The Atherogenic Dyslipidemia of Diabetes Mellitus-
Not just a question of LDL-C

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Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine
Prevalence of diabetes in 2030

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of people with diabetes (age 20-79)</td>
<td>285 million</td>
<td>438 million</td>
</tr>
<tr>
<td>Prevalence of diabetes (age 20-79)</td>
<td>6.6 %</td>
<td>7.8 %</td>
</tr>
</tbody>
</table>
Estimated life years lost among those with Diabetes

B  Estimated Future Years of Life Lost Owing to Diabetes

Men

- Death from unknown causes
- Noncancer, nonvascular deaths
- Cancer deaths
- Vascular deaths

Women

Seshasai, NEJM. 2011;364(9):829-841
Diabetes doubles the risk of vascular disease

Data from 528,877 participants in 103 studies (adjusted for age sex, cohort, SBP, smoking, BMI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>26 505</td>
<td>2.00 (1.83 - 2.19)</td>
<td>64 (54-71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11 556</td>
<td>2.31 (2.05 - 2.60)</td>
<td>41 (24-54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14 741</td>
<td>1.82 (1.64 - 2.03)</td>
<td>37 (19-51)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11 176</td>
<td>1.82 (1.65 - 2.01)</td>
<td>42 (25-55)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3799</td>
<td>2.27 (1.95 - 2.65)</td>
<td>1 (0-20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1183</td>
<td>1.56 (1.19 - 2.05)</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4973</td>
<td>1.84 (1.59 - 2.13)</td>
<td>33 (12-48)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3826</td>
<td>1.73 (1.51 - 1.98)</td>
<td>0 (0-26)</td>
</tr>
</tbody>
</table>

Lancet. 2010 Jun 26;375(9733):2215-22
The dyslipidemia of intra-abdominal obesity and Type 2 diabetes

**Normal**

**Insulin resistance**

- **VLDL**
  - ↑ VLDL triglycerides
  - ↑ VLDL apo B

- **LDL**
  - ↑ LDL apo B
  - ↑ Particle number
  - ↓ Particle size (small, dense)

- **HDL**
  - ↓ HDL cholesterol
  - ↓ Particle number
  - ↓ Particle size (small, dense)
Structure of Lipoproteins

- Free cholesterol
- Phospholipid
- Triglyceride
- Cholesteryl ester
- Apolipoprotein
Atherogenic Particles

MEASUREMENTS: Apolipoprotein B or Non-HDL-C

TG-rich lipoproteins
HDL can be categorised by shape, size & composition

Particle shape
- Discoidal
- Spherical

Particle size
- HDL_{2b}
- HDL_{2a}
- HDL_{3a}
- HDL_{3b}
- HDL_{3c}

Apolipoprotein composition
- eg A-I HDL
- A-I/A-II HDL
- E-containing HDL

Pre-beta HDL

Adapted from Barter PJ. Atheroscler Suppl. 2002;3:39–47.
Why Does HDL Protect?
Beyond Cholesterol Transport

- Protection against oxidation
- Modulation of endothelial function
- Endothelial repair
- Protection against oxidation
- Modulation of endothelial function
- Cholesterylester donor
- Antithrombotic
- Anti-inflammatory
- Anti-apoptotic
What is the best measure of atherogenic risk 
LDL-C, Non-HDL-C or apo B?

<table>
<thead>
<tr>
<th>Measure</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, per 0.84 mmol/L</td>
<td>1.38</td>
<td>1.09 - 1.73</td>
</tr>
<tr>
<td>Non-HDL-C, per 1.10 mmol/L</td>
<td>1.59</td>
<td>1.36 - 1.85</td>
</tr>
<tr>
<td>Apo B, per 29mg/dl</td>
<td>1.58</td>
<td>1.36 - 1.79</td>
</tr>
<tr>
<td>HDL-C, per 0.38 mmol/L</td>
<td>0.77</td>
<td>0.72 - 0.83</td>
</tr>
<tr>
<td>Apo A-I, per 29mg/dl</td>
<td>0.78</td>
<td>0.72 - 0.86</td>
</tr>
<tr>
<td>Non HDL-C/HDL-C, per 1.53 Unit</td>
<td>1.50</td>
<td>1.38 - 1.62</td>
</tr>
<tr>
<td>Apo B/ Apo A-I, per 0.27 Unit</td>
<td>1.49</td>
<td>1.39 - 1.60</td>
</tr>
<tr>
<td>TG, per 60% change</td>
<td>0.96</td>
<td>0.90 - 1.02</td>
</tr>
</tbody>
</table>

