- NPC1L1
- Bile Acids
- Free Chol
- Acetyl CoA
- Remnant receptors
- LDLR
- Hepatic Apo B-100
- VLDL
- IDL
- LDL
- Blood
- Peripheral Tissues

Biology of Atherosclerosis: Contributing Factors

- Aging
- High Blood Pressure
- Diabetes
- Genetic Predisposition
- Atherogenic Diet
- Lack of Physical Activity
- Smoking
- Obesity

Dyslipidemia

Atherogenic Lipoprotein Deposition & Inflammatory Infiltration

Ezetimibe/Statin Showed Complementary Effects on Cholesterol Absorption and Production

<table>
<thead>
<tr>
<th>Production Marker: Total Cholesterol Ratio(a)</th>
<th>Absorption Marker: Total Cholesterol Ratio(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Down Arrow]</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
</tr>
</tbody>
</table>

**Statin** had inverse effects on absorption and production

**Ezetimibe** had opposite effects vs. simvastatin

**Ezetimibe/Statin** had complementary effects

\(a\)Cholesterol production markers: lathosterol and desmosterol; \(b\)Cholesterol absorption markers: sitosterol and campesterol.

Inhibition of cholesterol absorption may lower LDL-C levels effectively

- **Object**: To evaluate the relationship between LDL-C lowering effect and baseline cholesterol absorption and synthesis markers in patients with CAD
- **Arm**: ATV 20mg/day, RSV 5mg/day, ATV 10mg/EZE 10mg, RSV 2.5mg/EZE 10mg
- **Patients**: 171 patients with CAD

Campesterol/TC ratio: an index of cholesterol absorption; Lathosterol/TC ratio: an index of cholesterol synthesis

Ezetimibe-plus- statin therapy may be useful for lowering LDL-C level, irrespective of baseline levels of cholesterol absorption and synthesis markers.

Serum apoB48 level might be a good marker for the detection of early atherosclerosis with normal-range levels of BP and TG

- **Objective:** To investigate the correlations between profiles of apoB48-containing lipoproteins and the progression of atherosclerosis in subjects with normal TG levels
- **Patients:** 164 Osaka police hospital (annual health check)
- **Conclusion:**
  - The accumulation of CMR might be an independent risk factor for the development of atherosclerosis among subjects with TG levels between 100 mg/dL-150 mg/dL.
  - The measurement of fasting apoB48 level is very useful for the detection of early onset of atherosclerotic plaques

BP blood pressure; TG, tryglyceride; CMR, chylomicron remnants

In patients not using statin,
The surrogate atherosclerosis marker IMT correlated best with apoB48

- **Objective**: To investigate whether fasting plasma levels of apoB48 can help to differentiate subjects with different conditions with remnant accumulation [e.g. FCH, T2DM and CAD] from subjects without remnant accumulation. The relationship between apoB48 and IMT was also investigated.

- **Method**: Patients-189 subject (FCH, FH, CAD, T2DM, Control, CAD+T2DM)

- **Conclusion**: 
  - ApoB48 concentrations are highest in patients with FCH and in atherosclerotic subjects with T2DM.
  - In patients not using statins, the surrogate atherosclerosis marker IMT correlates best with apoB48, suggesting that fasting apoB48 may help to detect subjects at risk.

T2DM, type 2 diabetes mellitus; FCH, familial combined hyperlipidaemia; FH, familial hypercholesterolaemia; CAD, coronary artery disease; IMT, Intima-media thickness