Type 2 Diabetes, Insulin Resistance, and ASCVD: Pathogenic Links and Therapeutic Interventions

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MICROVASCULAR DISEASE

Retinopathy

Nephropathy

Neuropathy
MACROVASCULAR DISEASE

Heart attack

Stroke

PVD (Amputation)
Atherosclerosis in Diabetes

● Accounts for ~ 80% of all mortality in diabetic patients
  – 75% from coronary atherosclerosis
  – 25% from cerebrovascular or peripheral vascular disease

● > 50% of patients with newly diagnosed type 2 diabetes have CHD

Heart diseases were involved in the majority of deaths (69.5%). Diabetes infrequently was listed as cause of death: 7.7% of males; 13.4% of females.
Type 2 Diabetes and Coronary Heart Disease
Seven-Year Incidence of Fatal/Nonfatal MI

WHAT ROLE DOES HYPERGLYCEMIA PLAY IN THE PATHOGENESIS OF ATHEROSCLEROSIS IN T2DM?

DOES GLYCEMIC CONTROL ALONE IMPROVE CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES?
UKPDS: RISK REDUCTION IN DIABETES-RELATED COMPLICATIONS FOR 1% DECLINE IN HbA$_{1c}$

Risk Reduction (%)

-37%**

-14%*

-12%*

-16%*

Microvascular MI Stroke CHF

UKPDS: EPIDEMIOLOGY ANALYSIS

Stratton et al, BMJ 321:405-412, 2000

- **FATAL AND NON-FATAL MYOCARDIAL INFARCTION**
  - 14% decrease per 1% reduction in HbA₁C
  - P<0.0001

- **FATAL AND NON-FATAL STROKE**
  - 12% decrease per 1% reduction in HbA₁C
  - P<0.035

- **MICROVASCULAR END POINTS**
  - 37% decrease per 1% reduction in HbA₁C
  - P<0.0001
SYNDROME OF INSULIN RESISTANCE

- Obesity
- Diabetes
- Hypertension
- Dyslipidemia
- Hypercoagulability (PAI-1, platelets)
- Endothelial Dysfunction
- ASCVD
- Hyperinsulinemia
- Insulin Resistance
TYPE 2 DIABETES IS 2 DISEASES

- MICROVASCULAR
- MACROVASCULAR

WITH 2 DISTINCT PATHOGENIC SEQUENCES

LEADING TO 2 DISTINCT CLINICAL PRESENTATIONS
<table>
<thead>
<tr>
<th>Components</th>
<th>NCEP ATP III</th>
<th>IDF</th>
<th>AHA-NHLBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>≥102 (m)</td>
<td>≥94 (m)</td>
<td>&gt;102 (m)</td>
</tr>
<tr>
<td></td>
<td>&gt;88 (f)</td>
<td>≥80 (f)</td>
<td>&gt;88 (f)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>≥150</td>
<td>≥150*</td>
<td>≥150*</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>&lt;40 (m) &lt;50 (f)</td>
<td>&lt;40 - 50 (m/f)*</td>
<td>&lt;40 - 50(m/f)*</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>≥130/85</td>
<td>≥130 or ≥85*</td>
<td>≥130 or ≥85*</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>≥110</td>
<td>≥100*</td>
<td>≥100*</td>
</tr>
</tbody>
</table>

*Or on drug treatment

ICD-9-CM Code = 277.7
Definitions of Metabolic Syndrome

Waist Circumference

**IDF:**
- Europoid: \( \geq 94 \text{ (m)} \), \( \geq 80 \text{ (f)} \)
- S. Asia: \( \geq 90 \text{ (m)} \), \( \geq 80 \text{ (f)} \)
- Japanese: \( \geq 85 \text{ (m)} \), \( \geq 90 \text{ (f)} \)

**AHA-NHLBI:**
- Asian Americans: \( \geq 90 \text{ (m)} \), \( \geq 80 \text{ (f)} \)
PREVALENCE AND CLINICAL IMPORTANCE OF THE METABOLIC (INSULIN RESISTANCE) SYNDROME
AGE-SPECIFIC PREVALENCE OF THE METABOLIC SYNDROME AMONG 8814 US ADULTS (NHANES III)