Adjusted for confounding factors and lipid markers

# Recommendations for lipid analyses as treatment target in the prevention of CVD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C is recommended as target for treatment.</td>
<td>I</td>
<td>A</td>
<td>15, 16, 17</td>
</tr>
<tr>
<td>TC should be considered as treatment target if other analyses are not available.</td>
<td>IIa</td>
<td>A</td>
<td>5, 15</td>
</tr>
<tr>
<td>TG should be analysed during the treatment of dyslipidaemias with high TG levels.</td>
<td>IIa</td>
<td>B</td>
<td>52</td>
</tr>
<tr>
<td>Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.</td>
<td>IIa</td>
<td>B</td>
<td>48</td>
</tr>
<tr>
<td>Apo B should be considered as a secondary treatment target.</td>
<td>IIa</td>
<td>B</td>
<td>48, 53</td>
</tr>
<tr>
<td>HDL-C is not recommended as a target for treatment.</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>The ratios apo B/apo A1 and non-HDL-C/HDL-C are not recommended as targets for treatment.</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

Consensus guidelines EHJ 2012
ANDROMEDA study
Comparison of Effectiveness of Rosuvastatin vs Atorvastatin on the Achievement of Combined C-Reactive Protein (<2 mg/L) and Low-Density Lipoprotein Cholesterol (<70 mg/dl) Targets in Patients With Type 2 Diabetes Mellitus

<LDL Cholesterol>

8 weeks
RSV 10 mg
ATV 10 mg
N=240
-51 *

16 weeks
RSV 20 mg
ATV 20 mg
N=229
-57 *

<Triglyceride>

8 weeks
RSV 10 mg
ATV 10 mg
N=240
-17

16 weeks
RSV 20 mg
ATV 20 mg
N=227
-20

<Apo B>

8 weeks
RSV 10 mg
ATV 10 mg
N=240
-31

16 weeks
RSV 20 mg
ATV 20 mg
N=229
-36

RSV = rosvastatin, ATV = atorvastatin
*p<0.001 RSV 10 mg vs ATV 10 mg; RSV 20 mg vs ATV 20 mg
#p=0.032 RSV 10 mg vs ATV 10 mg

CORALL study
A study to COmpare the effect of Rosuvastatin (10–40 mg) with Atorvastatin (20–80 mg) on apo B/apo A-1 ratio in patients with type 2 diabetes mellitus and dyslipidaemia

RSV=rosuvastatin (n=130); ATV=atorvastatin (n=132)
LSM=least-squares mean, *p<0.05 vs ATV; **p<0.01 vs ATV

Do statins work in Diabetes Mellitus?
## Primary Prevention Trials of Lipid-Altering Therapy Including Patients with Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Diabetic,* n</th>
<th>Total N in Study</th>
<th>Lipid-Altering Drug, mg/d</th>
<th>CHD* Risk vs Placebo in Diabetic Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDS †</td>
<td>2,838</td>
<td>2,838</td>
<td>Atorvastatin 10</td>
<td>-37 (p=.001)</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>155</td>
<td>6,605</td>
<td>Lovastatin 20–40 ‡</td>
<td>-44 (NS)</td>
</tr>
<tr>
<td>HPS §</td>
<td>2,912</td>
<td>7,150</td>
<td>Simvastatin 40</td>
<td>-33 (p=.0003)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>2,532</td>
<td>10,305</td>
<td>Atorvastatin 10</td>
<td>-16 (NS)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>623</td>
<td>5,804</td>
<td>Pravastatin 40</td>
<td>+27 (NS)</td>
</tr>
<tr>
<td>HHS</td>
<td>135</td>
<td>4,081</td>
<td>Gemfibrozil 1200</td>
<td>-68 (NS)</td>
</tr>
</tbody>
</table>

