Comprehensive approach for diabetic dyslipidemia management

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1. Importance of diabetic dyslipidemia management AND Features of dyslipidemia with diabetes
The prevalence of T2DM has increased and is likely to continue to rise in Korea
Patients with T2DM are at increased risk of CV mortality compared with those without diabetes

- 12-year follow-up of 10,532 patients with T2DM and 21,056 subjects without T2DM (individually matched to the patients with diabetes by sex, age, and deprivation).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>With diabetes</td>
<td>16.4</td>
<td>15.4</td>
</tr>
<tr>
<td>Without diabetes</td>
<td>10.8</td>
<td>10.6</td>
</tr>
<tr>
<td>Absolute CV Mortality</td>
<td>n=5,411</td>
<td>n=4,936</td>
</tr>
<tr>
<td>Rate per 1000 PY</td>
<td>n=10,821</td>
<td>n=9,865</td>
</tr>
</tbody>
</table>

HR (95% CI)<sup>a</sup>:
- Overall=1.23 (1.11–1.36)
- Men=1.26 (1.10–1.45)
- Women=1.19 (1.03–1.38)

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; PY=patient-years; T2DM=type 2 diabetes mellitus.

<sup>a</sup>HR adjusted for deprivation and previous CV disease.

Diabetic dyslipidemia: A cluster of lipid and lipoprotein abnormalities

Plasma lipid levels of diabetic subjects must be more strictly controlled than non-diabetic population in order to avoid an increased risk for coronary heart disease.¹

Diabetic dyslipidemia Triad

- sdLDL, CMR Increased
- HDL-C Decreased
- TG Increased

LDL, Low Density Lipoprotein; VLDL, very Low Density Lipoprotein; sdLDL : small, dense LDL ; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; CMR : chylomicron remnant ; ApoB, apolipoprotein B; ApoA1, apolipoprotein A1

Pathogenesis of diabetic dyslipidemia

Insulin Resistance (Muscle & Fat)

Increased Free Fatty Acids

Increased TG synthesis

VLDL, very low-density lipoprotein; TG, triglyceride; CE, cholesteryl ester; CETP, cholesterylester transfer protein; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein

Focus on LDL particle numbers in “Normal” LDL-C levels in patients with diabetes

Small, dense LDL particles may increase risk of atherosclerosis.¹

“Normal” LDL-C level, however:

- Number of LDL particles: ↑
- Concentration of apolipoprotein B: ↑

No Diabetes

Diabetes

LDL particles

Apolipoprotein B

LDL-C

“Normal” LDL-C level

Lower CHD risk

Higher CHD risk


LDL=low-density lipoprotein
ApoB is associated with CHD risk

ApoB and non-HDL-C each had very similar shape and magnitude of associations with CHD.¹

Study design: Individual records were supplied on 302,430 people without initial vascular disease from 68 long-term prospective studies, mostly in Europe and North America. During 2.79 million person-years of follow-up, there were 8857 nonfatal myocardial infarctions, 3928 coronary heart disease (CHD) deaths, 2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes. Reliably quantified. This was to assess major lipids and apolipoproteins in vascular risk. The primary outcome was CHD (ie, first-ever MI or fatal CHD).

CHD = coronary heart disease; IMT = carotid intima media thickness; LDL = low-density lipoprotein; T2DM = type 2 diabetes mellitus.

Multiple ApoB-containing lipoproteins are associated with CHD risk\textsuperscript{1}

ApoB-containing lipoproteins including small dense LDL and VLDL are atherogenic.\textsuperscript{3}

\begin{itemize}
  \item 90% of total plasma ApoB is contained within the LDL particles\textsuperscript{4}
\end{itemize}

Apo=apolipoprotein, VLDL=very low-density lipoprotein, IDL=intermediate-density lipoprotein, TG=triglyceride, C=cholesterol, ApoB=apolipoprotein B, CHD=coronary heart disease.

Increased Chylomicron (ApoB48) Synthesis in DM

MTTP/NPC1L1 mRNA

regulation of cholesterol absorption

MTTP: 8.76±5.65 vs 4.87±3.24, p<0.02, NPC1L1: 2.47±1.42 vs 1.39±1.78, p<0.02

ABCG5/G8 mRNA

regulation of cholesterol excretion to intestinal lumen

ABCG5: 0.12±0.07 vs 0.05±0.02, p<0.05, ABCG8: 0.17±0.08 vs 0.10±0.07, p<0.05

T2DM: increased MTTP and NPC1L1 mRNA, decreased ABCG5/8 mRNA

Lally S. et al. Diabetologia. 2006; 49;1008-1016
Non-fasting TG levels were associated with incident CV events

- Prospective study of 26,509 initially healthy US women (20,118 preprandial and 6,391 postprandial) participating in the Women’s Health Study.
- Undergoing follow-up for a median of 11.4 years.
- Hazard ratios for incident cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death).