~47 million (23.7%) US residents have the metabolic syndrome

PROCAM (Prospective Coronary Artery Munster) Study: Incidence of Myocardial Infarction

2,754 Men, Age 40-65, 4 Year Duration

INSULIN RESISTANCE

IS THE UNIFYING PATHOGENIC DISTURBANCE THAT LINKS ALL COMPONENTS OF THE METABOLIC SYNDROME
“INSULIN CLAMP” FOR EVALUATION OF INSULIN SENSITIVITY

Plasma Glucose

Plasma Insulin

GLUCOSE INFUSION “M” (mg/kg min)

“M” = Glucose infusion Rate = Glucose Metabolized

PLASMA GLUCOSE (mg/dl)

PLASMA INSULIN (mU/ml)

TIME (minutes)
GLUCOSE UPTAKE (mg/m² min)

* p<0.001 vs Control

CONTROL  NORMAL WEIGHT DIABETIC  OBESE NON-DIABETIC

Glucose Storage

Glucose Oxidation
INSULIN RESISTANT STATES ASSOCIATED WITH ACCELERATED Atherosclerosis

**Relative Risk**

- Obesity: $2-3X$
- IGT: $2-2.5X$
- T2DM: $3X$
EFFECT OF DIABETES ON ENDOTHELIAL FUNCTION

Johnstone, Circ 88:2510, 1993

Methacholine (mg/min)

<table>
<thead>
<tr>
<th>Methacholine (mg/min)</th>
<th>Non-diabetic (n=16)</th>
<th>Diabetic (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
EXCESSIVE CALORIC INTAKE  

INHERITED GENETIC DEFECT  

OBESITY  

DIABETES (T2DM)  

INSULIN RESISTANCE  

HYPERINSULINEMIA  

HYPERTENSION  

ATHEROSCLEROSIS  

HYPERTRIGLYCERIDEMIA  

ABNORMAL LDL CHOL PARTICLE  

DECREASED HDL CHOL
What does hypertension have in common with type 2 diabetes mellitus and obesity?
MECHANISM OF INSULIN RESISTANCE IN ESSENTIAL HYPERTENSION, T2DM, AND OBESITY

**Glucose Uptake (mg/m²-min)**

- Lean Control (n=109)
- Lean T2DM (n=57)
- Obese Non-Diabetic (n=42)
- HTN (n=22)

* p<0.001 vs Con

**Glucose Storage**

**Glucose Oxidation**
EFFECT OF HYPERTENSION ON ENDOTHELIAL FUNCTION IN NON-DIABETIC INDIVIDUALS

Panza, J Amer Coll Cardiol 21:1145, 1993

![Graph showing the effect of acetylcholine on forearm blood flow in normotensive and hypertensive individuals.](chart.png)
RELATIONSHIP BETWEEN QUARTILE OF INSULIN SENSITIVITY ($S_i$) AND INCIDENCE OF HYPERTENSION OVER 5 YEARS (n=840)

Goff, Diabetes Care 26:805, 2003
WHAT DOES DYSLIPIDEMIA HAVE IN COMMON WITH T2DM, OBESITY, AND HYPERTENSION?
CONTROLS HYPERCHOLESTEROLEMIA HYPERTRIGLYCERIDEMIA

* Non-oxidative Glucose Disposal

P<0.01

Glucose Oxidation

INSULIN-MEDIATED GLUCOSE DISPOSAL

INSULIN--MEDIATED GLUCOSE DISPOSAL

0 1 2 3 4 5 6

(mg/kg•min)

CONTROLS HYPERCHOLES- TEROLEMIA HYPERTRI- GLYCERIDEMIA
24.9 nm
26.2 nm
25.4 nm

LDL SUBCLASS PATTERN A

SSPG (mmol/l) 6.0 ± 0.4
OGTT - IRI (pmol/l•h) 856 ± 60

LDL SUBCLASS PATTERN B

SSPG (mmol/l) 10.4 ± 1.0 *
OGTT - IRI (pmol/l•h) 1,743 ± 293 **

*p<0.002
**p<0.001
FFA
Glucose

Lipoprotein
Lipase

Insulin

HDL
LDL
IDL
VLDL

Tissues

Insulin

+ 

+ 

−

+ 

−
WHAT DOES CORONARY ARTERY DISEASE HAVE IN COMMON WITH T2DM, OBESITY, DYSLIPIDEMIA, AND HYPERTENSION
INSULIN SENSITIVITY IN THE IRS

