Lessons from Recent Atherosclerosis Trials

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Change of concept

- Primary vs. secondary prevention
- Low risk vs. High risk
High Risk

CHD and equivalents

CHD; coronary heart disease
“CHD“ or “CHD equivalents“

- Diagnosed CHD

- Vascular disease in noncoronary vascular beds
  (symptomatic carotid disease, aortic aneurysm, peripheral arterial disease)

- Diabetes

CHD ; coronary heart disease
Major Risks
5 Major Risks (NCEP-III; 2002)

Major Risk Factors That Modify LDL Goals *
(Exclusive of LDL Cholesterol)

- Cigarette smoking
- Hypertension
  (blood pressure $\geq 140/90$ mmHg
  or on antihypertensive medication)
- Low HDL cholesterol
  ($< 40$ mg/dL)$^\dagger$
- Family history of premature CHD
  (CHD in male first-degree relative $< 55$ years
   ; CHD in female first-degree relative $< 65$ years)
- Age (men $\geq 45$ years; women $\geq 55$ years)

*Diabetes is regarded as a coronary heart disease (CHD) risk equivalent.
$^\dagger$HDL cholesterol $\geq 60$ mg/dL counts as a “negative” risk factor; its presence removes 1 risk factor from the total count.
Emerging Risks

Metabolic syndrome
Inflammation
Metabolic Syndrome

Diabetes

Atherogenic Dyslipidemia
Convergence
To
Statin
Statin effects:
- LDL reduction
- HDL elevation
- Lower CV events
- Lower Mortality
- Pleiotrophic effects
Statin Pyramid

Key Statin Trials and Spectrum of Risk

- 4S
- LIPID
- HPS
- CARE
- ASCOT-LLA
- WOSCOPS
- AFCAPS/TexCAPS

Increasing absolute CHD risk

- CHD/high cholesterol
- CHD/average to high cholesterol
- CHD*/average to high cholesterol
- CHD/average cholesterol
- Some patients with CHD/average cholesterol
- No MI/high cholesterol
- No CHD/average cholesterol

*CHD or CHD risk equivalent, e.g. diabetes
Diabetes

Major Risks

Emerging Risks
CARD Study; diabetes

2838 with NIDDM 40-75 years
atorvastatin 10 mg/day vs. placebo for 4 years
LDL-C reduction by 40% in atorvastatin group

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5%)</td>
<td>51 (3.6%)</td>
<td>0.64 (0.45-0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>34 (2.4%)</td>
<td>24 (1.7%)</td>
<td>0.69 (0.41-1.16)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.8%)</td>
<td>21 (1.5%)</td>
<td>0.52 (0.31-0.89)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>82 (5.8%)</td>
<td>61 (4.3%)</td>
<td>0.73 (0.52-1.01)</td>
<td>0.059</td>
</tr>
<tr>
<td>Any acute CVD event</td>
<td>189 (13.4%)</td>
<td>134 (9.4%)</td>
<td>0.68 (0.55-0.85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: Only the first acute coronary event, revascularization, or stroke is included in the primary end point.
Symbol size is proportional to amount of statistical information.
CARD = Collaborative Atorvastatin Diabetes Study.

