How to Stop the Progression of Metabolic Syndrome to CV events

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Metabolic syndrome

- Overweight
- Hypertension
- Insulin resistance/hyperglycemia
- Dyslipidemia
- Microalbuminuria
Obesity: an ill-defined modifiable cardiovascular disease risk factor

Global cardiovascular disease risk

- Obesity
  - BMI
- HTN
- DM
- Smoking

- Cholesterol
  - LDL
  - HDL
Features of the metabolic syndrome commonly found among viscerally obese patients

- Hypertriglyceridemia
- Low HDL-cholesterol
- Elevated apolipoprotein B
- Small, dense LDL particles
- Inflammatory profiles
- Insulin resistance
- Hyperinsulinemia
- Glucose intolerance
- Impaired fibrinolysis
- Endothelial dysfunction
The prevalent form of the metabolic syndrome

- Endothelial dysfunction
- Atherogenic dyslipidemia
- Hypertension
- Inflammatory profiles
- Insulin resistance
- Prothrombotic state
Glucotoxicity
- Oxidative stress
- AGE formation
- Hexosamine pathway
- Proinflammatory signaling

Lipotoxicity
- Oxidative stress
- Proinflammatory signaling
- Ceramide

Inflammation
- Proinflammatory factors (TNF-α, IL-1β, IL-6, PAI-1, CRP)
- Kinase & Transcription factors (JNK, IKKβ, IRAK, NK-Kb, AP-1)

Insulin Resistance
- Endothelial Dysfunction

Diabetes
- Obesity
- Dyslipidemia

CAD
- Hypertension
- Atherosclerosis
Insulin Resistance and Atherosclerosis

**Genetics**
- Metabolic Insulin Resistance
- Compensatory Hyperinsulinemia

**Environment**
- Lipotoxicity
- Glucotoxicity
- AGE
- Oxidative Stress

**Vasoconstriction**
- ↓NO, ↑ET-1, ↑VSMC

**Inflammation**
- ↓NO, ↑AngII, ↑IKKβ, ↑NKκB
- ↑TNFα, ↑IL-6, ↑VCAM-1, ↑ICAM-1

**Thrombosis**
- ↓NO, ↑PAI-1

**ACCELERATED ATHEROSCLEROSIS**

**CAD, Stroke, Hypertension, CHF, Vascular Insufficiency**
Relative risk of several cardiovascular disease outcomes associated with metabolic syndrome using WHO or NCEP-ATP III clinical criteria

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>6</td>
<td>1.35 (1.17 – 1.56)</td>
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<tr>
<td>CVD Mortality</td>
<td>6</td>
<td>1.74 (1.29 – 2.35)</td>
</tr>
<tr>
<td>CVD Incidence</td>
<td>8</td>
<td>1.53 (1.26 – 1.87)</td>
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<tr>
<td>CHD Incidence</td>
<td>8</td>
<td>1.52 (1.37 – 1.69)</td>
</tr>
<tr>
<td>Stroke Incidence</td>
<td>3</td>
<td>1.76 (1.37 – 2.23)</td>
</tr>
</tbody>
</table>
Intervention for metabolic syndrome

• **Life style modifications**
  – Dietary approaches
  – Exercise
  – Body weight reduction

• **Medications**
  – Drug targeting insulin resistance & hyperglycemia
  – Drug targeting dyslipidemia
  – Antihypertensive drugs
Links between the AMPK/malonyl-CoA fuel-sensing and signaling network and the metabolic syndrome

Obesity/diet

- Adiponectin
- Leptin
- Thiazolidinedione
- Metformin

Inactivity

Genetic

Altered malonyl-CoA/AMPK

Metabolic syndrome

Exercise

- Low calorie intake
Prevention of type 2 DM with LSM: Finnish Diabetes Prevention Study

• Subjects
  – Middle aged
  – Over-weighted
  – Impaired glucose tolerance
  – 74% metabolic syndrome

• Life style modification: weight reduction
  – Diet
    • Less saturated fat & cholesterol, much dietary fiber
    • Low calorie diet
  – Exercise
    • Moderate endurance exercise