* By history
† Prospective trial in diabetic subjects; others are subgroup analyses
‡ Mean 30 mg/d
§ Type 1 or 2 diabetes

Lower LDL-C reduces risk for CHD in DM patients

<CARDS>

**LDL Cholesterol (mmol/L)**

- Average difference 40% (95% CI -41 to -39)
- 1.20 mmol/L; P<0.0001

**The Primary Endpoint**

- Major CV Events Including Stroke

- Relative Risk Reduction 37% (95% CI, -52 to -17)
- P = 0.001

**Placebo**
- 127 events

**Atorvastatin 10mg**
- 83 events

**Median LDL-C (mmol/L)**

- Placebo
- Atorvastatin 10mg

**Years**

- 0 1 2 3 4 4.5

**Cumulative Hazard (%)**

- 0 5 10 15

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* CARDS: Collaborative Atorvastatin Diabetes Study

# LDL-C lowering efficacy on FDA website

## Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

<table>
<thead>
<tr>
<th>Statin</th>
<th>Fluva</th>
<th>Pitava</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Vytorin*</th>
<th>Simva</th>
<th>%↓ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorva</td>
<td>40 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>-----</td>
<td>-----</td>
<td>10 mg</td>
<td>30%</td>
</tr>
<tr>
<td>10 mg</td>
<td>80 mg</td>
<td>2 mg</td>
<td>40 or 80 mg</td>
<td>40 mg</td>
<td>-----</td>
<td>-----</td>
<td>20 mg</td>
<td>38%</td>
</tr>
<tr>
<td>20 mg</td>
<td>-----</td>
<td>4 mg</td>
<td>80 mg</td>
<td>80 mg</td>
<td>5 mg</td>
<td>10/10 mg</td>
<td>40 mg</td>
<td>41%</td>
</tr>
<tr>
<td>40 mg</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>10 mg</td>
<td>10/20 mg</td>
<td>80 mg</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>20 mg</td>
<td>10/40 mg</td>
<td>-----</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>40 mg</td>
<td>10/80 mg</td>
<td>-----</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

Atorva=Atorvastatin; Fluva=Fluvastatin; Pitava=Pitavastatin; Lova=Lovastatin; Prava=Pravastatin; Rosuva=Rosuvastatin; Simva=Simvastatin.

*No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.*
Atherosclerosis & the Diabetic Patient

- Vascular complication associated with type 2 diabetes are the major clinical problems facing patients. ¹
  - Atherosclerosis develops much earlier and progresses more rapidly in diabetic patients than non-diabetics.¹
  - Mortality rates from coronary heart disease are two- to four-fold higher in diabetic patients than in non-diabetics.¹

- Complication of atherosclerosis cause most morbidity & mortality in patients with diabetes.²

- Since most patients with diabetes die from complication of atherosclerosis, they should receive intensive preventive interventions proven to reduce their cardiovascular risk.²

2) Beckman et al. JAMA 2002; 287: 2570-2581
Development of an Atherosclerotic Lesion

Summary of trials employing IVUS to measure changes in atheroma burden. A-PLUS, CAMELOT, ILLUSTRATE and STRADIVARIUS investigated non-statin therapies but included placebo arms who received background statin therapy (62%, 80%, 84%, 100% and 82% respectively). † In ILLUSTRATE atorvastatin was initiated at 10mg during the run-in period and dose titrated up to 80mg to a target LDL-C within 15mg/dL of 100mg/dL. The average dose was 23mg. Patients then remained on this dose during the study. LDL-C levels in CAMELOT are baseline and in A-PLUS are calculated from change from baseline. *Median change in PAV from ASTEROID, REVERSAL & SATURN; LS mean change in PAV from A-PLUS, CAMELOT, ILLUSTRATE & STRADIVARIUS.

