Solution to Reduce CV risk:
Exploring the latest pathway to treat Hypertension & Dyslipidemia

- Reducing cardiovascular risk in high-risk patients
  : How we would apply new treatment guideline in a real practice?
  (연세의대 최동훈 교수님)

- The Significance of Uric acid for Hypertension treatment
  (연세의대 강석민 교수님)
Reducing cardiovascular risk in high-risk patients: How we would apply new treatment guideline in a real practice?

   - Three points of updates in 2011 ESC/EAS guideline are
     a. It is importance to get to LDL-C <70mg/dL or 50% reduction from baseline for high-risk patients.
     b. CKD is also CHD equivalent risk factor
     c. Management of atherogenic particle number is valuable approach for Metabolic syndrome and DM patients (non-HDL and ApoB is secondary target)

2. 80% of CHD patients are not at LDL-C goal(<70mg/dL) with statin in Korea
   - Because, Statin mono therapy has some limitation to get to target goal at once.
     a. Safety concern of high dose statin: hepatic and muscle injury
     b. Lack of additional value of doubling or switching: Rule of six
     c. (Risk of incident diabetes (FDA warning, 2012))
Reducing cardiovascular risk in high-risk patients: How we would apply new treatment guideline in a real practice?

3. VYTORIN is the smart option to be aligned with guideline change.

- VYTORIN proved superior efficacy vs. statin therapy (mono, doubling or switching)
  a. 9 out of 10 patients are getting to goal at once with initial dose of VYTORIN.
  b. Initial dose of VYTORIN cut off 50% reduction LDL-C at once.
     (EZT add-on to any statin provided additional 25% reduction of LDL-C.)
  c. EZT/VYTORIN attained triple target goal for managing atherogenic particle vs. statin mono therapy.

- VYTORIN proved long-term clinical benefits for high-risk patients safely.
  a. Initial dose of VYTORIN (10/20mg) proved 17% risk reduction of atherosclerotic event (coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization) in patients with high-risk patients.
  b. VYTORIN had proved safety profile for highest risk patient such as CKD in 5 years.
4. EZT / VYT provide additional benefits beyond LDL-C

- EZT / VYTORIN is better option for minimizing concern of increasing DM vs. statin.
  a. Based on RCT and meta analysis, statin (rosuvastatin, atorvastatin) seems to be associated with development of DM (meta-analysis data)
  b. In animal and human data, EZT / VYTORIN proved no deleterious effect on insulin resistance
  c. In SHARP, no report on DM incidence vs. placebo.

- EZT / VYTORIN improved endothelial function.
  a. Low dose Simvastatin and Eze preserved post-fat load endothelial function in male MS patients.
  b. Ezetimibe improves postprandial induced endothelial dysfunction.
  c. Impact of Ezetimibe therapy on Endothelial Dysfunction in patients on statin therapy with CAD and hyperTG.
Reducing cardiovascular risk in high-risk patients: How we would apply new treatment guideline in a real practice?

[Take Home Message]

VYTORIN is the smart option to be aligned with guideline change.

1. For better goal achievement, VYTORIN 10/20mg cut off 50% LDL-C reduction safely at once.
2. VYTORIN attained triple target goal for managing atherogenic particle vs. statin mono therapy
3. Reduction of LDL cholesterol with VYTORIN 10/20mg safely reduced the incidence of major atherosclerotic events in high-risk patients.
Reducing cardiovascular risk in high-risk patients: How we would apply new treatment guideline in a real practice?
Lower Is Better: Cholesterol Treatment Trialists

Proportional reduction in atherosclerotic event rate (95% CI)

Mean LDL cholesterol difference between treatment groups (mg/dL)

LDL-C 1mmol/L (39mg/dL)

Statin vs control (21 trials)

Major vascular event 22% RR

### 2004 NCEP ATP III guideline

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk: CHD or CHD risk equivalents</strong> (10-year risk 20%)</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥ 100 mg/dL (100 mg/dL: consider drug options)</td>
</tr>
<tr>
<td><strong>Moderately high risk: 2 risk factors</strong> (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL (optional goal: &lt;100 mg/dL)</td>
<td>≥ 130 mg/dL</td>
<td>≥ 130 mg/dL (100–129 mg/dL; consider drug options)</td>
</tr>
<tr>
<td><strong>Moderate risk: 2 risk factors‡</strong> (10-year risk 10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td><strong>Lower risk: 0–1 risk factor§</strong></td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥ 190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease transient ischemic attacks or stroke of carotid origin or 50% obstruction of a carotid artery), diabetes, and 2 risk factors with 10-year risk for hard CHD 20%.