## Prevalence of metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>Year 1</th>
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<th>End</th>
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<td></td>
<td>IG</td>
<td>CG</td>
<td>p</td>
<td>IG</td>
<td>CG</td>
</tr>
<tr>
<td>n</td>
<td>265</td>
<td>257</td>
<td>-</td>
<td>256</td>
<td>250</td>
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<tr>
<td>MS</td>
<td>74.0</td>
<td>73.9</td>
<td>0.913</td>
<td>58.0</td>
<td>67.6</td>
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<tr>
<td>AO</td>
<td>80.0</td>
<td>72.4</td>
<td>0.013</td>
<td>64.5</td>
<td>70.0</td>
</tr>
<tr>
<td>FBS↑</td>
<td>74.7</td>
<td>77.4</td>
<td>0.411</td>
<td>64.8</td>
<td>74.8</td>
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<tr>
<td>BP↑</td>
<td>80.0</td>
<td>80.1</td>
<td>0.937</td>
<td>69.5</td>
<td>70.8</td>
</tr>
<tr>
<td>HDL↓</td>
<td>54.5</td>
<td>51.4</td>
<td>0.286</td>
<td>48.6</td>
<td>52.4</td>
</tr>
<tr>
<td>TG↑</td>
<td>38.3</td>
<td>44.7</td>
<td>0.121</td>
<td>34.8</td>
<td>44.4</td>
</tr>
</tbody>
</table>

Ilanne-Parikka P et al. Diabetes Care 2008;31:805-7
Prevention of type 2 DM with LSM: Finnish Diabetes Prevention Study

Figure 1. Proportion of Subjects without Diabetes during the Trial.

Figure 2. Incidence of Diabetes during Follow-up, According to the Success Score.

Age-adjusted incidence rates (per 1000 person-years) of metabolic syndrome by thirds of Cardiorespiratory fitness in men and women

LaMonte, M. J. et al. Circulation 2005;112:505-12
Healthy food choice

• A wide variety of foods should be eaten
• Energy intake, adjusted to avoid overweight
• Encourage
  – fruit, vegetables, wholegrain cereals and bread, fish, lean meat, low fat dairy products
• Replace saturated fats with
  – above foods
  – with monounsaturated and polyunsaturated fats from vegetable and marine source
  – reduce total fat <30% of energy, of which less than 1/3 is saturated
• Reduce salt intake if blood pressure is raised by avoiding table salt and salt in cooking
  – Fresh or frozen unsalted foods
  – Avoid processed and prepared foods (including bread; high salt)

ESC guidelines for CVD prevention 2007;28:2375-414
Managing total CVD risk, Physical activity

- Stress that positive health benefit occur with almost any increase in activity
  - small amount of exercise have an additive effect
  - exercise opportunities exist in the workplace, for example by using stairs instead of lift
- Leisure activities that are positively enjoyable
- 30 min of moderately vigorous exercise on most days of the week
- Exercising with family or friends
- Sense of well-being, weight reduction, and better self-esteem
- Continued physician encouragement and support

ESC guidelines for CVD prevention 2007;28:2375-414
Modulation of insulin resistance

- Thiazolidinediones
- Metformin
- Acarbose
Systemic and cardiovascular beneficial and adverse effects of PPARγ

PPARγ ACTIVATION

+ INSULIN SENSITIVITY GLUCOSE UPTAKE
+ VASCULAR LESION FORMATION INFLAMMATORY MARKERS ENDOTHELIAL DYSFUNCTION BLOOD PRESSURE
+ OBESITY HEPATIC STEATOSIS
+ FLUID RETENTION FRACTURE

- CARDIAC HYPERTROPHY ↓
- SYSTEMIC BLOOD PRESSURE ↓
- GLUCOSE UPTAKE ↑

SYSTEMIC OEDEMA ↑
CONGESTIVE HEART FAILURE ↑

BENEFICIAL EFFECTS
ADVERSE EFFECTS
Thiazolidinediones: Pioglitazone and Rosiglitazone

- **Mechanism of action**
  - Enhance insulin sensitivity in muscle, adipose tissue
  - Inhibit hepatic gluconeogenesis
  - Reduce rate of beta cell dysfunction

- **Safety and efficacy**
  - Decrease HbA1c 1-2%
  - Adverse effects: edema, weight gain, anemia, peripheral fracture in women, macular edema (MI – rosiglitazone*)

- **Dosing**
  - Initial dose (monotherapy): 1/2 to 2/3 maximum; dosing, 1-2x/day
  - Maximum effective dose: maximum dose
  - Titration frequency: weeks to month(s)

