Hormones and the Heart:
Is Resistance Futile?

Paul D. Rosenblit MD, PhD, FACE, FNLA

10th Annual UC Irvine Health Orange County Symposium on Cardiovascular Disease Prevention:
"A Decade of Discovery – Then, Now, and Tomorrow “
Saturday, October 13, 2018, Doubletree Hotel,
100 City Drive South, Orange, CA 92868
Hormones and the Heart: Is Insulin Resistance Futile?

Paul D. Rosenblit MD, PhD, FACE, FNLA

10th Annual UC Irvine Health Orange County Symposium on Cardiovascular Disease Prevention: "A Decade of Discovery – Then, Now, and Tomorrow “ Saturday, October 13, 2018, Doubletree Hotel, 100 City Drive South, Orange, CA 92868
Faculty Disclosures*

Dr. Paul D. Rosenblit reported the following relevant financial relationships with commercial interests:

**Speaker/Teaching Faculty**
Akcea Therapeutics/Ionis, Amgen, Janssen, Merck, Novo Nordisk

**Clinical Research Trial Site**
Amgen, Astra-Zeneca (Bristol Myers Squibb), Akcea Therapeutics/Ionis Pharmaceuticals, Boehringer-Ingelheim, Dexcom, GlaxoSmithKline, Lexicon, Mylan Pharma, Novo Nordisk, Sanofi-Regeneron.

**Advisory Board/Consultant**
Akcea Therapeutics/Ionis Pharmaceuticals, Amarin, Amgen, Novo Nordisk, Sanofi-Regeneron.

* 12-month period: July 1, 2017 – June 30, 2018
Discussion Points

- ‘Insulin Resistance’ and relationship to ASCVD & T2DM
  - Insulin Resistance (Metabolic) Syndrome
- Therapeutic (Lifestyle and Pharmacologic) Approaches to Insulin Resistance:
  - Secondary management: T2DM and ASCVD
  - Components of the Syndrome.
  - Primary Prevention: T2DM & ASCVD
What is ‘Insulin Resistance’?
- A patho-physiological state in which a normal amount of insulin produces subnormal cellular responses.

Consequences:
- Hyperinsulinemia
- Hyperglycemia → Diabetes
- Dyslipidemia
- Inflammation
- VSMC Proliferation
- Endothelial Dysfunction
- ASCVD: Stroke & MI
- Affects > 50% non-diabetic stroke patients
- Affects > 60% non-diabetic MI patients
- Affects > 90% patients with Type 2 DM

Insulin Resistance: Changes in Peripheral Glucose Uptake Patients with and without Type 2 Diabetes Mellitus (DM)

For any given insulin level, nondiabetic patients have greater glucose disposal/metabolism (more insulin sensitive).

Glucose disposal was reduced in type 2 diabetic patients and is accounted for by defects in oxidative and nonoxidative glucose metabolism.

Syndrome X (1988)

“Metabolic disturbances commonly cluster in patients with cardiovascular disease” (even without diabetes mellitus)

- Resistance to insulin-stimulated glucose uptake
- Hyperinsulinemia (compensatory)
- Hypertension
- Glucose intolerance
- Increased VLDL-triglycerides
- Decreased HDL-cholesterol

- Resistance to insulin-stimulated suppression of adipose tissue lipolysis $\rightarrow$ ↑↑ free fatty acids
- And, while not required, ‘Syndrome X’ was more common in overweight or obese individuals

Syndrome X-1988
Reaven’s Syndrome

Syndrome of Hyperinsulinemia

DysMetabolic Syndrome-X 2002 AACE, CDC ICD-9 277.7
CardioMetabolic Risk Syndrome

Chronic Cardiovascular DysMetabolic Risk Syndrome
Metabolic Cardiovascular Disease Risk Syndrome

Cholesterol Hypertension Atherosclerosis Obesity Syndrome (CHAOS)- Australia
Carbohydrate Intolerance, Hypertension, Obesity (CHO) Syndrome
Avogaro and Creapaldi (Plurametabolic) Syndrome-1965, 1967
Deadly Quartet Syndrome 1989-Kaplan
Dyslipidemic Hypertension Syndrome
Pluripotential Syndrome
Hypertriglyceridemic Waist Phenotype
Atherogenic Lipoprotein Phenotype (ALP), Berkeley 1988
Pattern B Dyslipidemia Phenotype, 1988
Atherogenic Dyslipidemia Syndrome
Cardio-Metabolic Risk Initiative ADA-2006
Number of Clinical Events Observed as a Function of Tertiles of Insulin Resistance in 208 Non-Diabetic Volunteers
(at mean 6 years follow-up)

Insulin Resistance is a Predictor of Age-Related Diseases

- **CVA**: Type 2 DM
- **CHD**: CA
- **CA**: HTN
- **HTN**: CA

* SSPG = Steady State Plasma Glucose concentrations which represent a direct measure of the ability of insulin to mediate glucose disposal, with higher values representing relatively more insulin resistance

The Many Faces of the Metabolic (Insulin Resistance) Syndrome

PCOS (Polycystic Ovarian Syndrome)
- Infertility, Oligomenorrhea, Hirsutism

GDM (Gestational Diabetes)

Impaired glucose tolerance
Impaired fasting glucose

T2DM (Type 2 Diabetes Mellitus)

Thromboembolism
Atherosclerotic Cardiovascular Disease
- CAD (coronary artery disease)
- Carotid artery disease
- Cerebrovascular disease)
- Renal artery stenosis
- Peripheral artery disease
- Erectile dysfunction