### CARDs: Effect of Treatment on Primary End Point by Lipid Level

<table>
<thead>
<tr>
<th>Median baseline lipids</th>
<th>No. of patients with an event (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥120</td>
<td>66 (9.5%)</td>
<td>44 (6.1%)</td>
<td>0.62 (0.43-0.91)</td>
</tr>
<tr>
<td>&lt;120</td>
<td>61 (8.5%)</td>
<td>39 (5.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>HDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥54</td>
<td>62 (8.5%)</td>
<td>36 (5.2%)</td>
<td>0.59 (0.39-0.89)</td>
</tr>
<tr>
<td>&lt;54</td>
<td>65 (9.6%)</td>
<td>47 (6.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>TG (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥151</td>
<td>67 (9.5%)</td>
<td>40 (5.5%)</td>
<td>0.56 (0.38-0.82)</td>
</tr>
<tr>
<td>&lt;151</td>
<td>60 (8.4%)</td>
<td>43 (6.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>TC (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥209</td>
<td>71 (10.1%)</td>
<td>44 (6.2%)</td>
<td>0.59 (0.41-0.86)</td>
</tr>
<tr>
<td>&lt;209</td>
<td>56 (7.9%)</td>
<td>39 (5.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Symbol size is proportional to amount of statistical information.
P values are for test of heterogeneity.
CARDs=Collaborative Atorvastatin Diabetes Study.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Male/Female, %</th>
<th>62.7/37.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior CVD, %</td>
<td>78.3</td>
</tr>
<tr>
<td>Diabetes management with diet plus one oral hypoglycemic agent %</td>
<td>59.5</td>
</tr>
<tr>
<td>Median duration of diabetes, years</td>
<td>5</td>
</tr>
<tr>
<td>Median HbA1c, %</td>
<td>6.9</td>
</tr>
<tr>
<td>Diabetic complications</td>
<td></td>
</tr>
<tr>
<td>Retinopathy, %</td>
<td>8.3</td>
</tr>
<tr>
<td>Nephropathy, %</td>
<td>2.8</td>
</tr>
<tr>
<td>Lipid parameters, mg/dl</td>
<td></td>
</tr>
<tr>
<td>TC (mean)</td>
<td>194</td>
</tr>
<tr>
<td>LDL-C (mean)</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C (mean)</td>
<td>42</td>
</tr>
<tr>
<td>TG (median)</td>
<td>153</td>
</tr>
<tr>
<td>Dyslipidemic*, %</td>
<td>37</td>
</tr>
</tbody>
</table>

* TG > 150 mg/dL and HDL < 40 mg/dL for men or < 50 mg/dL for women
9,795 Patients With NIDDM

Fenofibrate 200 mg/day, n = 4,895

Placebo, n = 4,900

Average Follow-up: 5 Years and 500 CHD Events

Percentage of Patients

Placebo

Fenofibrate

Statin use At Study Close-Out

32%

16%
Lipid Effects of Fenofibrate At Study Close (patients without statins)

Percentage Change From Baseline at close out (corrected for placebo effect)

- TC: -13.1%
- LDL-C: -14.7%
- HDL-C: 2.1%
- TG: -27.3%
## Benefit on the Primary End Point

<table>
<thead>
<tr>
<th>Fenofibrate Treatment Effect</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>11% (-5 to 25)</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted for statin use*</td>
<td>19% (4 to 32)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Total CVD Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>11% (1 to 20)</td>
<td>0.035</td>
</tr>
<tr>
<td>Adjusted for statin use*</td>
<td>15% (5 to 24)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* Non-randomised comparison adjusting for on-study statin use
Fibrate as a shield

first nonfatal MI or CHD death *
- 19 %

Total CVD events *
- 15 %

retinopathy
- 30 %

microalbuminuria

* ; Adjusted for statin use
• Fenofibrate shows more effect to the patients without prior cardiovascular event
CHD and Diabetes

Major Risks

Emerging Risks
ASCOT-LLA ; hypertension

19342 with hypertension with at least 3 other RFs
40 - 79 yrs, LDL-C 132 mg/dl
Atorvastatin 10 mg, for 3.3 yrs – LDL-C reduction; 29 % 42 mg/dl

- Benefits – reducing
  - Stroke by 27 %
  - Total cardiovascular events by 21 %
  - Total coronary events by 29 %
Primary End Point: Nonfatal MI and Fatal CHD

- **Atorvastatin 10 mg**
  - Number of events: 100

- **Placebo**
  - Number of events: 154

HR = 0.64 (0.50-0.83)  
p=0.0005

36% reduction

Secondary End Point: Fatal and Nonfatal Stroke

27% reduction

HR = 0.73 (0.56-0.96)  p=0.0236

Atorvastatin 10 mg Number of events 89
Placebo Number of events 121

Cumulative Incidence (%)