Glucose Uptake (mg/m²·min)

- CON
- Lean T2DM
- Obese
- Hypertension
- Hyper-Trigly
- CAD

Hyper-tension
DOES THE PRESENCE OF INSULIN RESISTANCE PREDICT THE DEVELOPMENT OF ASCVD?
RELATIONSHIP BETWEEN CAROTID IMT AND IR* IN 4816 NON-DIABETICS IN MALMO, SWEDEN

Hedblad, Diab Med 17:299, 2000

* > 75th%, based on HOMA-IR

CON

IRS

P < 0.001
MULTIPLE PROSPECTIVE EPIDEMIOLOGIC STUDIES HAVE DEMONSTRATED THAT IRS PREDICTS FUTURE CAD (Botnia, Framingham, SAHS, Bruneck)
Studies Demonstrating Increased Cardiovascular Risk Associated With the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Year</th>
<th>Cardiovascular Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomaa B, et al.</td>
<td>2001</td>
<td>CHD and Stroke (3-fold)</td>
</tr>
<tr>
<td>Onat A, et al.</td>
<td>2002</td>
<td>CHD (70%)</td>
</tr>
<tr>
<td>Alexander CM, et al.</td>
<td>2003</td>
<td>CHD (37%)</td>
</tr>
<tr>
<td>Katzmarzyk PT, et al.</td>
<td>2004</td>
<td>CVD mortality (89%)</td>
</tr>
<tr>
<td>Ford ES, et al.</td>
<td>2004</td>
<td>CVD mortality (37%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke mortality (60%)</td>
</tr>
<tr>
<td>Girman CJ, et al.</td>
<td>2004</td>
<td>Major coronary events (40-50%)</td>
</tr>
<tr>
<td>Malik S, et al.</td>
<td>2004</td>
<td>CHD mortality (2-fold)</td>
</tr>
<tr>
<td>Hunt KJ, et al.</td>
<td>2004</td>
<td>CV mortality (2.8- to 4.7-fold)</td>
</tr>
<tr>
<td>Scuteri A, et al.</td>
<td>2005</td>
<td>Coronary events (38%)</td>
</tr>
</tbody>
</table>
ASSOCIATION BETWEEN HOMA-IR AND 8-YEAR INCIDENCE OF CVD IN NON-DIABETIC SUBJECTS IN SAHS:

187 events in 2,569 subjects

Hanly, Diabetes Care 25:1177, 2002

adjusted for age, sex, BP, LDL, HDL, TG, smoking, exercise, waist circum.
CARDIOVASCULAR MORBIDITY AND MORTALITY ASSOCIATED WITH THE METABOLIC SYNDROME IN BOTNIA STUDY: 3,606 SUBJECTS FOLLOWED FOR 6.9 YEARS

Isomaa, *Diabetes Care* 24:683, 2001

**Relative Risk**

- **CV Morbidity**: 2.96
- **CV Mortality**: 1.81
Isomaa, *Diabetes Care* 24:683, 2001

* highest HOMA quartile
INSULIN RESISTANCE

HYPERINSULINEMIA

DYSLIPIDEMIA

HYPERTENSION

OBESITY

T2DM

ATHEROSCLEROSIS
Syndrome of Insulin Resistance

- Obesity
- Diabetes
- Hypertension
- Aging
- Dyslipidemia
- Increased PAI-1
- Platelet Dysfunction
- Endothelial Dysfunction
- ASCVD
- Hyperinsulinemia
- Insulin Resistance
EXCESS CAROTID IMT IN RELATION TO IRS COMPONENTS: ARIC STUDY

Golden, *Diabetes* 51: 3069, 2002
MOLECULAR ETIOLOGY OF THE INSULIN RESISTANCE SYNDROME
IS THERE A BASIC UNDERLYING BIOCHEMICAL/MOLECULAR DISTURBANCE THAT ACCOUNTS FOR THE DIVERSE PHENOTYPE OF THE INSULIN RESISTANCE (METABOLIC) SYNDROME?
Insulin Receptor
Plasma Membrane