Atherosclerosis regression: what is the most important thing?

<ENHANCE Trial>

- ENHANCE: Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression

Atherosclerosis regression: what is the most important thing?

<ARBITER 6-HALTS>

- **HDL-C**
  - **Statin+Niacin**: HDL-C↑18.4% at 14 months (P<0.001)
  - **Statin+Ezetimibe**: No significant change

- **LDL-C**
  - **Statin+Niacin**: LDL-C↓19.2% at 14 months (P=0.01)
  - **Statin+Ezetimibe**: LDL-C↓15.5% at 14 months

· ARBITER 6-HALTS: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies.

Atherosclerosis regression: Manage not only LDL-C but also HDL-C

<ARBITER 6-HALTS>

Primary endpoint
(The change from baseline in the mean common cIMT after 14 months)

<table>
<thead>
<tr>
<th>Months</th>
<th>Statin+Niacin</th>
<th>Statin+Ezetimibe</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.018</td>
<td>-0.012</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-0.014</td>
<td>-0.006</td>
<td>0.003*</td>
</tr>
<tr>
<td>14</td>
<td>-0.010</td>
<td>-0.002</td>
<td></td>
</tr>
</tbody>
</table>

*The P value is given for the comparison of repeated measures of the carotid intima–media thickness over 14–month period.

Relationships Between Change in Percent Atheroma Volume and LDL-C, HDL-C, LDL-C/HDL-C

from REVERSAL, CAMELOT, ACTIVATE, ASTEROID

* PAV: Percent atheroma volume

Nicholls S et al. JAMA 2007; 297(5): 499-508
STELLAR study; 2268 hypercholesterolemic subjects randomized to the rosuvastatin, atorvastatin, simvastatin, and pravastatin groups and followed-up for 6 weeks.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Rosuvastatin</th>
<th>Atorvastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>n=156</td>
<td>n=158</td>
<td>n=165</td>
<td>n=160</td>
</tr>
<tr>
<td>20</td>
<td>n=154</td>
<td>n=156</td>
<td>n=162</td>
<td>n=164</td>
</tr>
<tr>
<td>40</td>
<td>n=156</td>
<td>n=156</td>
<td>n=158</td>
<td>n=161</td>
</tr>
</tbody>
</table>

LS mean % change from baseline:
- Rosuvastatin 10mg: -49.4
- Atorvastatin 10mg: -39.9
- Atorvastatin 20mg: -44.9
- Atorvastatin 40mg: *
- Simvastatin 10mg: -31.6
- Simvastatin 20mg: *
- Simvastatin 40mg: *
- Pravastatin 10mg: *
- Pravastatin 20mg: *
- Pravastatin 40mg: -33.2

*p<0.002 vs Rosuvastatin 10mg
The same LDL-C reduction but the different effect for atherosclerosis (REVERSAL trial)

The solid line indicates the relationship between mean change in low-density lipoprotein cholesterol and change in atheroma volume from linear regression analysis. The dash lines indicate the upper and lower 95% confidence limits for the mean values.

ARTMAP study

Comparison of Effect of Atorvastatin (20mg) Versus Rosuvastatin (10mg) Therapy on Mild Coronary Atherosclerosis Plaque for Korean patients

**<LDL Cholesterol>**

- RSV 10 mg: -49 %
- ATV 20 mg: -47 %

**<Primary endpoint: TAV>**

- RSV 10 mg: -7.4 %
- ATV 20 mg: -3.9 %

*P = 0.018*

* Analysis of covariance

Atherosclerosis and CV outcome
Level of plaque regression is associated with CV outcome?