‡Risk factors include cigarette smoking, hypertension (BP 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (40 mg/dL), family history of premature CHD (CHD in male first-degree relative 55 years of age; CHD in female first-degree relative 65 years of age), and age (men 45 years; women 55 years).

§TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence (Circulation. 2004;110:227-239.)
2011 ESC Update: Updated recommendations for Very high risk

**Very high risk**
- **Documented CVD, previous MI, ACS, coronary revascularization** (PCI, CABG) and other arterial revascularization procedures, ischemic stroke, PAD
- Patients with **type 2 diabetes**, patients with type 1 diabetes with target organ damage (such as microalbuminuria)
- Patients with **moderate to severe CKD** (GFR < 60mL/min/1.73m²)
- A calculated 10 year risk SCORE ≥ 10%

**Treatment targets**
- **Primary target** – LDL-C
  - In patients at **VERY HIGH CV risk** the LDL-C goal is < 70mg/dL and/or ≥ 50% LDL-C reduction when target level cannot be reached
- **Secondary target**
  - Specific target for **non-HDL-C** should be 30mg/dL higher than the corresponding LDL-C target.
  - **Apo B** appears to be a risk factor at least as good as LDL-C and a better index of the adequacy of LDL-lowering therapy than LDL-C.

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Therefore, 80% of CHD patients are **not at the goal** even with Statin Rx in Korea

**LDL-C distribution**

- **LDL-C Uncontrolled after Statin Rx.**
  - Total (n=925)
  - LDL-C Uncontrolled (above LDL-C 100) 39%
  - below 70 20
  - 70~100 41
  - 101~129 29
  - 130~159 8
  - 160~189 2
  - 190 or above 0

**LDL-C distribution by CV disease**

- **CHD (n=526)**
  - 75% (above LDL-C 70)
  - 75%
  - 44
  - 22
  - 2
  - 0

- **CHD equivalent (=DM) (n=118)**
  - 82% (above LDL-C 100 : 41%)
  - 82%
  - 41
  - 32
  - 4
  - 1

- **HTN with 2 more risk* (n=201)**
  - 53%
  - 36
  - 39
  - 13
  - 4
  - 1

- **No Risk (n=80)**
  - 54%
  - 34
  - 39
  - 15
  - 15
  - 4

*HTN with 2 more risks: HTN patients with 45+y/o (Male) or 55+y/o (Female) but who do not have CHD or DM

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Therefore, 80% of CHD patients are not at the goal even with Statin Rx in Korea.
Only highest dose of statins can achieve 50% LDL-C reduction

![Graph showing the percentage change from baseline with different doses of statins.]

- Rosuvastatin (n = 156 - 160)
- Atorvastatin (n = 158 - 165)
- Pravastatin (n = 158 - 165)
- Simvastatin (n = 161 - 164)
- Ezetimibe/Simvastatin

**Atorvastatin 80mg, Rosuvastatin 20mg**
Highest doses associated with increased hepatic toxicity

Data from prescribing information for atorvastatin, lovastatin, simvastatin.
This does not represent data from a comparative study.

Drug safety 2006;29(5):421-448
Highest doses associated with increased muscle injury (> 10X CK)
Statin up-titration has limitation on LDL-C reduction

“...With each doubling of the dose of statin, LDL-C levels fall by about 6 percent.”