IRS-1
p85 p110

PI-3K

Protein Synthesis
Lipid Synthesis
Glycogen Synthesis

GLUT 4
INSULIN SIGNAL TRANSDUCTION SYSTEM

Insulin Receptor → Plasma Membrane → IRS-1, IRS-2 → PI-3-Kinase → GLUT 4

Shc → MAP kinase → Mitogenesis/Atherosclerosis

TZD (Thiazolidinediones) activates PI-3-Kinase.

GLUT 4 (Glucose Transporter Type 4) is involved in glucose transport.

SNAP 23 and SYN 4 are involved in membrane trafficking.

p85 and p110 are regulatory subunits of PI-3-Kinase.

131361-5/05
TREATMENT OF THE IRS

Insulin Resistance
Hyperinsulinemia
COMPREHENSIVE TREATMENT OF TYPE 2 DIABETIC PATIENTS REDUCES CARDIOVASCULAR DISEASE
Primary Endpoint: CV Death, MI, Stroke, Revascularization, Amputation

Intervention: Diet, Exercise, BP, Lipids, OHA, ASA

HR = 0.47
P = 0.007
INSULIN RESISTANCE SYNDROME

NO STUDIES HAVE EXAMINED WHETHER ANY TREATMENT PREVENTS CAD IN PATIENTS WITH IRS
AT A MINIMUM, ONE MUST TREAT THE INDIVIDUAL COMPONENTS OF IRS
OBESITY
26-Year Incidence of Cardiovascular Disease Based Upon IBW at Entry: Framingham Study

<table>
<thead>
<tr>
<th>Ideal Body Weight (%)</th>
<th>Men Incidence/1,000</th>
<th>Women Incidence/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;110</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>≥110-129</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>130</td>
<td>400</td>
<td>300</td>
</tr>
</tbody>
</table>

Note: IBW = Ideal Body Weight
RELATION BETWEEN BODY MASS INDEX AND RISK OF DIABETES, HYPERTENSION, AND CAD

Nurses Health Survey & Health Prof Follow-up Study
Willata, NEJM 341:427, 1999
Fat Topography In Type 2 Diabetic Subjects

DeFronzo RA
JCEM 89:463-478, 2004
Adipocytes represent a storage depot for energy (i.e., fat). When the capacity of adipocytes to store fat is exceeded, there is an overflow of fat to:

- Muscle → insulin resistance
- Liver → HGP (GN)
- Pancreas ↓ insulin secretion
- Arteries → atherosclerosis
NFκB Serine Kinase

TNFα Inflam Cytokines
Growth factors
iNOS

INFLAMMATION
ATHEROSCLEROSIS

Insulin Receptor
Plasma Membrane

IRSI
p85
PI-3K

GLUT 4

FACoA
IKB
Phos
IKB

Nucleus
Cytosol
MODEST WEIGHT LOSS (5%) HAS A MAJOR BENEFICIAL EFFECT ON OBESITY-RELATED ILLNESSES IMPROVES INSULIN SENSITIVITY AND GLYCEMIC CONTROL
EFFECT OF WEIGHT LOSS ON INSULIN-MEDIATED GLUCOSE DISPOSAL IN OBESE T2DM PATIENTS

Henry, Diabetes 35:990, 1986

Glucose Disposal (mg/m² • min)

Before
Obese Diabetics

After

Lean Controls

*
EFFECT OF WEIGHT LOSS ON FASTING PLASMA GLUCOSE

<table>
<thead>
<tr>
<th>Days on Diet</th>
<th>Fasting Plasma Glucose (mg/dl)</th>
<th>CUM Weight Loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>200</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>
XENDOS:
Effect of Orlistat on Body Weight

Placebo + lifestyle
Orlistat + lifestyle

Change in Weight (kg)