*Use no longer endorsed by ADA*
Kaplan-Meier curves of event rates patients treated with **pioglitazone 45 mg/d vs placebo** in the PROactive study (patients with T2DM and CVD)

**Primary composite end point**
- All-cause mortality, MI, stroke, ACS, coronary or leg revascularization, leg amputation

**Secondary composite end point**
- All-cause mortality, MI, stroke

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*Circulation* 2008;117:440-449
Effect of rosiglitazone on the risk of MI and death from cardiovascular causes

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td></td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td></td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td></td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td></td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

<table>
<thead>
<tr>
<th>Comparator Drug</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.14 (0.70–1.86)</td>
<td>0.59</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1.24 (0.78–1.98)</td>
<td>0.36</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.78 (0.58–13.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.80 (0.95–3.39)</td>
<td>0.07</td>
</tr>
<tr>
<td>Combined comparator drugs</td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Effect of pravastatin for development of CHD and DM in MS (WOSCOPS)

TABLE 3. Univariate and Multivariate Analyses of Metabolic Syndrome as a Predictor of CHD Events (Definite CHD Death or Nonfatal Myocardial Infarction) and New-Onset Diabetes

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>Univariate HR (95% CI)</th>
<th>Multivariate HR (95% CI)§</th>
<th>New-Onset Diabetes Univariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>1.76 (1.44, 2.15)†</td>
<td>1.30 (1.00, 1.67)*</td>
<td>3.51 (2.47, 4.98)†</td>
</tr>
<tr>
<td>Age, 10 y</td>
<td>1.81 (1.51, 2.18)†</td>
<td>1.86 (1.54, 2.26)‡</td>
<td>1.09 (0.80, 1.48)</td>
</tr>
<tr>
<td>BMI, 5 kg/m²</td>
<td>1.13 (0.96, 1.31)</td>
<td>...</td>
<td>2.22 (1.78, 2.76)‡</td>
</tr>
<tr>
<td>SBP, 20 mm Hg</td>
<td>1.29 (1.17, 1.46)‡</td>
<td>1.17 (1.06, 1.32)†</td>
<td>1.22 (1.02, 1.49)*</td>
</tr>
<tr>
<td>DBP, 20 mm Hg</td>
<td>1.40 (1.15, 1.67)‡</td>
<td>...</td>
<td>1.37 (1.00, 1.88)</td>
</tr>
<tr>
<td>Triglycerides, log mmol/L</td>
<td>1.49 (1.17, 1.89)†</td>
<td>...</td>
<td>5.04 (3.34, 7.60)‡</td>
</tr>
<tr>
<td>LDL cholesterol, 38.7 mg/dL</td>
<td>1.22 (0.99, 1.50)</td>
<td>...</td>
<td>1.24 (0.87, 1.78)</td>
</tr>
<tr>
<td>HDL cholesterol, 7.7 mg/dL</td>
<td>0.79 (0.72, 0.87)†</td>
<td>...</td>
<td>0.69 (0.58, 0.81)‡</td>
</tr>
<tr>
<td>Chol:HDL ratio, 1 unit</td>
<td>1.21 (1.13, 1.29)†</td>
<td>1.13 (1.04, 1.22)†</td>
<td>...</td>
</tr>
<tr>
<td>CRP, log mg/L</td>
<td>1.36 (1.24, 1.49)‡</td>
<td>...</td>
<td>1.55 (1.32, 1.82)‡</td>
</tr>
<tr>
<td>Fasting glucose, 7.7 mg/dL</td>
<td>1.19 (0.98, 1.43)</td>
<td>...</td>
<td>7.65 (5.99, 9.31)‡</td>
</tr>
<tr>
<td>Pravastatin treatment</td>
<td>0.71 (0.58, 0.86)‡</td>
<td>0.70 (0.58, 0.86)‡</td>
<td>0.70 (0.49, 0.98)*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.73 (1.42, 2.10)‡</td>
<td>1.73 (1.41, 2.11)‡</td>
<td>1.15 (0.82, 1.61)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*P<0.05, †P<0.01, ‡P<0.001 for 1-SD change or presence/absence of a categoric variable.

§Multivariate analysis considered metabolic syndrome together with classic risk factors (age, lipids, blood pressure, smoking).