Progression:
- Compensatory concentric expansion maintains constant lumen
- Expansion overcome lumen starts to narrow

Regression:

Normal vessel → Minimal CAD → Moderate CAD → Severe CAD
Baseline Plaque Burden and CV events

Survival from cardiovascular events (death, myocardial infarction, and coronary revascularization) in 4137 patients in 6 clinical trials that used IVUS stratified according to quartiles (Q) of percent atheroma volume at baseline.

CV=cardiovascular; MI=myocardial infarction

Regression and Outcomes
Atorvastatin vs Pravastatin

Rosuvastatin reduced the risk for major CV event

JUPITER primary endpoint

HR 0.56, 95%CI 0.46-0.69
P < 0.00001

Number Needed to Treat to prevent
The occurrence of one primary endpoint
(NNT) = 25

Relative risk reduction 44%
1.9 yrs

Primary Endpoint : MI, Stroke, UA/Revascularization, CV Death

Moreover Rosuvastatin reduced all cause mortality in primary prevention.

**JUPITER : All cause mortality**

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>CRESTOR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8,901</td>
<td>8,901</td>
</tr>
<tr>
<td>1</td>
<td>8,847</td>
<td>8,852</td>
</tr>
<tr>
<td>2</td>
<td>8,787</td>
<td>8,775</td>
</tr>
<tr>
<td>3</td>
<td>6,999</td>
<td>6,987</td>
</tr>
<tr>
<td>4</td>
<td>4,312</td>
<td>4,319</td>
</tr>
<tr>
<td>5</td>
<td>2,268</td>
<td>2,295</td>
</tr>
<tr>
<td>6</td>
<td>1,602</td>
<td>1,614</td>
</tr>
<tr>
<td>7</td>
<td>1,192</td>
<td>1,196</td>
</tr>
<tr>
<td>8</td>
<td>683</td>
<td>684</td>
</tr>
<tr>
<td>9</td>
<td>227</td>
<td>246</td>
</tr>
</tbody>
</table>

Cumulative Incidence

HR 0.80, 95% CI 0.67-0.97

P = 0.02

Relative risk reduction 20%

*JUPITER secondary endpoints

Safety: New onset of diabetes
Statins & HbA1c levels

1. Removal of the recommendation for routine monitoring of liver enzymes
2. Reports of increased blood glucose and glycosylated hemoglobin (HbA1c) levels
3. New information about reversible cognitive adverse effects
4. New contraindications and dose limitations

Statin and new onset of diabetes (NOD) meta-analysis


Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials


<table>
<thead>
<tr>
<th>Statin</th>
<th>n</th>
<th>Events</th>
<th>Rate</th>
<th>Placebo or control</th>
<th>Events</th>
<th>Rate</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>7773</td>
<td>154</td>
<td>11.9</td>
<td>134</td>
<td>10.5</td>
<td>1.14 (0.89-1.46)</td>
<td>7.07%</td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>14573</td>
<td>335</td>
<td>9.2</td>
<td>293</td>
<td>8.0</td>
<td>1.15 (0.98-1.35)</td>
<td>13.91%</td>
<td></td>
</tr>
<tr>
<td>JUPITER</td>
<td>17802</td>
<td>270</td>
<td>16.0</td>
<td>216</td>
<td>12.8</td>
<td>1.26 (1.04-1.51)</td>
<td>11.32%</td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5974</td>
<td>75</td>
<td>5.2</td>
<td>93</td>
<td>6.5</td>
<td>0.79 (0.58-1.10)</td>
<td>4.24%</td>
<td></td>
</tr>
<tr>
<td>LIPID</td>
<td>6997</td>
<td>126</td>
<td>6.0</td>
<td>138</td>
<td>6.6</td>
<td>0.91 (0.71-1.17)</td>
<td>6.53%</td>
<td></td>
</tr>
<tr>
<td>CORONA</td>
<td>3534</td>
<td>100</td>
<td>20.9</td>
<td>88</td>
<td>18.5</td>
<td>1.14 (0.84-1.55)</td>
<td>4.65%</td>
<td></td>
</tr>
<tr>
<td>PROSPER</td>
<td>5023</td>
<td>165</td>
<td>20.5</td>
<td>127</td>
<td>15.8</td>
<td>1.32 (1.03-1.69)</td>
<td>6.94%</td>
<td></td>
</tr>
<tr>
<td>MEGA</td>
<td>6086</td>
<td>172</td>
<td>10.8</td>
<td>164</td>
<td>10.1</td>
<td>1.07 (0.86-1.35)</td>
<td>8.03%</td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>6211</td>
<td>72</td>
<td>4.5</td>
<td>74</td>
<td>4.6</td>
<td>0.98 (0.70-1.38)</td>
<td>3.76%</td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>4242</td>
<td>198</td>
<td>17.3</td>
<td>193</td>
<td>16.8</td>
<td>1.03 (0.84-1.28)</td>
<td>8.88%</td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>6087</td>
<td>238</td>
<td>16.4</td>
<td>212</td>
<td>14.4</td>
<td>1.15 (0.95-1.41)</td>
<td>10.23%</td>
<td></td>
</tr>
<tr>
<td>GISSI HF</td>
<td>3378</td>
<td>225</td>
<td>34.8</td>
<td>215</td>
<td>32.1</td>
<td>1.10 (0.89-1.35)</td>
<td>9.50%</td>
<td></td>
</tr>
<tr>
<td>GISSI PREV</td>
<td>3460</td>
<td>96</td>
<td>27.5</td>
<td>105</td>
<td>30.6</td>
<td>0.89 (0.67-1.20)</td>
<td>4.94%</td>
<td></td>
</tr>
</tbody>
</table>