NCEP ATP III Final Report

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

2. NCEP ATP III guideline 2002
What is your option to reach target goals (LDL-C<70mg/dL or ≥50% reduction)?

1. Escalation of Statin dose?
2. Utilization of dual action mechanism?
Ezetimibe: The 1st cholesterol absorption inhibitor

2. VYTORIN US prescribing Information

### Half-life: 22 hours

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo (%) N=205</th>
<th>Ezetimibe 10mg (%) N=622</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common treatment-emergent AEs</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Laboratory tests assessing liver and muscle function:

- Liver function tests (≥3XULN)
- Alanine aminotransferase: 0, <1
- Aspartate aminotransferase: 0, <1
- R-Glutamyltransferase: 3, 2
- Creatine phosphokinase ≥10XULN: 0, 0

- Half-life: 22 hours
**Vytorin:**

**DUAL INHIBITION in cholesterol**

Intestine: **EZETIMIBE**

Liver: **STATIN**

Cholesterol Pool (Micelles)

- Dietary chol
- NPC1L1
- Bile Acids
- Free Chol
- Fecal sterols
- Acetyl CoA

Remnant receptors

- Intestinal Apo B-48
- CMR
- CM

Peripheral Tissues

- Hepatic Apo B-100
- LDLR
- CMR
- LDL
- IDL
- VLDL

Blood

- Intestine: EZETIMIBE
- Liver: STATIN

**LDL:**

- Hepatic Apo B-100
- LDLR
- CMR
- LDL
- IDL
- VLDL

**VLDL:**

- Hepatic Apo B-100
- LDLR
- CMR
- LDL
- IDL
- VLDL

**CMR:**

- Hepatic Apo B-100
- LDLR
- CMR
- LDL
- IDL
- VLDL

**CM:**

- Hepatic Apo B-100
- LDLR
- CMR
- LDL
- IDL
- VLDL

**Atheroma:**

- Peripheral Tissues
- Intestine: EZETIMIBE
- Liver: STATIN

VYTORIN: 9 out of 10 patients achieved LDL-C Goal Attainment to <100 mg/dL

Percentage of Patients Who Achieved LDL-C 100mg/dL with Starting Dose

VYTORIN
10/20 mg (n=238)
90%*

Atorvastatin
10 mg (n=237)
70%

% Patients achieving LDL-C target at week 6

* p<0.001 vs. atorvastatin
Ezetimibe add-on vs. Statin doubling in LDL-C lowering

ONE-STEP COADMINISTRATION

THREE-STEP TITRATION

Simvastatin 10 mg

20 mg

40 mg

80 mg

Simvastatin 10 mg

Ezetimibe 10 mg

0

32.7%

44.8%

25~30%

48.5%

% Reduction in LDL-C

**VYTORIN:**
Superior LDL-C reduction at Starting Dose

The VYMET Study
with Metabolic Syndrome patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>LDL-C % Change (±SE) from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-50%</td>
</tr>
<tr>
<td>10mg</td>
<td>-37%*</td>
</tr>
<tr>
<td>20mg</td>
<td>-39%*</td>
</tr>
</tbody>
</table>

The VYRO Study
with primary hypercholesterolemia

<table>
<thead>
<tr>
<th>Dose</th>
<th>LDL-C % Change (±SE) from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-52%</td>
</tr>
<tr>
<td>10mg</td>
<td>-46%*</td>
</tr>
</tbody>
</table>

* p<0.001 vs. statin

VYTORIN:
Superior non HDL-C reduction at Starting Dose

The VYMET Study
with Metabolic Syndrome patients

The VYRO Study
with primary hypercholesterolemia

% Change (±SE) from baseline
non HDL-C

<table>
<thead>
<tr>
<th>Dose</th>
<th>10/20mg</th>
<th>10mg</th>
<th>20mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-44%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mg</td>
<td>-34%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20mg</td>
<td>-37%*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001 vs. statin

<table>
<thead>
<tr>
<th>Dose</th>
<th>10/20mg</th>
<th>10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-47%</td>
<td></td>
</tr>
<tr>
<td>10mg</td>
<td>-42%*</td>
<td></td>
</tr>
</tbody>
</table>

VYTORIN
Atorvastatin
Rosuvastatin

VYTORIN: Superior ApoB reduction at Starting Dose

The VYMET Study with Metabolic Syndrome patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>VYTORIN</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-37%*</td>
<td>-28%*</td>
</tr>
<tr>
<td>10mg</td>
<td>-32%*</td>
<td></td>
</tr>
<tr>
<td>20mg</td>
<td></td>
<td></td>
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* p<0.001 vs. statin

