Ischemic Heart and Cerebrovascular Disease

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Kathmandu  November 2010
Relationships Between Diabetes and Ischemic Heart Disease
Risk of Cardiovascular Disease in Different Categories of Glucose Tolerance

- **Normoglycemia**
- **Prediabetes**
- **Type 2 diabetes**

- **CHD**
  - 2-3-fold ↑

- **Stroke**
  - 2-3-fold ↑

- **PVD**
  - 3-5-fold ↑

**Impaired Fasting Glucose**

**Impaired Glucose Tolerance**
Endothelial dysfunction

Endothelial activation

Inflammation

Apoptosis

Fibrous cap formation

Angiogenesis

Thrombosis

HYPERGLYCEMIA

Atherosclerosis

Clinical Event

’East-West Study’: Risk Factors for Cardiovascular Disease in Type 2 Diabetes

- 1059 subjects with type 2 diabetes (Drug Reimbursement Register)
- 1378 non-diabetic subjects
- Age at baseline from 45 to 64 years
- Follow-up data up to 18 years
- Performed in Turku (Dr. Tapani Rönkämä) and Kuopio (ML)
Type 2 Diabetes is 'Coronary Heart Disease Equivalent': 7-year Follow-up Study in Finns


1059 subjects with type 2 diabetes; 1378 non-diabetic subjects
Incidence of Fatal or Nonfatal MI During a 7-Year Follow-up in Relation to History of MI in Nondiabetic vs Diabetic Subjects: *East-West Study*

Type 2 Diabetes is ‘Coronary Heart Disease Equivalent’: 18-year Follow-up Study in Finns

Diabetes Patients Requiring Glucose-Lowering Therapy and Nondiabetics With a Prior Myocardial Infarction Carry the Same Cardiovascular Risk
A Population Study of 3.3 Million People

Elevated Risk of CVD Prior to Clinical Diagnosis of Type 2 Diabetes: Nurses’ Health Study

Relative Risk

- Nondiabetic throughout the study: 1
- Prior to diagnosis of diabetes: 2.82
- After diagnosis of diabetes: 3.71
- Diabetic at baseline: 5.02
EPIC-Norfolk study: risk of CV events or death associated with HbA$_{1c}$ level

HbA$_{1c}$ level: 5–5.4% 5.5–5.9% 6.0–6.4% 6.5–6.9% ≥7%

$P < 0.001$ for linear trend across HbA$_{1c}$ categories for all endpoints.

Dysglycemia and coronary artery disease
Reliability of OGTT in clinical practice

Oral Glucose Tolerance Test: A Reliable Tool for Early Detection of Glucose Abnormalities in Patients With Acute Myocardial Infarction in Clinical Practice

OGTT at discharge
OGTT at 3 months
OGTT after 1 year

Abnormal 67%
Abnormal 66%
Abnormal 65%

(Wallander et al. Diabetes Care 2008; 31:36)
Cardiovascular events in the GAMI trial

OGTT at discharge (n=168)
- DM 33%
- IGT 34%
- NGT 33%

Abnormal 67%

Probability of event free survival

Time to Major Cardiovascular Event

Follow-up (months)

Probability of event free survival

two-sided p = 0.002

(Bartnik et al Eur Heart J 2004;25:1990)
Aspects on prevalence and detection
Euro Heart Survey Diabetes and the Heart

n=4 961

Abnormal glucose regulation 71%
Normal glucose regulation

NGT 31%
IFG 12%
IGT 25%
DM (new) 3%
DM (known) 29%

(Bartnik et al Eur Heart J 2004; 26:1880)
Glycemic control
Experiences from the Euro Heart Survey
Glucose lowering drugs at follow up in patients with newly detected diabetes

Newly detected diabetes
n = 452

Prescribed glucose lowering drugs
77 (17%)

Not prescribed glucose lowering drugs
375 (83%)

(Anselmino et al Eur Heart J 2008;29:177)
Euro Heart Survey diabetes and the heart
Impact of glucose-lowering drugs in newly detected diabetes

Log rank test $p=0.047$

Cumulative event free rate

Glucose-lowering drug

Yes

No

Time of follow up (days)

Cumulative event free rate

(Anselmino et al Eur Heart J 2008;29:177)
CV Risk Factors Cluster Together

The Diabetic Population

DYSLIPIDAEMIA
- 8% of US population has diabetes and dyslipidaemia

OBESITY
- 7% of US population has diabetes and obesity

HYPERTENSION
- 6% of US population has diabetes and HBP

11% of the US adult population has diabetes, but only 0.1% has no co-morbidity
Pathogenesis of CHD in Patients with Type 2 diabetes

Insulin Resistance in Skeletal Muscle
FFAs ↓, Glucose ↓

Hyperinsulinemia

Insulin Resistance in Endothelium
NO synthesis ↓
Adhesion molecules ↓

Aging, Smoking, LDL-C
Elevated blood pressure
Genetic factors

Hyperglycemia
ROS
AGEs

Thrombosis
Plaque rupture

Atherosclerosis

Insulin Resistance in Liver
PAI-1 ↓
Fibrinogen ↓
CRP ↓

Dyslipidemia
HDL ↓, VLDL ↓

Adiponectin
TNF-α, IL-6

FFA ↑

PAI-1
Fibrinogen
CRP

Insulin Resistance- and Hyperglycemia-Related Cardiovascular Disease

LDL cholesterol, smoking and elevated blood pressure are similar risk factors for CVD in non-diabetic and type 2 diabetic subjects.
Prevalence of CHD Is Increased With the Metabolic Syndrome