Overall (I²=11.2% [95% CI 0.0-50.2%]) 1.09 (1.02-1.17) 100%
Age, independent risk factor for statin-induced NOD

Meta-regression
Age, $p = 0.019$
BMI, $p = 0.177$
$\Delta$ LDLc, $p = 0.102$
Risk for diabetes in participants with and without diabetes risk factor*(JUPITER)

Almost all the excess risk of diabetes with rosuvastatin group occurred in participants with baseline evidence of IFG

*Metabolic Syndrome, IFG, Obesity, HbA1c > 6% at entry
Incident of diabetes according to baseline clinical predictors in the TNT trial

Waters DD. Et al. JACC. 2011;57(14):1535-1545

Patients with new onset diabetes (%)

- Fasting glucose >100 mg/dL
- Triglycerides >150 mg/dL
- BMI >30kg/m²
- History of hypertension

Characteristic absent
Characteristic present

Waters DD. Et al. JACC. 2011;57(14):1535-1545
# Prognosis of Patients with New-Onset T2DM

Waters DD et al. JACC. 2011;

<table>
<thead>
<tr>
<th>Incidence of MCVE</th>
<th>TNT, IDEAL and SPARCL</th>
<th>TNT, IDEAL and SPARCL Atorvastatin 80 mg groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With new-onset T2DM</td>
<td>Without new-onset T2DM</td>
</tr>
<tr>
<td><strong>Univariate analysis</strong></td>
<td>157 / 1,387 (11.3%)</td>
<td>1,884/ 17,472 (10.8%)</td>
</tr>
<tr>
<td>(HR=1.03, 95% CI 0.78-1.35, p=0.83)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td>(HR=1.02, 95% CI 0.77-1.35, p=0.69)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Patients were excluded from the new-onset T2DM study

**MCVEs in patients with and without new-onset T2DM were assessed with an extensive time-dependent Cox proportional hazard analysis
Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:

- With overt CVD (A)
- Without CVD who are over the age of 40 & have one or more other CVD risk factors (A)
Summary

- Diabetes increases risk of cardiovascular event and causes atherogenic dyslipidemia
  (TG↑, small dense LDL↑, HDL↓)
- The vascular disease is main cause of death in diabetes patient, so managing atherosclerosis is essentially needed and rosuvastatin has a strong evidence in this area
- The cardiovascular and mortality benefits of statin therapy exceed the risk for diabetes, including subjects at high risk of developing diabetes.