The VYRO Study with primary hypercholesterolemia

<table>
<thead>
<tr>
<th>Dose</th>
<th>VYTORIN</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/20mg</td>
<td>-42%</td>
<td>-37%*</td>
</tr>
<tr>
<td>10mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001 vs. statin

VYTORIN was Generally Well Tolerated

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>VYTORIN 10/20 mg/day (n=314)</th>
<th>Rosuvastatin 10 mg/day (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Clinical event</td>
<td>7.1%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Drug–related clinical event</td>
<td>2.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Discontinuation due to drug–related clinical event</td>
<td>2.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>ALT and/or AST ≥3 × ULN (consecutive)</td>
<td>0.7%</td>
<td>0</td>
</tr>
<tr>
<td>CK ≥5 × ULN</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Farnier M. et al
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase.

The effects of lowering LDL cholesterol with Simvastatin plus Ezetimibe in patients with chronic kidney disease

(Study of Heart And Renal Protection : SHARP)
Hazard ratios for cardiovascular events

*Adjusted for baseline age, sex, income, education, coronary disease, chronic heart failure, stroke or transient ischemic attack, peripheral artery disease, diabetes, hypertension, dyslipidemia, cancer, hypoalbuminemia, dementia, liver disease, proteinuria, prior hospitalizations, and subsequent dialysis requirement.

Cardiovascular Disease and CKD: Core Curriculum 2010. American Journal of Kidney Diseases, 2010(56); 2: 399-417
By CV disease, Patient with DM shows higher portion of CKD risk patients as 45% compared to other CV disease.

**CKD risk patients (below GFR 60) are 28%**

![GFR Score by MDRD II (Tally-Results) by CV disease](image)
Deficiency of Renal function in patient with NSTEMI  
(from the Korea Acute Myocardial Infarction Registry)

Baseline clinical characteristics according to renal function and management

<table>
<thead>
<tr>
<th>Variable</th>
<th>Renal Function</th>
<th>EI Group</th>
<th>DI Group</th>
<th>Conservative Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>1,154 (32%)</td>
<td>1,663 (46%)</td>
<td>799 (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>58 (33%)</td>
<td>74 (43%)</td>
<td>42 (24%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>464 (36%)</td>
<td>628 (48%)</td>
<td>224 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>562 (33%)</td>
<td>814 (47%)</td>
<td>353 (20%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>68 (18%)</td>
<td>143 (37%)</td>
<td>174 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (55–71)</td>
<td>65 (56–73)</td>
<td>69 (59–71)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>826 (72%)</td>
<td>1,110 (67%)</td>
<td>459 (58%)</td>
<td>&lt;0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 (22–26)</td>
<td>24 (22–26)</td>
<td>23 (21–25)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>601 (52%)</td>
<td>893 (54%)</td>
<td>437 (55%)</td>
<td>0.333</td>
<td>0.420</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>314 (27%)</td>
<td>565 (34%)</td>
<td>265 (33%)</td>
<td>0.262</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>148 (13%)</td>
<td>221 (13%)</td>
<td>97 (12%)</td>
<td>0.549</td>
<td>0.777</td>
</tr>
<tr>
<td>Previous coronary artery disease</td>
<td>224 (19%)</td>
<td>331 (20%)</td>
<td>241 (30%)</td>
<td>&lt;0.001</td>
<td>0.736</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>63 (5.5%)</td>
<td>146 (8.8%)</td>
<td>105 (13.1%)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>11 (1.0%)</td>
<td>53 (3.2%)</td>
<td>72 (9.0%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>677 (59%)</td>
<td>881 (53%)</td>
<td>350 (44%)</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>93 (8.1%)</td>
<td>182 (11%)</td>
<td>155 (20%)</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>165 (15%)</td>
<td>383 (24%)</td>
<td>313 (40%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of chest symptom on admission</td>
<td>950 (83%)</td>
<td>1,323 (81%)</td>
<td>549 (71%)</td>
<td>&lt;0.001</td>
<td>0.070</td>
</tr>
<tr>
<td>Presence of dyspnea on admission</td>
<td>228 (20%)</td>
<td>461 (29%)</td>
<td>312 (41%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina before admission</td>
<td>660 (57%)</td>
<td>878 (52%)</td>
<td>353 (45%)</td>
<td>&lt;0.001</td>
<td>0.037</td>
</tr>
<tr>
<td>ST-T change on admission</td>
<td>645 (56%)</td>
<td>990 (60%)</td>
<td>482 (60%)</td>
<td>0.272</td>
<td>0.043</td>
</tr>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>41 (3.6%)</td>
<td>63 (3.9%)</td>
<td>61 (7.8%)</td>
<td>&lt;0.001</td>
<td>0.762</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≤35%</td>
<td>62 (5.9%)</td>
<td>156 (9.9%)</td>
<td>131 (18.4%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)</td>
<td>58 (47–69)</td>
<td>57 (46–68)</td>
<td>52 (34–66)</td>
<td>&lt;0.001</td>
<td>0.017</td>
</tr>
<tr>
<td>Thrombolysis In Myocardial Infarction risk score ≥5</td>
<td>140 (12%)</td>
<td>236 (14%)</td>
<td>160 (20%)</td>
<td>&lt;0.001</td>
<td>0.114</td>
</tr>
<tr>
<td>Modified Global Registry of Acute Coronary Events score ≥140</td>
<td>310 (27%)</td>
<td>563 (33%)</td>
<td>434 (54%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