0  0.0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1.0

Week

Sjostrom et al. 9th ICO, Sao Paulo 2002. Poster Presentation

p<0.001 vs placebo
XENDOS: Cumulative Incidence of Type 2 Diabetes

Sjostrom et al. 9th ICO, Sao Paulo 2002. Poster Presentation

**Incidence of T2DM (%)**

- Placebo + lifestyle: 9.0% (RR 37%)
- Orlistat + lifestyle: 6.2%

**p=0.0032**
EFFECT OF ORLISTAT PLUS DIET (WEIGHT LOSS) ON PREVALENCE OF THE METABOLIC SYNDROME BY ATP III CRITERIA

Data on file, Hoffman-La Roche, Nutley, NJ

<table>
<thead>
<tr>
<th>Percent</th>
<th>Before Weight Loss</th>
<th>After Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>33%</td>
<td>23%</td>
</tr>
</tbody>
</table>

BASAL

AFTER WEIGHT LOSS
Incidence of hypercholesterolemia in T2DM patients is similar to that in the general population. HOWEVER,

- The number of LDL particles is increased.
- LDL particles are small and dense.
- HDL cholesterol concentration is reduced.
- Triglyceride level is increased.

This atherogenic lipid/lipoprotein profile contributes to a 2-4-fold excess risk of CVD in patients with type 2 diabetes.

HDL-C and Coronary Artery Disease (CAD) Risk: Framingham Heart Study (Men)

Relationship Between Apo B, LDL Size, and CVD Risk: Quebec CV Study (N=2,057)


Adjusted for DM, SBP, Meds

<table>
<thead>
<tr>
<th>LDL Peak Particle Diameter</th>
<th>Relative Rate for IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>1.0</td>
</tr>
<tr>
<td>Small</td>
<td>1.6</td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>3.4</td>
</tr>
<tr>
<td>Middle Tertile</td>
<td>2.6</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>4.0</td>
</tr>
</tbody>
</table>
TRIGLYCERIDES: INDEPENDENT PREDICTOR OF CHD & STROKE

Asia Pacific Cohort Studies Collaboration

- Fatal CHD
- Fatal or Non-fatal Stroke

Triglycerides (178 mg/dl)

<table>
<thead>
<tr>
<th>Triglycerides (mmol/L)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>HR 1.33 (1.09-1.62)</td>
</tr>
<tr>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

Most patients with TG > 2.0 mM have small dense LDL (Grundy, 2005)

- N=96,224
- Meta-analysis of prospective studies
- Adjusted for CV risk factors

Lancet April 16, 2005;365:1415
Circ. Oct 26, 2004;110:2678-2686
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Control Event Rate</th>
<th>Drug Event Rate</th>
<th>Rel. RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td>4,081</td>
<td>41.4%</td>
<td>27.3%</td>
<td>34%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td>3,090</td>
<td>15.0%</td>
<td>13.6%</td>
<td>9.4%</td>
<td>0.26</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>2,531</td>
<td>21.7%</td>
<td>17.3%</td>
<td>22%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Relationship Between Baseline Triglyceride Concentration and Response to Bezafibrate

**TG <200 mg/dL**
- Placebo: 18, 12, 6
- Bezafibrate: 0, 2, 4, 6

**TG ≥200 mg/dL**
- Placebo: 18
- Bezafibrate: 12

**P = 0.86**

Baseline LDL-C = 148-149 mg/dL

VA-HIT: CHANGE IN LIPIDS FROM BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Gemfibrozil</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-CHOL</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>TRIGLY-CERIDES</td>
<td>3.8</td>
<td>-28.6</td>
</tr>
<tr>
<td>HDL-CHOL</td>
<td>6.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Baseline values:
- LDL-CHOL: 112 mg/dL
- HDL-CHOL: 111 mg/dL
- TRIGLY-CERIDES: 160 mg/dL
- HDL-CHOL: 161 mg/dL
- TG: 32 mg/dL

2351 men with CHD
HDL &leq; 40 mg%
LDL &leq; 140 mg%
TG &leq; 300 mg%

Primary Outcome = Nonfatal MI + Cardiac Mortality

VA-HIT: CVD Risk Reduction in Diabetic Versus Nondiabetic subjects

% Change In Cumulative Event Rate

<table>
<thead>
<tr>
<th></th>
<th>Combined End Point</th>
<th>Nonfatal MI</th>
<th>CHD Death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DM</td>
<td>18</td>
<td>22</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>DM</td>
<td>32</td>
<td>21</td>
<td>41</td>
<td>40</td>
</tr>
</tbody>
</table>