Years

CHD and Diabetes

Major Risks

Emerging Risks

How?
CARDS
FIELDS
ASCOT-LLA

More?
<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Treatment Comparison</th>
<th>Duration</th>
<th>LDL-C Targets</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>Stable chronic angina</td>
<td>Atorva 80 mg vs. prava 40 mg, for 4.9 yrs</td>
<td>4.9 yrs</td>
<td>130-250 mg/d, TG&lt;600 mg/d</td>
<td>LDL-C in atorva 80 mg/d: 70 mg/dl, in prava 40 mg/d: 97 mg/dl</td>
</tr>
<tr>
<td>TNT</td>
<td>Old myocardial infarction</td>
<td>Atorva 80 mg vs. simva 20 mg, for 4.8 yrs</td>
<td>4.8 yrs</td>
<td>130-250 mg/d, TG&lt;600 mg/d</td>
<td>LDL-C in atorva 80 mg/d: 70 mg/dl, in simva 20 mg/d: 99.8 mg/dl</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Acute coronary syndrome</td>
<td>Atorva 80 mg vs. prava 40 mg, for 2 yrs</td>
<td>2 yrs</td>
<td>130-250 mg/d, TG&lt;600 mg/d</td>
<td>LDL-C in atorva 80 mg/d: 67 mg/dl, in prava 40 mg/d: 97 mg/dl</td>
</tr>
</tbody>
</table>
PROVE-IT: Significant reduction in all-cause mortality, MI, unstable angina, revascularization ≥30 days, and stroke

TNT: Significant reduction in MI and stroke

IDEAL: Significant reduction in nonfatal MI and PVD

LDL-C < 70 mg/dl
Modified LDL Goal; absolute LDL-C levels

**High** risk patients;
<100 mg/dl as a ‘minimal’ goal with ‘standard’ statin dose

**“Very high”** risk patients;
<70 mg/dl is favored (and CRP <2 mg/L)

- very high; CVD with
  1. multiple RFs (esp. DM)
  2. poorly controlled RFs (esp. smoking)
  3. multiple factors of the Metabolic syndrome
     (high TG ≥ 200 plus nonHDL-C ≥ 130 with low HDL-C ≤ 40)
  4. with ACS
“VERY” high risk

Metabolic syndrome

More Risk?

CHD

Diabetes

Major Risks

3 or More? (esp. HT)

high risk
“VERY” high risk "LDLc < 70 mg/dl !!"

Metabolic syndrome

More Risk ?

CHD

high risk "LDLc < 100 mg/dl"

Diabetes

3 or More ? (esp. HT)

Major Risks

high risk "LDLc < 100 mg/dl"
Major Risks

Diabetes: "VERY" high risk

Metabolic syndrome: high risk

LDLc < 70 mg/dl !!

LDLc < 100 mg/dl

3 or More? (esp. HT) → high risk

Statins may be beneficial regardless LDL reduction !!!

LDLc < 100 mg/dl
More High Risks?

GALAXY outcome trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURORA</td>
<td>A long-term, randomised, double-blind, placebo-controlled study to evaluate the effects of CRESTOR 10mg on survival and major cardiovascular events in 2775 subjects with end-stage renal disease on chronic haemodialysis&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>JUPITER</td>
<td>A long-term, randomised, double-blind, placebo-controlled study to assess CRESTOR 20mg in the primary prevention of cardiovascular events in 15000 subjects with low LDL-C levels and elevated levels of C-reactive protein (CRP)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CORONA</td>
<td>A long-term, randomised, double-blind, placebo-controlled study to evaluate CRESTOR 10mg on cardiovascular mortality and morbidity and overall survival in 5016 patients with chronic symptomatic systolic heart failure (NYHA II-IV) of ischaemic aetiology receiving standard treatment</td>
</tr>
</tbody>
</table>

CORONA – Heart Failure

5011 with HF (II or higher) with at least 60 years old
LDL-C around 130 mg/dl
Rosuvastatin 10 mg, for 32.8 mos – LDL-C reduction; 45%

HR = 0.92  HR = 0.95  HR = 0.92
Lowering LDL - Not only how low, But how long?
Brown MS and Goldstein JL
Science 2006, 311:1721

- Statins; lowering LDL–C by 80 mg/dl reducing heart attack only by 40%
- Loss of function of PCSK9;
  lowering LDL–C by only 20 mg/dl reducing heart attack by 80%

- Time really matters.
High Risk?