68%

SHARP: Eligibility and Key outcome

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: \( \geq 1.7 \text{ mg/dL (150 } \mu\text{mol/L) } \)
    - Women: \( \geq 1.5 \text{ mg/dL (130 } \mu\text{mol/L) } \)
  - 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

1. SHARP Collaborative Group *Am Heart J* 2010;0:1-10.e10
SHARP: Study of Heart And Renal Protection

Major Atherosclerotic Events composite endpoint: coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization

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

Number at risk
- Placebo 4620
- Simvastatin plus ezetimibe 4650

Years of follow-up
- Placebo: 4204, 3849, 3469, 2566, 1269
- Simvastatin plus ezetimibe: 4271, 3939, 3546, 2655, 1265
Major atherosclerotic event subdivided type

<table>
<thead>
<tr>
<th>Event</th>
<th>Simvastatin plus ezetimibe (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>0.12</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>0.95</td>
</tr>
<tr>
<td>Subtotal: any major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>0.92 (0.76–1.11)</td>
<td>0.37</td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>114 (2.5%)</td>
<td>157 (3.4%)</td>
<td>0.72 (0.57–0.92)</td>
<td>0.0073</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>0.85</td>
</tr>
<tr>
<td>Subtotal: any non-haemorrhagic</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td>0.75 (0.60–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Revascularisation procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>149 (3.2%)</td>
<td>203 (4.4%)</td>
<td>0.73 (0.59–0.90)</td>
<td>0.0027</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>0.36</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>0.0036</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>0.0021</td>
</tr>
</tbody>
</table>

## SHARP: Safety

<table>
<thead>
<tr>
<th>Condition</th>
<th>Simv/Eze (n=4650)</th>
<th>Placebo (n=4620)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myopathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK &gt;10 x but ≤40 x ULN</td>
<td>17 (0.4%)</td>
<td>16 (0.3%)</td>
</tr>
<tr>
<td>CK &gt;40 x ULN</td>
<td>4 (0.1%)</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>21 (0.5%)</td>
<td>18 (0.4%)</td>
</tr>
<tr>
<td>Persistently elevated ALT/AST &gt;3x ULN</td>
<td>30 (0.6%)</td>
<td>26 (0.6%)</td>
</tr>
<tr>
<td><strong>Complications of gallstones</strong></td>
<td>85 (1.8%)</td>
<td>76 (1.6%)</td>
</tr>
<tr>
<td>Other hospitalization for gallstones</td>
<td>21 (0.5%)</td>
<td>30 (0.6%)</td>
</tr>
<tr>
<td>Pancreatitis without gallstones</td>
<td>12 (0.3%)</td>
<td>27 (0.6%)</td>
</tr>
</tbody>
</table>

Additional benefit of Ezetimibe beyond LDL-C

1. Better option for minimizing concerns of increasing DM

2. Improvement of endothelial dysfunction
A small increased risk of raised blood sugar levels and the development of Type 2 diabetes have been reported with the use of statins.