RR for CHD in patients with MS 0.73 (95%CI 0.53-1.01)
≈
RR in patients without MS 0.69 (95%CI 0.54-0.89)

Influence of low HDL & high TG on CHD events: 4S

**A**
- Lipid Triad
- Isolated ↑LDL

**B**
- Lipid Triad
- Isolated ↑LDL

**C**
- Lipid Triad
- Isolated ↑LDL

**D**
- Lipid Triad
- Isolated ↑LDL

- Major coronary events
- Coronary mortality
- Total mortality
- Revascularization

*Ballantyne CM et al. Circulation 2001;104:3046-3051*
Reduction of CHD events by Gemfibrozil: Influence of BMI and baseline plasma TG

### Laboratory Findings

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1,182)</td>
<td>(n=808)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (mg/dL)</td>
<td>74.1±43.2</td>
<td>67.8±27.8</td>
<td>&lt;0.001</td>
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<tr>
<td>CK-MB (U/L)</td>
<td>187.2±251.6</td>
<td>190.2±229.6</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Troponin-I (ng/mL)</td>
<td>68.4±101.8</td>
<td>64.4±96.8</td>
<td>0.43</td>
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<td></td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>187.4±46.5</td>
<td>177.4±39.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>150.1±108.7</td>
<td>86.9±45.2</td>
<td>&lt;0.001</td>
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<td></td>
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<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>120.8±41.1</td>
<td>114.0±39.0</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>42.0±11.9</td>
<td>49.5±11.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>hs-CRP (mg/dL)</td>
<td>24.3±116.9</td>
<td>28.0±129.9</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NT-pro-BNP (pg/mL)</td>
<td>2887.4±6938.7</td>
<td>1843.9±3859.7</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
<td>MS (n=1,182)</td>
<td>Control (n=808)</td>
<td>P</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 m F/U</td>
<td>Cardiac death, n (%)</td>
<td>99 (8.4)</td>
<td>57 (7.1)</td>
<td>0.3</td>
<td></td>
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<tr>
<td></td>
<td>Non-cardiac death, n (%)</td>
<td>4 (0.3)</td>
<td>2 (0.3)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, n (%)</td>
<td>10 (0.9)</td>
<td>5 (0.6)</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat PCI, n (%)</td>
<td>20 (1.7)</td>
<td>8 (1.0)</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CABG, n (%)</td>
<td>1 (0.1)</td>
<td>3 (0.4)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 m F/U</td>
<td>Cardiac death, n (%)</td>
<td>110 (9.3)</td>
<td>66 (8.2)</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-cardiac death, n (%)</td>
<td>6 (0.5)</td>
<td>5 (0.6)</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, n (%)</td>
<td>115 (1.3)</td>
<td>7 (0.9)</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat PCI, n (%)</td>
<td>95 (8)</td>
<td>51 (6.3)</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CABG, n (%)</td>
<td>6 (0.5)</td>
<td>3 (0.4)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 m F/U</td>
<td>Cardiac death, n (%)</td>
<td>113 (9.6)</td>
<td>67 (8.3)</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-cardiac death, n (%)</td>
<td>8 (0.7)</td>
<td>11 (1.4)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, n (%)</td>
<td>16 (1.4)</td>
<td>10 (1.2)</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat PCI, n (%)</td>
<td>104 (8.8)</td>
<td>62 (7.7)</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CABG, n (%)</td>
<td>7 (0.6)</td>
<td>4 (0.5)</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Independent Predictors of In-hospital Death

### Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low EF (≤ 40%)</td>
<td>3.98</td>
<td>2.338–6.776</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Old age (≥ 65 years)</td>
<td>3.69</td>
<td>1.856–7.345</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>2.38</td>
<td>1.340–4.223</td>
<td>0.003</td>
</tr>
<tr>
<td>Multivessel involve</td>
<td>1.48</td>
<td>1.080–2.030</td>
<td>0.016</td>
</tr>
<tr>
<td>NT pro-BNP (pg/mL)</td>
<td>1.46</td>
<td>0.823–1.578</td>
<td>0.113</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>1.51</td>
<td>0.857–2.650</td>
<td>0.154</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.27</td>
<td>0.723–2.246</td>
<td>0.403</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.23</td>
<td>0.566–2.691</td>
<td>0.597</td>
</tr>
<tr>
<td>Cr clearance (mL/min)</td>
<td>1.09</td>
<td>0.974–1.103</td>
<td>0.687</td>
</tr>
</tbody>
</table>
Diagnosis and Treatment of MS for the prevention of development of CV disease