CVD, cardiovascular disease; TG, triglyceride; CV, cardiovascular; MI, myocardial infarction; CVA, cerebrovascular accident; F/U, follow-up; US, united states

Considering non-fasting TG level is more important than fasting TG level

**Figure 2.** Association of Triglyceride Levels With Individual Cardiovascular End Points, According to Fasting Status

Hazard ratio (HR) and 95% confidence interval (CI) for highest vs lowest tertiles of triglyceride level (see Table 3 for values), adjusted for age, blood pressure, smoking, hormone use, levels of total and high-density lipoprotein cholesterol, diabetes mellitus, body mass index, and high-sensitivity C-reactive protein level.
ApoB48 level was increased in postprandial state

RLP, remnant like particle (CM remnant)

J atheroscler Thromb 2011:18:1062-1070
Intestinal lipoprotein (ApoB48) production was increased in hyperinsulinemic, insulin-resistant subjects

- ApoB-48 containing lipoprotein metabolism was examined in 14 nondiabetic men with a broad range of body mass index (BMI) and insulin sensitivity.
- ApoB-48 PR was significantly higher in hyperinsulinemic, insulin-resistant subjects (1.73 ± 0.39 vs. 0.88 ± 0.13 mg/kg per day; \( P < 0.05 \)) and correlated with fasting plasma insulin concentrations (\( r = 0.558; \ P = 0.038 \)).

ApoB48, apolipoprotein B48; HOMA-IR, homeostasis model assessment-insulin resistance; PR, production rate; FCR, fractional clearance rate

2. Controversies of current lipid treatment
(limitation of statin mono therapy & lipid guidelines)
Guidelines of Dyslipidemia Treatment

- ESC/EAS 2011 Guidelines
- 2013 ACC/AHA Guideline
- ADA Guideline
- KDA Guideline
- Reimbursement Guideline
- NCEP, ATPIII Guideline

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

Guideline-recommended treatment target levels for high-risk patient populations

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes mellitus/metabolic syndrome</strong></td>
<td></td>
<td></td>
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<tr>
<td>ADA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Without ≥100</td>
<td>&lt;100</td>
<td>-</td>
<td>-</td>
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<tr>
<td>overt CVD risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With overt CVD risk</td>
<td>&lt;70 (high-dose statins)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADA/ACC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest risk</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High risk</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

Catapano AL et al. Atherosclerosis 237 (2014) 319-335
LDL-C target attainment rates according to the 2008 ADA/ ACC consensus statement.

## Percentage of people achieving glycemic, BP and LDL-C target levels among those with diagnosed diabetes in Korea from 1998 to 2010

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>1,255,824</td>
<td>1,962,105</td>
<td>2,039,591</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt;6.5%</td>
<td>22.2 (16.4-28.0)</td>
<td>26.7 (23.7,29.7)</td>
<td>31.1 (25.4,36.8)</td>
<td>0.0996</td>
<td></td>
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<tr>
<td>HbA1c &lt;7%</td>
<td>42.5 (35.8-49.2)</td>
<td>47.9 (44.4-51.4)</td>
<td>49.1 (43.2-55.0)</td>
<td>0.3034</td>
<td></td>
<td></td>
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<tr>
<td>Type of antidiabetes treatment</td>
<td></td>
<td></td>
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<tr>
<td>Oral hypoglycemic agents (%)</td>
<td>70.8 (68.1-73.4)</td>
<td>75.7 (72.8-78.6)</td>
<td>80.7 (76.0-85.4)</td>
<td>0.003</td>
<td></td>
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<tr>
<td>Insulin injections (%)</td>
<td>8.1 (6.5-9.6)</td>
<td>7.8 (6.10-9.5)</td>
<td>8.7 (5.7-11.7)</td>
<td>0.77</td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>1,026,490</td>
<td>1,114,705</td>
<td>1,616,881</td>
<td>2,050,728</td>
<td>1,972,965</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol &lt;100 mg/dL</td>
<td>25.7 (19.8-31.6)</td>
<td>27.0 (20.7-33.3)</td>
<td>26.9 (21.2-32.6)</td>
<td>38.9 (35.6-42.2)</td>
<td>47.7 (42.2-53.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>10.9 (9.2-12.6)</td>
<td>20.3 (17.7-22.9)</td>
<td>33.3 (27.5-39.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia treatment (%)</td>
<td>6.8 (5.5-8.1)</td>
<td>12.4 (10.4-14.5)</td>
<td>22.9 (17.7-28.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1,025,786</td>
<td>1,157,084</td>
<td>1,779,409</td>
<td>2,249,601</td>
<td>2,347,828</td>
<td></td>
</tr>
<tr>
<td>Blood pressure &lt;130/80 mmHg</td>
<td>25.9 (20.8-31.0)</td>
<td>26.3 (19.6-33.0)</td>
<td>36.1 (30.2-42.0)</td>
<td>47.4 (44.3-50.5)</td>
<td>57.2 (51.9-62.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>23.8 (20.9-26.7)</td>
<td>36.1 (33.0-39.2)</td>
<td>49.2 (46.2-52.1)</td>
<td>51.2 (47.9-54.4)</td>
<td>54.2 (48.6-59.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension treatment (%)</td>
<td>42.2 (39.4-45.1)</td>
<td>48.1 (44.9-51.3)</td>
<td>51.7 (45.7-57.7)</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt;7%, LDL cholesterol &lt;100 mg/dL and blood pressure &lt;130/80 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1,783,640</td>
<td>2,258,299</td>
<td>2,363,697</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.7 (1.1-4.3)</td>
<td>8.7 (6.9-10.5)</td>
<td>8.7 (5.8-11.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; HbA1c, glycosylated hemoglobin. Data are expressed as mean (95% confidence interval). P-value was derived from the chi square test.
The rule of 6: Limitation of LDL-C reduction with statin titration

For each doubling of statin dose, only an additional 6% further lowering of LDL-C is achieved.¹

Effect of statin therapy on LDL-C levels: “The Rule of 6”

LDL-C= Low Density Lipoprotein-cholesterol.