“Clearly we think that the heart benefit of statins outweighs this small increased risk,” says Egan.

But what this means for patients taking statins and the health care professionals prescribing them is that blood-sugar levels may need to be assessed after instituting statin therapy,” she says.
In a pooled analysis, intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy.

- As compared with moderate-dose statin, the number needed to harm per year for intensive-dose statin was **498 for new-onset DM** while the number needed to treat per year for intensive-dose statin was **155 for C-V events**.

**Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy**

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>101/1707 (5.9)</td>
<td>96/1688 (5.9)</td>
<td>1.01 (0.76-1.34)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>65/1766 (3.7)</td>
<td>47/1738 (2.7)</td>
<td>1.37 (0.94-2.01)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>419/3798 (11.0)</td>
<td>359/3797 (9.4)</td>
<td>1.19 (1.02-1.38)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>240/3737 (6.4)</td>
<td>203/3724 (5.6)</td>
<td>1.15 (0.95-1.40)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>625/6398 (11.9)</td>
<td>587/5399 (10.9)</td>
<td>1.07 (0.85-1.31)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>1449/16408 (8.8)</td>
<td>1300/16344 (8.0)</td>
<td><strong>1.12 (1.04-1.22)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident CVD</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>315/1707 (18.4)</td>
<td>355/1688 (21.0)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>212/1766 (12.0)</td>
<td>234/1738 (13.5)</td>
<td>0.87 (0.72-1.07)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>647/3798 (17.0)</td>
<td>830/3797 (21.9)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>776/3737 (20.6)</td>
<td>917/3724 (24.6)</td>
<td>0.60 (0.52-0.68)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>1164/5399 (21.9)</td>
<td>1214/5399 (22.5)</td>
<td>0.87 (0.88-1.06)</td>
</tr>
<tr>
<td>Pooled odds ratio</td>
<td>3134/16408 (19.1)</td>
<td>3550/16344 (21.7)</td>
<td><strong>0.64 (0.75-0.94)</strong></td>
</tr>
</tbody>
</table>

Preiss D, JAMA. 2011;305:2556-2564

Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.
Ezetimibe might be a good option for reducing risk of high dose statin on insulin resistance

**In animal data**

- Ezetimibe might decrease hepatic insulin resistance by reducing hepatic cholesterol


**In Human data**

- Ezetimibe, inhibiting molecules of NPC1L1 improved HOMA-IR compared with baseline in NAFLD patients

  *J Gastroenterol (2011) 46:101–107*
Inhibition of hepatic Niemann-Pick C1-like 1 improves hepatic insulin resistance

Mitsunori Nomura,¹ Hideto DM

¹Life Science and Bioethics Research Institute, Medical and Dental University, T"or"okmamingu, Fukuoka, Japan

Submitted 26 May 2009; accepted in final form 15 September 2009

The mechanism of improved HOMA-IR might be related with inhibition of hepatic NPC1L1 by Ezetimibe
Ezetimibe, inhibiting molecules of NPC1L1 improved HOMA-IR compared with baseline in NAFLD patients

Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease

Hyojun Park · Toshihide Shima · Kanji Yamaguchi · Hironori Mitsuyoshi · Masahiko Minami · Kohichiroh Yasui · Yoshihito Itoh · Toshikazu Yoshikawa · Michiaki Fukui · Goji Hasegawa · Naoto Nakamura · Mitsuhiro Ohta · Hiroshi Obayashi · Takeshi Okanoue

Received: 8 May 2010/ Accepted: 6 July 2010/Published online: 24 July 2010 © Springer 2010

Table 2 Clinical and laboratory parameters of baseline and after ezetimibe treatment

<table>
<thead>
<tr>
<th></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>
</tbody>
</table>
| Visceral fat area (cm²) | 155.9 ± 38.9| 150.8 ± 33.6 | 146.5 ± 34.8*
| Subcutaneous fat area (cm²)| 170.9 ± 51.3| 166.4 ± 41.5| 167.1 ± 41.5|
| HbA1c (%)               | 6.3 ± 0.8 | 6.5 ± 0.7    | 6.4 ± 0.9    |
| Fasting glucose (mg/dl) | 113 ± 24  | 112 ± 27     | 112 ± 28     |
| Fasting insulin (U/l)   | 10.0 ± 5.6| 9.2 ± 5.8*   | 9.4 ± 5.1*   |
| HOMA-R                  | 3.04 ± 1.17| 2.60 ± 1.33* | 2.62 ± 1.24* |