P-values:
- Combined End Point: P=0.004, P=0.07, P=0.17, P=0.09
- CHD Death: P=NS
- Stroke: P=NS

P=0.26

VA-HIT: CVD RISK REDUCTION IN NONDIABETIC PATIENTS


Quartiles of FPI (\(\mu\)U/mL)

- Risk Reduction
  - Favors Placebo
  - Favors Gemfibrozil

N=434
N=442
N=426
N=431

Quartiles:
- <23
- 24-29
- 30-38
- >39
ANTIHYPERTENSIVE TRIALS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

ALLHAT, ASCOT, VALUE, HOPE, HOT, CONVINCE, LIFE, UKPDS, SHEP, Syst-Eur, ABCD, ANBP-2
Diabetics Benefit More From Blood Pressure Control

**Diabetes**

**Non-diabetes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Myocardial Infarction (% reduction)</th>
<th>CV Mortality (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>*</td>
<td>NS</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HOT</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>HOPE</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*Significant reduction

NS: Not significant
INSULIN SENSITIZERS

- Metformin
- Thiazolidinediones
UKPDS: EFFECT OF METFORMIN ON DIABETIC COMPLICATIONS

- Microvascular: 29% risk reduction
- MI: 39% risk reduction
- Stroke: 41% risk reduction
- Death: 42% risk reduction
CARDIOVASCULAR RISK FACTORS

CVRF

1. Hyperglycemia
2. Hypertriglyceridemia
3. Hypercholesterolemia
4. Obesity
5. Hyperinsulinemia
6. Insulin Resistance
7. PAI-1
8. Endothelial Dysfunction

Metformin
INSULIN SENSITIZERS

- Metformin
- Thiazolidinediones
THIAZOLIDINEDIONES AND CARDIOVASCULAR RISK FACTORS

- Hyperglycemia
- Insulin resistance
- Hyperinsulinemia
- Hypertriglyceridemia
- Small, dense LDL-cholesterol
- Decreased HDL-cholesterol
- Increased PAI-1
- Elevated inflammatory cytokines
- Hypertension
- Endothelial dysfunction
- Obesity
EFFECT OF THIAZOLIDINEDIONES ON INSULIN-MEDIATED GLUCOSE DISPOSAL

Miyazaki, *Diabetologia* 44: 2210, 2001
*Diabetes Care* 24: 710, 2001

Before PIO RO SI

NOGD

GOX
PPARγ LIGANDS

- MONOCYTES/ MACROPHAGES
  - EC attachment
  - Migration (MCP-1)
  - Inflammation (TNFα, IL-1, IL-6)
  - Chemokines (IP 10, Mig, I-TAC)

- VSMC
  - Proliferation
  - Migration
  - MMP
  - Adhesion molecules
  - PAI-1

- ENDOTHELIAL CELLS
  - Growth
  - Migration
  - Angiogenesis
  - Nitric Oxide
  - Endothelin
  - PAI-1

ATHEROSCLEROSIS
Effect of Thiazolidinediones on Fat Topography

DeFronzo RA, JCEM 89:463-478, 2004
PROACTIVE

In high risk type 2 diabetics:

- To examine whether pioglitazone reduces total mortality and macrovascular morbidity

19 European Countries

5238 Type 2 Diabetics
PROACTIVE (n=5238)
TIME TO DEATH, MI OR STROKE

LANCET 366:1279-89, 2005

**Plc vs PIO**

Plc vs PIO

**HR** 0.84
**P value** 0.027
Of the total PROactive cohort, 2,445 patients (46.7%) had a previous MI ≥6 months prior to randomization:
- n=1,230 in pioglitazone group
- n=1,215 in placebo group

Pre-specified analyses for MI subgroup:
- Time to fatal or non-fatal MI
- Time to CV death or non-fatal MI
- Time to CV death, non-fatal MI, or stroke

American Heart Association, 2005
Time to Fatal/Nonfatal MI (excluding silent MI)