A higher rate of myopathy* according to higher dose of statins

Frequency of CK>10xULN elevations of different statins (across dose range) normalized for LDL-C lowering

LDL-C= low density lipoprotein-cholesterol; CK= creatinine kinase; ULN= upper limit of normal.

2. Galson SK for FDA. Docket No. 2004P-0113CP1
Important safety label changes to statins (FDA Drug Safety Communication 2012) ¹

**Monitoring Liver Enzymes**

Labels have been revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter.

FDA has concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury.

**Adverse Event Information**

Information about the potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated hemoglobin (HbA₁c) levels has been added to the statin labels.

FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks.

**Drug Interactions**

The lovastatin label has been extensively updated with new contraindications (situations when the drug should not be used) and dose limitations when it is taken with certain medicines that can increase the risk for muscle injury.

Statin therapy was associated with a 9% increased risk for incident diabetes

In meta-analysis of 13 major trials with 91,140 participants, Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity between trials.

The risk of new onset diabetes of higher potency statin therapy: Intensive statin vs. moderate statin

- In meta-analysis of 5 large trials comparing intensive-dose to moderate-dose statin therapy, the data demonstrated that intensive-dose statin therapy was associated with a 12% increased risk for new-onset diabetes compared with moderate-dose statin therapy.

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Cases/Total, No. (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22,18 2004</td>
<td>101/1707 (5.9)</td>
<td>1.01 (0.76-1.34)</td>
</tr>
<tr>
<td>A to Z,17 2004</td>
<td>65/1756 (3.7)</td>
<td>1.37 (0.94-2.01)</td>
</tr>
<tr>
<td>TNT,15 2005</td>
<td>418/3798 (11.0)</td>
<td>1.19 (1.02-1.36)</td>
</tr>
<tr>
<td>IDEAL,16 2005</td>
<td>240/3737 (6.4)</td>
<td>1.15 (0.95-1.40)</td>
</tr>
<tr>
<td>SEARCH,5 2010</td>
<td>625/5398 (11.6)</td>
<td>1.07 (0.95-1.21)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>1449/16408 (8.8)</td>
<td>1.12 (1.04-1.22)</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$; $P = .60$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>Cases/Total, No. (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22,18 2004</td>
<td>315/1707 (18.4)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>A to Z,17 2004</td>
<td>212/1756 (12.0)</td>
<td>0.87 (0.72-1.07)</td>
</tr>
<tr>
<td>TNT,15 2005</td>
<td>647/3798 (17.0)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>IDEAL,16 2005</td>
<td>776/3737 (20.8)</td>
<td>0.60 (0.72-0.89)</td>
</tr>
<tr>
<td>SEARCH,5 2010</td>
<td>1184/5398 (21.9)</td>
<td>0.97 (0.88-1.06)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>3134/16408 (19.1)</td>
<td>0.84 (0.75-0.94)</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 74%$; $P = .004$</td>
<td></td>
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</tr>
</tbody>
</table>

DM, diabetes mellitus; CI, confidence intervals; OR, odds ratio

3. Benefits of ezetimibe/statin combination therapy in dyslipidemia with diabetes: focus on ezetimibe

- Ezetimibe MOA and NPC1L1,
- Efficacy in lowering atherogenic particles (sdLDL, ApoB)
- Updated clinical data from recent studies: postprandial TG, IR, NA FLD etc)
Ezetimibe action in cholesterol metabolism

NPC1L1 = Niemann-Pick C1 Like 1; Acetyl CoA = acetyl coenzyme A; LDLR = low-density lipoprotein receptor; Apo B = apolipoprotein B; CM = chylomicron; CMR = chylomicron remnant; IDL = intermediate-density lipoprotein; VLDL = very low-density lipoprotein

According to cholesterol homeostasis, statin induced cholesterol absorption in intestine

Changes in synthesis (lathosterol) and absorption (cholestanol) of cholesterol in response to statins use in CHD patients

Ezetimibe action in cholesterol metabolism

NPC1L1 = Niemann-Pick C1 Like 1; Acetyl CoA = acetyl coenzyme A; LDLR = low-density lipoprotein receptor; Apo B = apolipoprotein B; CM = chylomicron; CMR = chylomicron remnant; IDL = intermediate-density lipoprotein; VLDL = very low-density lipoprotein.