Lower is Better
Earlier is Better
Low Risk Abandoned? No

MEGA study

Low dose statin to Low risk patients
Primary prevention of cardiovascular disease in Japan. Results of the randomized MEGA Study with pravastatin.
H. Nakamura et. al. AHA2005 (Dallas) MVL-04SL-0206

15,210 consented (Feb 1994 – Mar 1999)
8,214 randomized

Diet (N=4,146)
180 excluded*
2,853 completed f/u at 5 yrs
1,113 consented to continue
3,966 included in analysis

Diet + pravastatin (10-20mg/day) (N=4,068)
202 excluded*
2,756 completed f/u at 5 yrs
1,110 consented to continue
3,866 included in analysis

Average follow-up: 5.3 yrs (Feb 1994 – Mar 2004)

*Excluded patients were selected under blinding, based on information of pre-randomization by data reviewing committee before end of study.
**MEGA Study**

Relatively low-risk Japanese population  
Majority of study subjects; women (68%)  
Baseline LDL-C: 156 mg/dl HDL-C: 57 mg/dl  
LDL-C reduction 18% vs. 3%

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<table>
<thead>
<tr>
<th>End Points At 5-year (35,962 person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
</tr>
<tr>
<td>CHD</td>
</tr>
<tr>
<td>CHD + Cerebral Infarction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Total Mortality</td>
</tr>
</tbody>
</table>
Offense makes the game
Changing Concept

Retard the plaque growth

Stabilize the plaque

Regress the plaque

ASTEROID

ORION

REVERSAL
Example of regression of atherosclerosis (ASTEROID, measured by IVUS)

Baseline IVUS

Follow-up IVUS
24 months statin

Ref: Nissen S et al. JAMA 2006; 295: e-publication ahead of print
ASTEROID – a 2-year study

A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden

Patients (n=507)
CAD, undergoing PCI
Left main coronary artery: ≤50% reduction in lumen diameter
Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment ≥18 years

Rosuvastatin 40 mg (n=507)

Visit: 1–6
Week: 0–6

Eligibility assessment
QCA
Lipids
Tolerability
IVUS
Lipids
Tolerability
Tolerability
Tolerability
Tolerability
Tolerability
QCA
Lipids
Tolerability

CAD=coronary artery disease; PCI=percutaneous coronary intervention; QCA=quantitative coronary angiography; IVUS=intravascular ultrasound
Nissen S. ISA Sep 2003. Poster presentation
Endpoint analysis: Changes in atheroma volume

* p<0.001 for difference from baseline values. Wilcoxon signed rank test
Atherosclerosis Regression Studies

**REVERSAL**
- Atorva 80 mg/d
- For 1.6 yrs
- Basal LDLc 150
- LDLc down to 80
- CRP down by 30 %

**ASTEROID**
- Rosuva 40 mg/d
- For 2 yrs
- 130 mg/dl
- 60-70 mg/dl
- HDL up by 15 %
### Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials

<table>
<thead>
<tr>
<th>Median change in Percent Atheroma Volume (%)</th>
<th>Mean LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>60</td>
</tr>
<tr>
<td>1.2</td>
<td>70</td>
</tr>
<tr>
<td>1.8</td>
<td>80</td>
</tr>
<tr>
<td>-0.6</td>
<td>90</td>
</tr>
<tr>
<td>-1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

#### Citations
- Ref: Nissen S et al. JAMA 2006; 295: e-publication ahead of print
Changing Concept

Quantify the plaque mass

Qualify the plaque composition

ORION
ORION – a 2-year study

Patients (n=33)
Neurologically asymptomatic
Carotid stenosis: 16-79%
LDL; 100-250 mg/dl
TG <400 mg/dl

Rosuvastatin 40 mg or 5 mg

Visit:
1 – 6
2 – 0
3, 4, 5, 6
7, 8
9 – 11
12, 104

Week:

Eligibility assessment
MRI x 2
2 weeks apart
Lipids
Tolerability
Lipids
Tolerability
Lipids
Tolerability
Tolerability
Tolerability
MRI
Changes of plaque composition