NHANES III; age ≥50 years

<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalence, age-adjusted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metabolic syndrome, No diabetes</td>
<td>8.7</td>
</tr>
<tr>
<td>No metabolic syndrome, With diabetes</td>
<td>7.5</td>
</tr>
<tr>
<td>With metabolic syndrome, No diabetes</td>
<td>13.9</td>
</tr>
<tr>
<td>With metabolic syndrome, With diabetes</td>
<td>19.2</td>
</tr>
</tbody>
</table>

% of total population

- No metabolic syndrome, No diabetes: 54.2%
- No metabolic syndrome, With diabetes: 2.3%
- With metabolic syndrome, No diabetes: 28.7%
- With metabolic syndrome, With diabetes: 14.8%

NHANES = National Health and Nutrition Examination Survey

CARDS: Primary Prevention of CVD with Atorvastatin in Patients with Type 2 Diabetes

Major coronary events (%)

- Atorvastatin 10 mg (n=1428)
- Placebo (n=1410)

37% relative risk reduction (P=0.001)

Aggressive Statin Intervention in Patients with Diabetes

Previous Statin Trials in Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Intensive</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>159</td>
<td>142</td>
<td>0.89</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 9</td>
<td>61 ± 9</td>
<td>0.89</td>
</tr>
<tr>
<td>NHW</td>
<td>69</td>
<td>62</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>12.0 ± 7.7</td>
<td>12.2 ± 8.3</td>
<td>0.77</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>31.7 ± 4.3</td>
<td>31.3 ± 4.4</td>
<td>0.47</td>
</tr>
<tr>
<td>History of CVD</td>
<td>39</td>
<td>37</td>
<td>0.67</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15</td>
<td>15</td>
<td>0.94</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>78</td>
<td>81</td>
<td>0.49</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132 ± 18</td>
<td>130 ± 16</td>
<td>0.32</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 ± 10</td>
<td>75 ± 11</td>
<td>0.72</td>
</tr>
<tr>
<td>A1C</td>
<td>9.3 ± 1.4</td>
<td>9.3 ± 1.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.64 ± 0.96</td>
<td>4.67 ± 1.01</td>
<td>0.73</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.92 ± 0.27</td>
<td>0.98 ± 0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.65 ± 0.79</td>
<td>2.77 ± 0.79</td>
<td>0.23</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.48 ± 1.64</td>
<td>2.04 ± 1.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin use</td>
<td>57</td>
<td>64</td>
<td>0.23</td>
</tr>
<tr>
<td>TZD use</td>
<td>12</td>
<td>10</td>
<td>0.56</td>
</tr>
<tr>
<td>ASA use</td>
<td>86</td>
<td>86</td>
<td>0.95</td>
</tr>
<tr>
<td>BP medication</td>
<td>91</td>
<td>89</td>
<td>0.61</td>
</tr>
</tbody>
</table>
VA-DT Study: Intensive vs ordinary glycemic control: Effects on CV outcomes as a function of baseline coronary artery calcification

Glycemic Control

Diabetes 58:2642-2648, 2009
VA-DT Study: Intensive vs ordinary glycemic control: Effects on CV outcomes as a function of baseline coronary artery calcification

Diabetes 58:2642-2648, 2009
VA-DT Study: Intensive vs ordinary glycemic control: Effects on CV outcomes as a function of baseline coronary artery calcification

<table>
<thead>
<tr>
<th>CAC Subgroups</th>
<th>Persons</th>
<th>Events</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;100) CAC</td>
<td>180</td>
<td>73</td>
<td>0.21</td>
</tr>
<tr>
<td>Low (≤ 100) CAC</td>
<td>113</td>
<td>12</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific CAC Levels; CAC Modeled on the Log Scale</th>
<th>Persons</th>
<th>Events</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC = 0</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>CAC = 10</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>CAC = 100</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>CAC = 1000</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
</tbody>
</table>

Diabetes 58:2642-2648, 2009
Hypertension Optimal Treatment Trial
Effect on Major Cardiovascular Events - 4 years

51% Risk Reduction vs. < 90 group

Diabetic Patients
n=1501, P=0.005

Non-Diabetic Patients
n=18790, P=NS

Lancet 351: 1755-1762, 1998
Multi-factorial Intervention in Type 2 Diabetes
STENO 2 TRIAL: Targets achieved during the intervention trial

Cumulative Incidence of Death

Cumulative Incidence of CV Events

Stroke in Diabetes

- 2-4 times increased prevalence
- May account for 12-16% of all diabetic deaths
- As high as 20% of people with diabetes have evidence of carotid artery occlusive disease
- BP control can reduce risk by 44%
- Cholesterol reduction can reduce risk by 28%
Risk Ratios of CV Events in Adults with Diabetes Age 35-64