NPC1L1 is associated with cholesterol absorption in intestine
Pooled-analysis of 27 clinical trials comparing the efficacy of
Eze/Statin vs Statin therapies in patients with and without diabetes

<table>
<thead>
<tr>
<th></th>
<th>LDL-C with diabetes</th>
<th>LDL-C without diabetes</th>
<th>Non-HDL-C with diabetes</th>
<th>Non-HDL-C without diabetes</th>
<th>ApoB/ApoA1 with diabetes</th>
<th>ApoB/ApoA1 without diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3043</td>
<td>3394</td>
<td>7012</td>
<td>7831</td>
<td>3044</td>
<td>3397</td>
</tr>
<tr>
<td></td>
<td>-23.7</td>
<td>-22.3</td>
<td>-21.7</td>
<td>-20.3</td>
<td>-16.3</td>
<td>-15.9</td>
</tr>
<tr>
<td>% change from baseline</td>
<td>-41.1</td>
<td>-37.2</td>
<td>-36.7</td>
<td>-33.9</td>
<td>Δ -16.3</td>
<td>-29.4</td>
</tr>
<tr>
<td></td>
<td>Δ -17.4%</td>
<td>Δ -14.9%</td>
<td>Δ -15.0%</td>
<td>Δ -13.6%</td>
<td>Δ -13.0%</td>
<td>Δ -11.9%</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.0001</td>
<td></td>
<td>p = 0.0015</td>
<td></td>
<td>p = 0.0297</td>
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</tr>
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</table>

Δ = difference vs statin alone

Leiter et al. Diab Obes Metab 2011; online Feb 18

NPC1L1 is associated with cholesterol absorption in intestine
Pooled-analysis of 27 clinical trials comparing the efficacy of
Eze/Statin vs Statin therapies in patients with and without diabetes
Evaluation of non-statins for high risk patients of ASCVD

Background
1. Some patients do not tolerate or respond to high intensity statin monotherapy
2. Lower-intensity statin combined with nonstatin medication may be an alternative

Purpose
To compare the clinical benefits, adherence, and harms of lower-intensity statin combination therapy with those of higher intensity statin monotherapy among adults at high risk for atherosclerotic cardiovascular disease (ASCVD)

Method
Meta analysis of 36 randomized, controlled trials

Insufficient evidence to evaluate LDL cholesterol for fibrates, niacin, and ω-3 fatty acids

Could consider using lower-intensity statin combined with ezetimibe or bile acid sequestrant

Figure 2. Difference in mean percentage change in LDL cholesterol among high-risk groups by nonstatin agent between higher-intensity statin monotherapy and lower-intensity statin combination therapy.

The effect of ezetimibe in postprandial hyperlipidemia state

- Objective: To assess the effects of ezetimibe about postprandial lipid and glucose metabolism.
- Study design
  - Subject: 20 male volunteers, Arms: Ezetimibe 10 mg, Period: 4 weeks
  - Endpoint: postprandial lipid, glucose metabolism parameters
  - Method: Intake fast food meal (1001 kcal: hamburger with sausage, egg, apple pie, coca cola)

Ezetimibe Reduces ApoB48

Sixteen hyperlipidemic men were enrolled in a randomized, placebo-controlled, double-blind, cross-over study to evaluate the effect of ezetimibe 10 mg and simvastatin 40 mg, coadministered and alone, on the in vivo kinetics of apolipoprotein (apo) B-48 and B-100 in humans. Subjects underwent a primed-constant infusion of a stable isotope in the fed state.

P < 0.05 for both ezetimibe and simvastatin vs. placebo

Comparison of Apo B-48, TG, LDL-C from 0 to 6 h postprandially between diabetic and nondiabetic patients.

- Diabetic n=43
- Non-Diabetic n=50

Unpublished data
Reduction of insulin resistance with ezetimibe monotherapy

Ezetimibe monotherapy can reduce insulin resistance in NAFLD patients.¹

Clinical and laboratory parameters of baseline and after ezetimibe treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>At 12 months</th>
<th>At 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9 ± 3.3</td>
<td>26.0 ± 3.5</td>
<td>26.1 ± 3.2</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.3 ± 5.7</td>
<td>90.5 ± 5.8</td>
<td>90.9 ± 6.0</td>
</tr>
<tr>
<td>Visceral fat area (cm²)</td>
<td>155.9 ± 38.9</td>
<td>150.8 ± 33.6</td>
<td>146.5 ± 34.8*</td>
</tr>
<tr>
<td>Subcutaneous fat area (cm²)</td>
<td>170.9 ± 51.3</td>
<td>166.4 ± 41.5</td>
<td>167.1 ± 41.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.3 ± 0.8</td>
<td>6.5 ± 0.7</td>
<td>6.4 ± 0.9</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>113 ± 24</td>
<td>112 ± 27</td>
<td>112 ± 28</td>
</tr>
<tr>
<td>Fasting insulin (IU/ml)</td>
<td>10.9 ± 5.6</td>
<td>9.2 ± 5.8*</td>
<td>9.4 ± 5.1*</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>3.04 ± 1.17 *</td>
<td>2.60 ± 1.33*</td>
<td>2.62 ± 1.24*</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/l)</td>
<td>40 ± 22</td>
<td>36 ± 16</td>
<td>36 ± 16</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/l)</td>
<td>62 ± 25</td>
<td>48 ± 25**</td>
<td>49 ± 23**</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>168 ± 94</td>
<td>136 ± 90*</td>
<td>138 ± 88*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>228 ± 44</td>
<td>193 ± 36**</td>
<td>194 ± 36**</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49 ± 13</td>
<td>53 ± 15</td>
<td>52 ± 14</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mg/dl)</strong></td>
<td>136 ± 33</td>
<td>117 ± 34*</td>
<td>114 ± 31*</td>
</tr>
<tr>
<td>Oxidative LDL (U/ml)</td>
<td>14.1 ± 6.9</td>
<td>13.6 ± 7.1</td>
<td>11.8 ± 5.5*</td>
</tr>
<tr>
<td>Electronegative charge modified-LDL (ecd)</td>
<td>6.4 ± 3.5</td>
<td>3.5 ± 3.6#</td>
<td>3.4 ± 3.2#</td>
</tr>
<tr>
<td>Type IV collagen 7S (ng/dl)</td>
<td>5.1 ± 2.9</td>
<td>4.7 ± 2.5</td>
<td>4.7 ± 2.5</td>
</tr>
<tr>
<td>Adiponectin (lg/ml)</td>
<td>5.8 ± 3.1</td>
<td>6.1 ± 3.4</td>
<td>6.1 ± 3.4</td>
</tr>
<tr>
<td>Leptin (ng/l)</td>
<td>4.0 ± 2.9</td>
<td>3.8 ± 3.1</td>
<td>3.8 ± 3.1</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>7.7 ± 3.1</td>
<td>7.4 ± 3.4</td>
<td>7.4 ± 3.4</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein (ng/ml)</td>
<td>883 ± 408</td>
<td>677 ± 392*</td>
<td>685 ± 377*</td>
</tr>
</tbody>
</table>