Kaplan-Meier Event Rate

Events/Number
65/1,230
88/1,215

RR=28%
P=0.045

American Heart Association; 2005
Time to Composite Cardiac Endpoint (Cardiac Death, Non-fatal MI, Coronary Revascularization or ACS) (n=2445)

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Placebo Events</th>
<th>Pioglitazone Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>180/1,230</td>
<td>217/1,215</td>
</tr>
</tbody>
</table>

RR = 19%
P = 0.034

American Heart Association; 2005
CARE Subgroup: Major Coronary Events in Patients With Diabetes and Glucose-Intolerant MI

Placebo vs. Pravastatin vs. Pioglitazone: PROactive

RR=19%

Follow-up (years)

0 1 2 3 4 5 6

Major Coronary Events (%)

0 10 20 30 40

RR=25%, P=0.05

HPS Subgroup: Major Vascular Events (Major Coronary Events, Stroke, and Revascularization) in Patients With Diabetes

RR = 22%
P = 0.0001

Placebo

RR = -17%

Simvastatin

Follow-up (years)

Major Coronary Events (%)

- Pioglitazone: PROactive
- Placebo: PROactive

Therapy Effect of Statin Therapy on Five Year Risk of Recurrent MI in Type 2 Diabetic Patients

Lancet June 14, 2003;361:2005

Baseline Risk: 37.8%

Statin Therapy: 33.4%
Time to Acute Coronary Syndrome

Kaplan-Meier Event Rate

Events/Number
35/1,230
54/1,215
RR=37%
P=0.035

American Heart Association; 2005
PROACTIVE: EFFECT OF PIOGLITAZONE ON PREVENTION OF RECURRENT STROKE IN 894 T2DM INDIVIDUALS WHO ALREADY EXPERIENCED A STROKE

- Placebo: 10.2%
- PIO: 5.6%

P = 0.008

47%
DIABETES PREVENTION PROGRAM (n=3234)

Screening
(age = 51y; BMI = 34 kg/m²)

Intensive Lifestyle Change*

Metformin, 850 mg bid#

Standard Lifestyle Change#

Follow up = 3 years

*Reduce weight by 7%; low-fat diet; exercise for 150 min/wk
#Received information on diet and exercise
DIABETES PREVENTION PROGRAM

% Decrease

IGT T2DM

DIET + EXERCISE

58%

METFORMIN

31%
DIABETES PREVENTION PROGRAM

58% decrease in T2DM

- Diet + Exercise: 58%
- Metformin: 31%
- Troglitazone: 23%

% Decrease
TROGLITAZONE AND PREVENTION OF T2DM IN INDIVIDUALS WITH IGT: 1.5 YEAR FOLLOW-UP

Diabetes Prevention Program, ADA, 2003

*p<0.01 vs LS-Light
**p<0.01 vs LS-Heavy
TREATMENT OF CAD

Insulin Resistance
Hyperinsulinemia

DRUG A

DRUG B

HDL
TG
ASCVD
BP
DIAB

Insulin Resistance
Hyperinsulinemia

BP
DIAB
HDL
TG
ASCVD
IDENTIFICATION OF INSULIN RESISTANT INDIVIDUALS IN CLINICAL PRACTICE

- 2321 INDIVIDUALS
  - 2138 non-diabetic
  - 183 type 2 diabetics
- 17 European sites (EGIR), San Antonio (SAM), Pimas
- Euglycemic insulin clamp
- Measures of obesity, FPG, FPI, lipids, blood pressure, FHD
DISTRIBUTION OF INSULIN SENSITIVITY IN DIABETIC AND NON-DIABETIC SUBJECTS

Relative Frequency

M (µmol/min•kg LBM)

Diabetics
Non-diabetics
Normal Mixture Density Estimate

28
INSULIN RESISTANCE
M<28 umol/kg•min

Fasting plasma insulin >21 uU/ml and HOMA-IR*>4.65 were equally predictive

or

BMI>28.9 kg/m²

*HOMA-IR=[(FPIXFPG)/135]
INSULIN RESISTANCE
M < 28 umol/kg.min

Fasting plasma insulin
≥ 16 uU/ml

and

BMI ≥ 27.5 kg/m²

*HOMA-IR=[FPIXFPG)/135]