- Total CVD: Men 3, Women 4
- CHD: Men 1.8, Women 3.9
- Cardiac Failure: Men 6.1, Women 9.8
- Intermittent Claudication: Men 2.8, Women 9.1
- Stroke: Men 2.8, Women 1.9

JAMA 259: 1520-1524, 1988
## Death Rate in MRFIT: 12-Year Follow-up

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Diabetes</th>
<th>No Diabetes</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 5,163$</td>
<td>$n = 342,815$</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>85.13</td>
<td>22.88</td>
<td>3.0 (2.8-3.3)</td>
</tr>
<tr>
<td>• CHD</td>
<td>65.91</td>
<td>17.05</td>
<td>3.2 (2.9-3.5)</td>
</tr>
<tr>
<td>• Stroke</td>
<td>6.72</td>
<td>1.75</td>
<td>2.8 (2.0-3.7)</td>
</tr>
<tr>
<td>• Other</td>
<td>12.99</td>
<td>4.08</td>
<td>2.3 (1.8-2.9)</td>
</tr>
<tr>
<td>All Other</td>
<td>160.13</td>
<td>53.20</td>
<td>2.5 (2.4-2.7)</td>
</tr>
</tbody>
</table>

*Age-adjusted. Relative risk adjusted for age, race, income, systolic BP, and smoking.
All male cohort.

*Ann Int Med 124: 123-126, 1996*
UKPDS: Glucose Control Study Results

Intensive Blood Glucose Control Produced a HbA1c Improvement of 0.9% which Resulted in:

<table>
<thead>
<tr>
<th>Change in risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>-12%</td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>-10%</td>
</tr>
<tr>
<td>Myocardial infarction (fatal/nonfatal)</td>
<td>-16%</td>
</tr>
<tr>
<td><strong>Stroke (fatal/nonfatal)</strong></td>
<td><strong>-11%</strong></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>-25%</td>
</tr>
</tbody>
</table>

UKPDS Blood Pressure Study
Tight vs. Less Tight Control

- BP lowered to avg. of 144 / 82 mmHg (controls: 154/87); 9 year follow-up
- 1,148 Type 2 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Risk Reduction (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>24</td>
<td>0.0046</td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>32</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56</td>
<td>0.0043</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td><strong>44</strong></td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>37</td>
<td>0.0092</td>
</tr>
</tbody>
</table>

*BMJ 317: 703-713, 1998*
Risk Reduction (Ramipril vs. Placebo)

## Effects of Simvastatin Treatment on CV Endpoints

<table>
<thead>
<tr>
<th>Type of Major Vascular Event</th>
<th>Simvastatin-allocated (10,269)</th>
<th>Placebo-allocated (10,267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>357 (3.5%)</td>
<td>574 (5.6%)</td>
</tr>
<tr>
<td>Coronary Death</td>
<td>587 (5.7%)</td>
<td>707 (6.9%)</td>
</tr>
<tr>
<td>Subtotal: Major Coronary Event</td>
<td>898 (8.7%)</td>
<td>1212 (11.8%)</td>
</tr>
<tr>
<td>Strokes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>366 (3.6%)</td>
<td>499 (4.9%)</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>96 (0.9%)</td>
<td>119 (1.2%)</td>
</tr>
<tr>
<td>Subtotal: Any Stroke</td>
<td>444 (4.3%)</td>
<td>585 (5.7%)</td>
</tr>
</tbody>
</table>

CARDS: Reduction of Strokes

Risk reduction (95% CI) = 48% (31%, 89%), P = 0.016

No. at risk:
- Atorvastatin: 1428, 1401, 1377, 1093, 714, 343
- Placebo: 1410, 1369, 1341, 1061, 676, 320

TNT Study: Diabetic Population

- 1500 known diabetics
- 5 years treatment
- 753 Atorvastatin 10 mg/day; 748 Atorvastatin 80 mg/day
- Baseline: HbA1c 7.4 % ; BMI 30-31 kg/m² ; BP 135/77 mm Hg
- LDL cholesterol  98.6 vs 76.7 mg/dl
- Triglyceride 177.9 vs 145.1 mg/dl
- HDL cholesterol 44.9 vs 44.0 mg/dl
- Outcomes: Composite CV events 135 vs 103 (RRR = ↓ 25 %
  Cerebrovascular events RRR = ↓ 31 %

TNT primary outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>10.9%</td>
<td>0.78</td>
</tr>
<tr>
<td>CHD death</td>
<td>8.7%</td>
<td>0.80</td>
</tr>
<tr>
<td>NFM</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Resusc arrest</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>All stroke</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>

P value: < 0.001 0.09 0.004 NS 0.02

SUMMARY

☑ Coronary Heart Disease and Stroke are increased 2 to 4 fold in patients with diabetes

☑ Early intensive glycemic control reduces coronary heart disease

☑ Lipid management and blood pressure control have major effects in reducing coronary heart disease

☑ The major factors in reducing strokes are angiotensin converting enzyme inhibitors, blood pressure control and staten therapy