Data are the mean ± SD
ecd electronegative charge density
* P<0.05, ** P<0.01, and
# P<0.005 versus baseline

Study design; A total of 45 patients with newly diagnosed liver biopsy-proven NAFLD were treated with EZ (10 mg/day) for 24 months. This study was designed to assess the efficacy of long-term EZ monotherapy in patients with NAFLD.

NAFLD, nonalcoholic fatty liver disease

Effects of atorvastatin 20mg, rosuvastatin 10mg, and atorvastatin/ezetimibe 5mg/5mg on lipoproteins

- Purpose: to compare the effects of 3 different statin regimens that have equivalent LDL-C lowering efficacy on the apolipoprotein B/A1 ratio and glucose metabolism
- 90 hypercholesterolemic patients were randomly assigned to 1 of 3 treatment groups for 8 weeks: atorvastatin 20 mg, rosuvastatin 10 mg, or atorvastatin/ezetimibe 5 mg/5 mg.
- At drug treatment week 8, we compared the percentage changes in lipid parameters, apolipoprotein B/A1 ratio, hemoglobin A1c, and homeostasis model assessment-insulin resistance (HOMA-IR) from baseline.

J Cardiovascular Pharm and Therapeutics 15(2) 167–174, 2010
SEAS study
Ischemic Cardiovascular Event in Aortic Stenosis

- 1873 patients with mild to moderate, asymptomatic aortic stenosis
- Median FU: 52.2 months

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe/Simvastatin 10/40 mg</td>
<td>917</td>
<td>867</td>
<td>823</td>
<td>769</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>898</td>
<td>838</td>
<td>788</td>
<td>729</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio: 0.78, \( P=0.024 \)

Rossebø et al. *NEJM* 2008;359
SHARP:
Major Atherosclerotic Events in Chronic kidney disease
(Composite endpoint: coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization)

- Randomized double-blind trial included 9270 patients with chronic kidney disease
- Median FU 4.9 years

Number at risk
Placebo 4,620 4,204 3,849 3,469 2,566 1,269
Simbastatin plus ezetimibe(20/10 mg) 4,650 4,271 3,939 3,546 2,655 1,265

Numbers remaining at risk of a first major atherosclerotic event ar the beginning of each year are shown for both treatment groups.

Rate reduction 17% (95% CI 6-26%)
Log-rank P=0.0021
Ezetimibe/simvastatin was Generally Well Tolerated

<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></td>
<td></td>
</tr>
</tbody>
</table>

* All VYTORIN 10/20, 10/40mg/day (n=442)
†All atorvastatin 10, 20, 40mg/day (n=657)

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

IMPROVE-IT study design

Patients stabilized post-ACS ≤ 10 days
LDL-C < 125 mg/dL or (≤ 100 if on prior lipid lowering therapy)

Double blind

ASA + Standard Medical Therapy

Simvastatin 40 mg*

Ezetimibe/
Simvastatin 10/40 mg*  

Follow-up day 30, every 4 months

Duration: minimum 2 1/2 year follow-up (5250 events)

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

• Specific approach is needed for the diabetic dyslipidemia management because of its unique features.

• Combination therapy with Ezetimibe is more effective than statin mono therapy in reduction of LDL-C, Apo B and Non-HDL-C.

• Combination therapy with Ezetimibe reduced the postprandial TG level similarly with high dose statin.

• Combination therapy with Ezetimibe may be a better option for minimizing the concern of increasing DM compared with high dose mono statins

• Ezetimibe/simvastatin is the good option for balanced diabetic dyslipidemia management
Baseline fasting glucose level and features of the metabolic syndrome are predictive of new-onset T2DM

Prediction of new-onset T2DM across the 3 trials
- **Objective**: to examine the incidence and clinical predictors of new-onset T2DM within 3 large randomized trials with atorvastatin.

