Strategy for Retarding Diabetic Macroangiopathy

- Targeting Risk Factors -

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Today’s Talk on Atherosclerosis in Type 2 DM

1. Atherosclerosis in Japanese with DM

2. New Risk Factors for Early Atherosclerosis

3. Medical Treatment Retards Carotid Atherosclerosis

4. Customized Treatment for Subjects With Diabetes
## CVA Rate of T2D in Japan

<table>
<thead>
<tr>
<th></th>
<th>CHD</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JDCS</strong></td>
<td>8.9</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>(M10.7 F6.8)</td>
<td>(M8.5 F7.0)</td>
</tr>
<tr>
<td><strong>Hisayama</strong></td>
<td>5.0</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Non-DM</strong></td>
<td>1.6</td>
<td>1.9-2.3</td>
</tr>
<tr>
<td>(Hisayama)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UKPDS</strong></td>
<td>17.4/14.7</td>
<td>5.6 / 5.0</td>
</tr>
</tbody>
</table>

(CVA Event Rate per 1000 pt x year)
Diabetic Pt Showed High Risk of CHD

Haffner SM et al. NEJM 1998; 339: 229
Approach for CVA in T2D

Detection of High Risk Patients

Diabetes

Custom-made Therapy For Individual Risk

CHD

CVD
Measurement of IMT Using High-Resolution Echo Tomography
Risk Factors Contributing to IMT in Diabetic Subjects

1. Coagulation
2. Genetic Factors
3. Inflammation
4. Oxidative Stress

Yamasaki Y et al. Diabetes 43:634, 1994
Primary Endpoint
Acute CHD Event, Revascularisation, Stroke

Relative risk reduction 37% (95% CI: 17-52)

NNT (4 yrs) = 27

Atorvastatin
83 events

Placebo
127 events

P = 0.001*

* Cox-regression survival analysis

Correlation between Hs-CRP and mean-IMT, max-IMT

Mean-IMT

Max-IMT

y = 0.1015x + 0.7029
$R^2 = 0.1726$

y = 0.0876x + 0.7878
$R^2 = 0.099$

y = 0.0747x + 0.7512
$R^2 = 0.119$
LTA 252 G/G and MTHFR 677 T/T Synergetically Contribute to IMT in Type 2 Diabetes

Yamasaki Y et al. Diabetes Care 29: 2445, 2006
Genetic Risk Factors Synergetically Contribute High Risk of CHD

- ABCA1 1051 G/?
- ACE DD
- LTA 252 GG
- MTHFR 677 TT

Odds Ratio of CHD
## Characteristics of Subjects With This SNP Combination

<table>
<thead>
<tr>
<th>Area (n)</th>
<th>Without (n)</th>
<th>With (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male)</td>
<td>315 / 331</td>
<td>8 / 10</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62.6 ± 7.2</td>
<td>64.6 ± 15.2</td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>12.5 ± 9.4</td>
<td>12.3 ± 9.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 3.2</td>
<td>22.7 ± 3.6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 ± 1.5</td>
<td>7.3 ± 1.0</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>198 ± 37</td>
<td>193 ± 33</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>148 ± 115</td>
<td>143 ± 108</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>54 ± 16</td>
<td>55 ± 18</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 ± 15</td>
<td>143 ± 15</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77 ± 8</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>AveIMT</td>
<td>1.04 ± 0.34</td>
<td>1.43 ± 0.58</td>
</tr>
<tr>
<td>CHD (no/yes)</td>
<td>573/ 73</td>
<td>12/ 6</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. Yamasaki Y et al. Diabetes Care 29: 2445, 2006
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Tight BG Control Retards Carotid Atherosclerosis

HbAic Change

- Poor Control (n=67)
  - Mean ± SE: 6.5%
- Excellent Control (n=33)
  - Mean ± SE: 5.5%

Annual Change in IMT

- Poor Control (n=67)
  - Mean ± SE: 0.08 mm/year
- Excellent Control (n=33)
  - Mean ± SE: 0.04 mm/year

Effects of Cylostazol on IMT & MRI

**IMT**

- **Off**
- **On**

**MRI Image**

- **No Change**
  - Off: 30%
  - On: 41%

- **Worsening**
  - Off: 16%
  - On: 2%

*Tagawa-Shinoda T, Yamasaki Y, et al. Diabetologia 2002*
## Risk Reduction of Stroke by Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subjects</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>High Risk D M</td>
<td>47%</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>D M</td>
<td>44%</td>
</tr>
<tr>
<td>Atrovastatin</td>
<td>Previous C V D</td>
<td>16%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>D M</td>
<td>10%</td>
</tr>
<tr>
<td>Cylostazol</td>
<td>D M with Stroke</td>
<td>64%</td>
</tr>
<tr>
<td>Cylostazol</td>
<td>DM</td>
<td>86%</td>
</tr>
</tbody>
</table>
Several Medication Retard Carotid Atherosclerosis

HbA1c Control vs IMT Retardation

\[ R^2 = 0.35, \ p = 0.01 \]

総頸動脈IMT（Mean IMT）の変化量（最終評価時点）

ピオグリタゾン投与群
ピオグリタゾン非投与群

p; vs. baseline

-0.058mm
p=0.0110

-0.043mm
p=0.0019

NS
総頸動脈IMT（Mean: 左右の平均値）の変化量
—CHICAGO試験との比較—

ピオグリタゾン投与群
- 81 77 74 71 69 66 40 7 (n)

CHICAGO試験群
- 175 166 175 175 (n)

ピオグリタゾン投与群

**p≦0.01（投与前との比較）
*: p≦0.05（投与前との比較）
Methods

Patients with type 2 diabetes and arteriosclerosis obliterans from the Eastern Asian countries were registered online and randomly assigned either to the aspirin group (81–100 mg/day) or the cilostazol group (100–200 mg/day) in this international, 2-year, prospective follow-up interventional study.
# Baseline patient characteristics