<table>
<thead>
<tr>
<th></th>
<th>Combined</th>
<th>Low-dose Rosuvastatin</th>
<th>High-dose Rosuvastatin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LRNC</td>
<td>n</td>
<td>18</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Baseline</td>
<td>10.7 ± 2.5</td>
<td>10.0 ± 5.3</td>
<td>11.3 ± 2.0</td>
<td>.15</td>
</tr>
<tr>
<td>End of study</td>
<td>8.0 ± 2.5</td>
<td>7.9 ± 5.2</td>
<td>8.1 ± 2.0</td>
<td>.14</td>
</tr>
<tr>
<td>Median/mean % change</td>
<td>± 8.1</td>
<td>16.2</td>
<td>± 7.5</td>
<td>.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>–60.3 to –81.5 to 16.9§</td>
<td>–56.8 to –10.8§</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>% Calcification</td>
<td>n</td>
<td>14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0 ± 1.2</td>
<td>4.6 ± 2.3</td>
<td>3.6 ± 1.3</td>
<td>.7</td>
</tr>
<tr>
<td>End of study</td>
<td>4.1 ± 1.1</td>
<td>3.9 ± 2.2</td>
<td>4.3 ± 1.1</td>
<td>.4</td>
</tr>
<tr>
<td>Median/mean % change</td>
<td>0.7/32.4</td>
<td>10.6/6.8</td>
<td>16.7/56.1</td>
<td>.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>–20.8 to 130.3</td>
<td>–68.3 to 281.5</td>
<td>–18.7 to 235.8</td>
<td>–</td>
</tr>
<tr>
<td>P‡</td>
<td>.005</td>
<td>.1</td>
<td>.014</td>
<td>–</td>
</tr>
<tr>
<td>% Fibrous tissue</td>
<td>n</td>
<td>33</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Baseline</td>
<td>92.4 ± 1.9</td>
<td>91.7 ± 3.9</td>
<td>92.9 ± 1.9</td>
<td>.9</td>
</tr>
<tr>
<td>End of study</td>
<td>93.9 ± 1.7</td>
<td>93.3 ± 3.6</td>
<td>94.2 ± 1.7</td>
<td>.95</td>
</tr>
<tr>
<td>Median/mean % change</td>
<td>0.0/1.8</td>
<td>0.0/2.2</td>
<td>0.0/1.6</td>
<td>.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.2-5.5</td>
<td>–0.1 to 6.8</td>
<td>–1.6 to 8.3</td>
<td>–</td>
</tr>
<tr>
<td>P‡</td>
<td>.02</td>
<td>.1</td>
<td>.2</td>
<td>–</td>
</tr>
</tbody>
</table>

* Comparison between low- and high-dose groups.
‡ Comparison to zero of mean percent change from baseline to end of study.
† Robust percent change (SE via bootstrap).
§ 95% CI for mean percent change.
‖ 95% CI for median percent change.
Summary – statin trials

- Identification of high risk
  - Diabetes; **CARDS, FIELD**
  - Hypertension; **ASCOT-LLA**
  - Inflammation; **JUPITER**
  - ESRD?; **AURORA**
  - CHF?; **CORONA**

- New classification; ‘Very’ high risk
  - **MIRA CL - PROVE-IT - TNT - IDEAL**

- Statin effect in low risk
  - **MEGA**

- Beyond prevention; plaque regression/stabilization
  - **REVERSAL**
  - **ASTEROID**
  - **ORION**
Divergence
Statin is like Salt

Statins

Ezetimibe

Torsetrapib

Fibrates

Niacin

Omega-3-fatty acid

Oral Apo A-1
Era of Combination

- Statins
- Ezetimibe
- CETP inhibitor
- Oral Apo A-1
- Fibrates
- Niacin
- Omega-3-fatty acid
Era of Combination

- Statins
- Ezetimibe
- CETP inhibitor
- Oral Apo A-1
- Fibrates
- Omega-3-fatty acid

Studies:
- HATS
- HPS2
- FIELD
- ACCORD
- GISSI-PREVENTIONE
- ENHANCE
- IMPROVE-IT

Phase II - III studies
Conclusion

- Statin treatment shows benefits in high- and very high risk patients regardless basal LDL cholesterol levels

- Ultimate goal of LDL lowering management to those high-risk group is to regress and stabilize the atherosclerotic plaque

- More precise risk stratification is needed to find high- and very high- risk patients ; ex; Metabolic syndrome ?

- More evidence is needed to introduce combination with stain treatment in mixed dyslipidemia