**Risk Factors:**
1) baseline fasting glucose > 100 mg/dl
2) fasting triglycerides > 150 mg/dl
3) BMI >30 kg/m²
4) History of hypertension

**Risk of New-Onset T2DM according to number of risk factors at baseline**

<table>
<thead>
<tr>
<th># of risk factors</th>
<th>TNT trial (n=7,595)</th>
<th>IDEAL trial (n=7,595)</th>
<th>SPARCL trial (n=3,803)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>25.4</td>
<td>18.78</td>
<td>20.16</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Baseline fasting glucose level and features of the MS are predictive of new-onset T2DM.**

T2DM= type 2 diabetes mellitus; BMI= body mass index; DM= diabetes mellitus; MS= metabolic syndrome.

ESC/EAS 2011 Guidelines
: Very High– and High CV Risk Level Classification

- **Very High Risk** includes subjects with any of the following:
  - Documented CVD by invasive or noninvasive testing, 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; M, myocardial infarction; ACS, acute coronary syndrome; PAD, peripheral artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; SCORE, Systematic Coronary Risk Estimation; CV, cardiovascular

ESC/EAS 2011 Guidelines: Lipid Targets

<table>
<thead>
<tr>
<th>Very high risk</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>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%</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td></td>
<td>And/or ≥50% reduction from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markedly elevated single risk factors such as familial dyslipidemia and severe hypertension, or a calculated SCORE ≥5% and &lt;10% for 10 year risk of fatal CVD</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate risk</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE is ≥1% and &lt;5% at 10 years</td>
<td>&lt;115 mg/dL</td>
<td>&lt;145 mg/dL</td>
<td>Not defined</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. LDL-C: low-density lipoprotein cholesterol. Non-HDL-C: Non high-density lipoprotein cholesterol.

What is new in the 2013 ACC/AHA Guideline

The systematic review of evidence from the highest quality RCTs with ASCVD outcomes identified strong evidence to indicate who should get which therapy at what intensity.

ASCVD = Atherosclerotic cardiovascular disease

2013 ACC/AHA Blood Cholesterol Guideline
Major recommendations for statin therapy for ASCVD prevention

**Group 1**
Individuals with **clinical ASCVD**

- Adults age > 21 y and a candidate for statin therapy
- Clinical ASCVD
  - Age < 75 y: 
    - High-intensity statin
    - (Moderate-intensity statin if not candidate for high-intensity statin)
  - Age > 75 y OR if not candidate for high-intensity statin
    - Moderate-intensity statin

**Group 2**
Individuals with primary elevations of **LDL-C ≥ 190 mg/dL**

- LDL-C ≥ 190 mg/dL
- High-intensity statin
  - (Moderate-intensity statin if not candidate for high-intensity statin)

2013 ACC/AHA Blood Cholesterol Guideline
Major recommendations for statin therapy for ASCVD prevention

**Group 3**
Individuals 40 to 75 years of age with **diabetes** with LDL-C 70-189 mg/dL

- Diabetes
  - Type 1 or 2
  - Age 40-75 y

  - yes
    - Moderate-intensity statin

  - Estimated 10-y ASCVD risk ≥7.5%

- yes
  - High-intensity statin

**Group 4**
Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an **estimated 10-year ASCVD risk of 7.5% or higher**

- ≥7.5% estimated 10-y ASCVD risk and age 40-75 y

  - yes
    - Moderate-to-high intensity statin

**Intensity of statin therapy based on the efficacy of LDL-C lowering in ACC/AHA guideline**

**Recommended more 50% of LDL-C lowering in very high risk patients.**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately <strong>≥50%</strong></td>
<td>Daily dose lowers LDL–C on average, by approximately <strong>30-50%</strong></td>
<td>Daily dose lowers LDL–C on average, by <strong>&lt;30%</strong></td>
</tr>
</tbody>
</table>

- **Atorvastatin (40†)**–80 mg
- Rosuvastatin 20 (40) mg
- Atorvastatin 10 (20) mg
- Rosuvastatin (5) 10 mg
- Simvastatin 20–40 mg ‡
- Pravastatin 40 (80) mg
- Lovastatin 40 mg
- Fluvastatin 40 mg
- **Fluvastatin XL 80 mg**
- Fluvastatin 40 mg bid
- **Pitavastatin 2–4 mg**
- **Simvastatin 10 mg**
- Pravastatin 10–20 mg
- Lovastatin 20 mg
- Fluvastatin 20–40 mg
- Pitavastatin 1 mg

Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

LDL–C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.

### Shared points of 2011 ESC/EAS guideline & 2013 ACC/AHA Guidelines

1. Both guidelines conclude that **LDL-C is unequivocally a causal factor** for ASCVD
2. It is mentioned that **statin therapy has limitations** such as **side effect** and **intolerance for some patients** at the same time.