Aspartate aminotransferase (IU/l) 40 ± 22 36 ± 16 36 ± 16
Alanine aminotransferase (IU/l) 62 ± 25 48 ± 25** 49 ± 23***
Triglycerides (mg/dl) 168 ± 94 136 ± 90* 138 ± 88*
Total cholesterol (mg/dl) 228 ± 44 193 ± 36** 194 ± 36**
HDL cholesterol (mg/dl) 49 ± 13 53 ± 15 52 ± 14
LDL cholesterol (mg/dl) 136 ± 33 117 ± 34* 114 ± 31*
Oxidative LDL (U/ml) 14.1 ± 6.9 13.6 ± 7.1 11.8 ± 5.5*
Electronegative charge modified-LDL (ecd) 6.4 ± 3.5 3.5 ± 3.6* 3.4 ± 3.2*
Type IV collagen 7S (ng/dl) 5.1 ± 2.9 4.7 ± 2.5 4.7 ± 2.5
Adiponectin (µg/ml) 5.8 ± 3.1 6.1 ± 3.4 6.1 ± 3.4
Leptin (ng/l) 4.0 ± 2.9 3.8 ± 3.1 3.8 ± 3.1
Resistin (ng/ml) 7.7 ± 3.1 7.4 ± 3.4 7.4 ± 3.4
High-sensitivity C-reactive protein (ng/ml) 883 ± 408 677 ± 392* 685 ± 377*

Data are the mean ± SD
ecd electronegative charge density

* P < 0.05, ** P < 0.01, and * P < 0.005 versus baseline

Baseline characteristics

Hyperlipidemia, obesity, pre-DM, NAS >5
Ezetimibe significantly diminished postprandial lipemia in obese patients

Figure 2 Oral fat loading (OFL) test before and after administration of ezetimibe. Patients with type IIb hyperlipidaemia (n = 10, two females and eight males) were given OFTT cream (containing 35% fat without sugar, 30 g fat m⁻² body surface area) after overnight fasting before (open squares) and after (closed squares) administration of ezetimibe. Blood samples were drawn during fasting and 1, 2, 3, 4, 6 and 8 h after OFL, and serum and plasma were separated immediately. Concentrations of (a) total cholesterol (TC), (b) triglyceride (TG), (c) apolipoprotein B-48(apoB-48), (d) remnant lipoprotein cholesterol (RemL-C), (e) free fatty acids (FFA) and (f) apoB-100 were measured as described in Materials and methods. *P < 0.05, #P < 0.01.
Serum TG levels were reduced by Ezetimibe but did not differ between Ezetimibe group and control group in non-fasting state.
Ezetimibe/statin affect on postprandial TG and lipoproteins

Prospective, randomized, double blind, crossover trial. Male obese metabolic syndrome patients (*n* = 19) were treated with simvastatin 80 mg and simvastatin/ezetimibe 10 mg/10 mg for 6 weeks.

Fig. 1. Postprandial triglyceride content in lipoprotein fractions. Fig. 2. Postprandial cholesterol content in lipoprotein fractions.

Ezetimibe combination therapy is reduced more postprandial TG than mono-statin after comparable LDL-C lowering.

- Randomized, open-label study, 8 weeks of treatment;
- 60 patients with LDL-C > 130 mg/dL and TG 150-499 mg/dL

* PP TG=post-prandial TG (2h after an oral fat load test)

Lee et al. J Cardiol Pharmacol Ther 2012; 17: 65–71
Take home messages

- For better goal achievement, VYTORIN 10/20mg safely reduced 50% LDL-C from baseline safely at week 6

- VYTORIN achieved non-HDL-C & apo B target goals as well as LDL-C better than statin monotherapy

- VYTORIN 10/20mg reduced incidence of major atherosclerotic events in high risk patients