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>Cilostazol G (n=116)</th>
<th>Aspirin G (n=134)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent/SDR/PPDR/PDR</td>
<td>87/ 21 / 7 / 1</td>
<td>89 / 28 / 11 / 6</td>
<td>0.1014*</td>
</tr>
<tr>
<td>max IMT-CCA (Left ; mm)</td>
<td>1.22±0.52</td>
<td>1.07±0.33</td>
<td>0.0053</td>
</tr>
<tr>
<td>(Right ; mm)</td>
<td>1.09±0.43</td>
<td>1.04±0.28</td>
<td>0.2956</td>
</tr>
<tr>
<td>mean IMT-CCA (Left ; mm)</td>
<td>0.93±0.35</td>
<td>0.87±0.24</td>
<td>0.0823</td>
</tr>
<tr>
<td>(Right ; mm)</td>
<td>0.84±0.25</td>
<td>0.82±0.19</td>
<td>0.5239</td>
</tr>
<tr>
<td>Resting ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No abnormality;%)</td>
<td>18.1</td>
<td>14.9</td>
<td>0.4985</td>
</tr>
<tr>
<td>Past history of cerebrovascular disorder attacks (%)</td>
<td>10.3</td>
<td>11.2</td>
<td>0.8292</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>4.3</td>
<td>4.5</td>
<td>0.9487</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>4.3</td>
<td>6.7</td>
<td>0.4093</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0.9</td>
<td>0</td>
<td>0.2815</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>0.9</td>
<td>1.5</td>
<td>0.6480</td>
</tr>
<tr>
<td>ABI (Right)</td>
<td>1.06±0.13</td>
<td>1.05±0.12</td>
<td>0.7790</td>
</tr>
<tr>
<td>ABI (Left)</td>
<td>1.04±0.14</td>
<td>1.07±0.11</td>
<td>0.1834</td>
</tr>
</tbody>
</table>

* : Kruskal-Wallis rank-sum test
DAPC study

Study of Diabetic Atherosclerosis Prevention by Cilostazol

Yoshimitsu Yamasaki¹, Young-Seol Kim² and Ryuzo Kawamori³

¹Department of Internal Medicine and Therapeutics, Osaka University Faculty of Medicine
²Department of Internal Medicine, Kyunghee University College of Medicine
³Department of Medicine, Metabolism & Endocrinology, Juntendo University School of Medicine
Patients with type 2 diabetes and arteriosclerosis obliterans from the Eastern Asian countries were registered online and randomly assigned either to the aspirin group (81–100 mg/day; Group A) or the cilostazol group (100–200 mg/day; Group C) in this international, 2-year, prospective follow-up interventional study.
Inclusion criteria

1. Type 2 diabetes mellitus
2. Age between 40 to 85 years
3. Clinical findings suggestive of arteriosclerosis obliterans (ASO)

Note 1: Definition of ASO: Patient who has the following lesions in either of the lower limbs
  • ABI (ankle brachial pressure index) < 1.0
  • A weakened or bilaterally different pulsation of popliteal artery or dorsal artery of foot
  • Clinical signs and symptoms suggestive of ASO
Addition of Genetic Risk Factors Improve IMT Estimation

Classic Risk Factors

Classical & Genetic Risk Factors
MTHFR遺伝子多型と動脈硬化症

頸動脈肥厚

P<0.05

MTHFR Genotype

IMT (mm)

0
1
2
3

P<0.05

MTHFR Genotype

0
1
2
3

頻度（％）

P<0.05

MTHFR Genotype

0
1
2
3

頻度（％）

糖尿病 46:2102, 1997
IMT Change by Pioglitazone on DM With ACE–D allele

Saito et al. J Atherosclerosis & Thrombosis, in press 2009
ACE遺伝子多型と動脈硬化症

頸動脈壁肥厚

- 頸動脈壁肥厚度
- P<0.05

陳旧性心筋梗塞の頻度

- 頻度
- P<0.05

ACE Genotype

Circulation 96: 3782, 1997
IMT Change by Pioglitazone on DM With MTHFR-T allele

Saito et al. J Atherosclerosis & Thrombosis, in press 2009
CVD & Diabetes; Risk Factors

1. Japanese diabetics have high appearance rate of CVD similar to recurrence rate in non-diabetics. (J-ACCESS I)
2. Japanese diabetics with CHD shows high mortality rate, which is related with BG level & MVD. (OACIS Study)
3. HT, dyslipidemia, and chronic inflammation but not MetS are additive risk factors of CVD in Japanese diabetics.
1. Preventive effect of strict glycemic control remains to be resolved. (ACCORD Study, ADVANCE Study)
2. Pioglitazone, ACE-I, Statins reduce CVA of diabetes (PROACTIVE, HOT, CARD, Mega-substudy)
3. Intervention on IGT is more effective compared with that on diabetics. (STOP-NIDDM Study)
4. Carotid IMT as a surrogate marker of CVA in Japanese diabetics is comparable to that of Caucasian diabetics.
5. Pioglitazone is more preventive for IMT of Japanese diabetics compared with that of US diabetics. (Probe Study vs CHICAGO Study)
Custom-made Therapy for Atherosclerosis in Subjects With IGT or Type 2 Diabetes

1. Estimate Atherosclerosis of IGT Subjects or Early-diagnosed Type 2 Diabetes

2. Prescribe Customized Treatment Respecting Individual’s Classical and Genetic Risk Factors

3. Prevent Progression of Atherosclerosis in Subjects with IGT or Type 2 Diabetes

4. Maintain Patients’ QOL within Normal Range