<table>
<thead>
<tr>
<th>ESC/EAS</th>
<th>ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Statins side effects are summarized as myopathy, elevated hepatic transaminases and incidence of diabetes</td>
<td></td>
</tr>
<tr>
<td>• The recent finding that the incidence of diabetes may increase with statins should not discourage institution of treatment</td>
<td></td>
</tr>
<tr>
<td>• There are also patients who are statin intolerant or are not able to tolerate higher statin doses</td>
<td></td>
</tr>
<tr>
<td>• During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms</td>
<td></td>
</tr>
<tr>
<td>• Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy</td>
<td></td>
</tr>
<tr>
<td>• Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines</td>
<td></td>
</tr>
</tbody>
</table>

---

ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerosis cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation.

Possible to apply the ACC/AHA guidelines in the rest of the world?

The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011


Population and economic impact of the 2013 ACC/AHA guidelines compared with European guidelines to prevent cardiovascular disease

Julien Vaucher1*, Pedro Marques-Vidal2, Martin Preisig3, Gérard Waeber1†, and Peter Vollenweider1†
Possible to apply the ACC/AHA guidelines in the rest of the world?

- Most world guidelines including those in Asia, Australia, and Canada provide some form of lipid targets for monitoring the response to lipid modification therapy and patient compliance.

- Most world guidelines (similar to ESC/EAS 2011) consider evidence beyond clinical trials to provide a practical and more comprehensive clinical management base for a wider group of patients.

- The 2013 ACC/AHA guidelines will result in a much larger proportion of patients being treated with statins and especially at higher doses.

- The new pooled mixed cohorts equation used for risk prediction in primary prevention requires further evaluation.

- The 2013 ACC/AHA guidelines are impractical in the Asia-Pacific region.

Possible to apply the ACC/AHA guidelines in the rest of the world?

### Table I
Simulations of the population impact and of daily costs related to treatment with atorvastatin in Switzerland according to the European Society of Cardiology (ESC) or 2013 American College of Cardiology and the American Heart Association (ACC/AHA) guidelines

<table>
<thead>
<tr>
<th></th>
<th>Swiss population</th>
<th>Population at risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ratio ACC/AHA to ESC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Daily cost of treatment&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>ESC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(50–60)</td>
<td>561 013</td>
<td>551 105</td>
<td>1 112 118</td>
<td>8976</td>
</tr>
<tr>
<td>(60–70)</td>
<td>429 528</td>
<td>448 861</td>
<td>878 389</td>
<td>204 026</td>
</tr>
<tr>
<td>(70–75)</td>
<td>176 448</td>
<td>205 307</td>
<td>381 755</td>
<td>175 389</td>
</tr>
<tr>
<td>All</td>
<td>1 814 130</td>
<td>1 841 332</td>
<td>3 655 462</td>
<td>388 391</td>
</tr>
</tbody>
</table>

|          | Men      | Women     | Total   |                     |                     | 30.6 | NA    | 33.2 | 447 |
| ACC/AHA  |          |           |         | Atorvastatin<sup>d</sup> |                     |      |       |     |     |
| (50–60)  | 561 013 | 551 105  | 1 112 118 |                    |                     | 298 033 |      | 30.6 |     |
| (60–70)  | 429 528 | 448 861  | 878 389  |                    |                   | 588 869 | 2.1  | 5.8  | 2.5 | 884 |
| (70–75)  | 176 448 | 205 307  | 381 755  |                    |                   | 380 934 | 1.0  | 1.1  | 1.1 | 572 |
| All      | 1 166 989 | 1 205 273 | 2 372 262 |                    |                   | 1 267 836 | 2.2  | 1.9  | 2.1 | 2023 |

<sup>a</sup>According to the ACC/AHA (new pooled cohort atherosclerotic CV disease risk equation) or ESC (Swiss SCORE equation) guidelines.

<sup>b</sup>Ratio of the number of subjects at risk according to ACC/AHA guidelines to the number of subjects at risk according to ESC guidelines. NA, not assessable.

<sup>c</sup>Expressed in 1000 CHF. To obtain €, multiply by 0.814; to obtain USD, multiply by 1.10. Currency exchange rates as of 3 January 2014 were applied.

<sup>d</sup>Fixed daily price independent of dosing (10–80 mg).

<sup>*</sup>SCORE equation do not predict CV risk for women under 60 years.

Ezetimibe significantly decreased the postprandial ApoB48 levels in 20 obese men with hypertriglyceridaemia

- Upper graph: seven time-point profiles of postprandial ApoB48 levels
  - ●: Before ezetimibe administration
  - ○: After ezetimibe administration
  - ■: Before placebo administration
  - □: After placebo administration

- Lower graph: AUC was calculated using the seven time-point profiles of postprandial ApoB48 levels
  - ■: Before administration
  - □: After administration

\[ (*p < 0.05) \]

High-dose statin vs low-dose statin/ezetimibe?

- **Objective**: To assessed whether similar LDL-cholesterol lowering with simvastatin/ezetimibe combination therapy improves fasting and postprandial arterial endothelial function compared to high-dose statin therapy alone.

- **Subject**: 100 abdominally obese with metabolic syndrome.