- No single treatment
- No therapeutic trials targeting prevention of progression to CV disease in MS

- Advantage in certain populations who have multiple borderline risk factors
- Should emphasize early management of risk factors
## Therapy of MS risk factors

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Goals and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td>5-10% Wt loss or Wt maintenance&lt;br&gt; LMS with diet and increased physical activity&lt;br&gt; Pharmacological wt loss therapy&lt;br&gt; Bariatric surgery</td>
</tr>
<tr>
<td><strong>Insulin resistance</strong></td>
<td>Prevention of delay of progression to T2DM&lt;br&gt; LMS and Wt loss as above&lt;br&gt; Pharmacotherapy&lt;br&gt; Treatment of DM&lt;br&gt; Appropriate glycemic control</td>
</tr>
<tr>
<td><strong>Metabolic dyslipidemia</strong></td>
<td>LDL lowering as per NCEP:ATPIII goals&lt;br&gt; If TG ≥200mg/dL, lower non-HDL to &lt;30 mg/dL+LDL goal&lt;br&gt; If HDL &lt;40 mg/dL in men or &lt;50 in women, consider therapy for HDL raising</td>
</tr>
<tr>
<td><strong>Elevated BP</strong></td>
<td>Goal &lt;140/90 mmHg (&lt;130/80 mmHg if DM or CKD)</td>
</tr>
</tbody>
</table>

*Cornier et al. Endocrine Rev 2008;29:777-822*
Multifactorial intervention and CVD in patients with type 2 DM

Intensive Therapy
1. Dietary intervention
2. Light-to-moderate exercise
   + Intensive Medications

Table 1. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional Therapy</th>
<th>Intensive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>&lt;160 &lt;135</td>
<td>&lt;140 &lt;130</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>&lt;95 &lt;85</td>
<td>&lt;85 &lt;80</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>&lt;7.5 &lt;6.5</td>
<td>&lt;6.5 &lt;6.5</td>
</tr>
<tr>
<td>Fasting serum total cholesterol (mg/dl)</td>
<td>&lt;250 &lt;190</td>
<td>&lt;190 &lt;175</td>
</tr>
<tr>
<td>Fasting serum triglycerides (mg/dl)</td>
<td>&lt;195 &lt;180</td>
<td>&lt;150 &lt;150</td>
</tr>
<tr>
<td>Treatment with ACE inhibitor irrespective of</td>
<td>No Yes Yes Yes</td>
<td></td>
</tr>
<tr>
<td>blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with known ischemia</td>
<td>Yes Yes Yes Yes</td>
<td></td>
</tr>
<tr>
<td>For patients with peripheral vascular disease</td>
<td>No No Yes Yes</td>
<td></td>
</tr>
<tr>
<td>For patients without coronary heart disease</td>
<td>No No No Yes</td>
<td></td>
</tr>
<tr>
<td>or peripheral vascular disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multifactorial intervention and CVD in patients with type 2 DM
Comparison of risk factors

Metabolic risk factors
- BP↑
- DM/hyperglycemia
- Low HDL
- TG↑
- Obesity

Conventional risk factors
- BP↑
- DM
- Total cholesterol↑
- LDL↑
- Smoking
- Advanced age
- Male
- Family Hx. of premature CVS

Prevention
Young age
Elderly
Summary: Management of MS

Metabolic syndrome
- Body fat accumulation↓
- Insulin sensitivity↑
- Glucose tolerance↑
- Plasma LDL cholesterol↓
- Plasma HDL cholesterol↑
- Plasma TG↓
- Blood pressure↓
- Susceptibility to thrombosis↓
- Systemic low-grade inflammation↓
- Arterial endothelial function↑

T2DM↓
Atherosclerosis↓
Myocardial infarction↓
Ischemic stroke↓
PAD↓

Genetics
Age
Gender

Appl Physiol Nutr Metab 2007;32:76-88
• Therapeutic implications in MS to CVD (????)

• LSM is very important

• MS는 각개 격파 하자