- **Arms**: *Simvastatin 80 mg vs. ezetimibe/simvastatin 10/10 mg*

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Δ</th>
<th>p-Value</th>
<th>Fasting</th>
<th>Δ</th>
<th>p-Value</th>
<th>Treatment difference</th>
<th>P-value</th>
<th>Treatment difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol (mmol/L)</strong></td>
<td>3.71 ± 0.035</td>
<td>0.11 ± 0.013</td>
<td>&lt;0.001</td>
<td>3.76 ± 0.035</td>
<td>0.10 ± 0.013</td>
<td>&lt;0.001</td>
<td>0.04 ± 0.049</td>
<td>0.377</td>
<td>0.00 ± 0.019</td>
<td>0.815</td>
</tr>
<tr>
<td><strong>LDL-cholesterol (mmol/L)</strong></td>
<td>1.79 ± 0.033</td>
<td>-0.09 ± 0.018</td>
<td>&lt;0.001</td>
<td>1.81 ± 0.033</td>
<td>-0.06 ± 0.018</td>
<td>0.002</td>
<td>0.02 ± 0.047</td>
<td>0.597</td>
<td>0.03 ± 0.026</td>
<td>0.194</td>
</tr>
<tr>
<td><strong>HDL-cholesterol (mmol/L)</strong></td>
<td>1.33 ± 0.019</td>
<td>-0.04 ± 0.017</td>
<td>0.011</td>
<td>1.31 ± 0.019</td>
<td>-0.02 ± 0.017</td>
<td>0.222</td>
<td>-0.03 ± 0.027</td>
<td>0.294</td>
<td>0.02 ± 0.024</td>
<td>0.338</td>
</tr>
<tr>
<td><strong>Non-HDL cholesterol (mmol/L)</strong></td>
<td>2.38 ± 0.038</td>
<td>0.15 ± 0.019</td>
<td>&lt;0.001</td>
<td>2.45 ± 0.037</td>
<td>0.13 ± 0.019</td>
<td>&lt;0.001</td>
<td>0.07 ± 0.052</td>
<td>0.173</td>
<td>-0.03 ± 0.027</td>
<td>0.304</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>1.18 ± 0.633</td>
<td>0.88 ± 0.791</td>
<td>&lt;0.001</td>
<td>1.24 ± 0.744</td>
<td>1.03 ± 0.809</td>
<td>&lt;0.001</td>
<td>0.02 ± 0.165</td>
<td>0.549</td>
<td>0.06 ± 0.014</td>
<td>0.841</td>
</tr>
<tr>
<td><strong>Apolipoprotein A1 (g/L)</strong></td>
<td>1.49 ± 0.014</td>
<td>0.00 ± 0.010</td>
<td>0.693</td>
<td>1.47 ± 0.015</td>
<td>0.00 ± 0.010</td>
<td>0.915</td>
<td>-0.02 ± 0.020</td>
<td>0.329</td>
<td>0.00 ± 0.014</td>
<td>0.841</td>
</tr>
<tr>
<td><strong>Apolipoprotein B48 (mg/dL)</strong></td>
<td>0.56 ± 0.023</td>
<td>0.42 ± 0.021</td>
<td>&lt;0.001</td>
<td>0.52 ± 0.023</td>
<td>0.43 ± 0.021</td>
<td>&lt;0.001</td>
<td>-0.03 ± 0.032</td>
<td>0.288</td>
<td>0.01 ± 0.030</td>
<td>0.669</td>
</tr>
<tr>
<td><strong>Apolipoprotein B100 (g/L)</strong></td>
<td>0.75 ± 0.008</td>
<td>0.02 ± 0.005</td>
<td>&lt;0.001</td>
<td>0.77 ± 0.008</td>
<td>0.03 ± 0.005</td>
<td>&lt;0.001</td>
<td>0.02 ± 0.011</td>
<td>0.097</td>
<td>0.01 ± 0.007</td>
<td>0.247</td>
</tr>
<tr>
<td><strong>Glucose (mmol/L)</strong></td>
<td>5.48 ± 0.033</td>
<td>-0.42 ± 0.041</td>
<td>&lt;0.001</td>
<td>5.53 ± 0.034</td>
<td>-0.46 ± 0.043</td>
<td>&lt;0.001</td>
<td>0.06 ± 0.047</td>
<td>0.244</td>
<td>-0.04 ± 0.059</td>
<td>0.539</td>
</tr>
</tbody>
</table>

Based on ANOVA model with terms for treatment, period, sequence, and subject (sequence). LDL: low-density-lipoprotein, HDL: high-density-lipoprotein.

The post-fat load minus fasting treatment difference denotes the difference in the fasting to post-fat load change in lipids and glucose between the two treatments. For example, LDL-cholesterol decreased by 0.09 mmol/L from the fasting to the post-fat load state under simvastatin and LDL-cholesterol decreased by 0.06 mmol/L under simvastatin/ezetimibe combination leading to post-fat load minus fasting treatment difference of 0.03 mmol/L.

**Δ** Post-fat load minus fasting difference.

**a** Treatment difference is defined as simvastatin/ezetimibe minus simvastatin.

**c** Measured using β-quantification.

**d** Non-parametric analysis using raw medians and SD = (Q3 – Q1)/1.75, where Q3 = 75th percentile and Q1 = 25th percentile. Within-treatment p-values are from a Wilcoxon signed rank test. Treatment differences are based on Hodges-Lehmann estimates and P-values are from an ANOVA model using Tukey's normalized ranks.