Glomerulosclerosis (Nephropathy)
- Renal insufficiency, Albuminuria, CKD→ESKD

NASH [Non-alcoholic (fatty) liver disease] \(\rightarrow\) ‘Cryptogenic’ cirrhosis

Hypertension
Obesity
Sleep Apnea
Osteoarthritis

Dyslipidemia (TG, HDL)
Alzheimer’s Disease

Gallbladder Disease

Cancer (certain)
- Breast
- Endometrial
- Prostate
- Renal
- Pancreatic

Hyperuricemia (Gout)

Acanthosis Nigricans
“Common Soil” Hypothesis

Type 2 Diabetes Mellitus

Cardiovascular Disease

Atherogenic Dyslipidemia
Hypertension
Inflammation
Glucose intolerance
Metabolic Syndrome
Insulin Resistance
Thrombosis Hypofibrinolysis
Endothelial Dysfunction
Visceral Obesity

Metabolic Syndrome (ATP III def.): Most Common Risk Precursor for Cardiovascular Disease (>60%) and Type 2 Diabetes Mellitus (86-92%)

Metabolic Syndrome (IRS) (24% general pop., 44% pop. >60 yrs old*)

Genetics
Environment
- obesity
- physical inactivity
- high calorie diet (high CHO diet)

Familial beta-cell defect
Type 2 Diabetes Mellitus 86-92%

Glycemia, Duration IRS, Severity IRS

Cardiovascular Disease Morbidity / Mortality (60-75% all CAD)

* NHANES III by NCEP, ATP-III def.
### NCEP-ATP III 2001 Guidelines: Clinical Identification of the Metabolic Syndrome

*(3 or more of the following are needed for the diagnosis)*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>-men</td>
<td>&gt;102 cm (&gt;40 in) → ≥ 94 cm (37.5 in.) males</td>
</tr>
<tr>
<td>-women</td>
<td>&gt;88 cm (&gt;35 in) → ≥ 80 cm (32.0 in.) females</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
</tr>
<tr>
<td>-men</td>
<td>&lt;40 mg/dl</td>
</tr>
<tr>
<td>-women</td>
<td>&lt;50 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dl → *≥100 mg/dL</td>
</tr>
</tbody>
</table>

RIDF) Global Consensus Statement: Worldwide Definition of the Metabolic Syndrome 2005

WOSCOPS: Metabolic Syndrome as a Predictor of CHD and Diabetes

Proposed Role of Insulin Resistance and Compensatory Hyperinsulinemia in Coronary Heart Disease

Genetic Influences → Insulin Resistance → Hyperinsulinemia

Environmental Influences

Glucose Metabolism

Dyslipidemia

PCOS

Hemostatic

Hemodynamic

Endothelial Dysfunction

Uric Acid Metabolism

↑ Triglycerides
PP Lipemia
HDL(2)-C
sd LDL

↑ PAI-1
Fibrinogen

↑ SNS Activity
Na Retention
Blood Pressure

↑ CAMs
ADMA
CNC Binding

↑ Uric Acid
↓ Uric Acid Clearance

 Coronary Heart Disease

Reaven GM. Handbook of Physiology 2001 (supp. 21), The Endocrine System, The Endocrine Pancreas and Regulation of Metabolism
Intra-Abdominal Obesity is Associated with Adverse Metabolic Consequences

Intra-abdominal AT

Subcutaneous AT

Normal Metabolic Profile
- Low Triglycerides
- Normal HDL Cholesterol
- Insulin Sensitive
- Normal Glucose Tolerance
- Normal Inflammatory and Thrombotic Profile

NO METABOLIC SYNDROME

CVD Risk

Altered Metabolic Profile
- Hypertriglyceridemia
- Low HDL Cholesterol
- Insulin Resistance
- Glucose Intolerance
- Pro-inflammatory and Pro-thrombotic Profile

METABOLIC SYNDROME

CVD Risk

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org
Role of Insulin Resistance and Visceral Fat in Atherogenesis

- Overnutrition, Malnutrition, Sedentary state
- Abdominal obesity
- genetics

Macrophages
- Endocrine, Paracrine, Autocrine
- Inflammatory signals
- Fatty acids (Lipotoxicity)

Insulin Resistance hyperinsulinemia

- Hypertension, Dyslipidemia, Hyperglycemia

Fatty Liver
- NAFLD, NASH

TG content
- in Skeletal and Heart Muscle & Epicardium

Monocyte chemotactic protein (MCP)-1, Tumor necrosis factor (TNF)-α, Interlukin (IL)-1, IL-6 and IL-8, have been reported to promote insulin resistance.

‘Chronic Subclinical Inflammation’ as Part of the Insulin Resistance Syndrome: The Insulin Resistance Atherosclerosis Study (IRAS).

Adjusted mean levels of log CRP according to the number of metabolic disorders*

Linear increases in CRP levels paralleled an increase in the number of metabolic disorders.

Mean Values, log ultrasensitive CRP

*Metabolic Disorders (Highest tertiles of):
- Dyslipidemia (TG)
- Upper-body obesity (BMI)
- Insulin resistance
- Hypertension

Mechanisms of Dyslipidemia in Insulin Resistance, Obesity, and Cardiovascular Disease

Resistance to insulin-stimulated suppression of adipose tissue lipolysis → ↑↑↑ free fatty acids

LDL Fractionation via Gradient Gel Electrophoresis

Adapted from Austin M et al. Am J Med (1990)
Greater Atherogenicity of small, dense LDL Relative to Normal LDL

- Susceptible to oxidation
- Binds to arterial wall
- Penetrates arterial wall
- Toxic to endothelial cells
- Promotes PAI-1 production by endothelial cells
- Promotes thromboxane production by endothelial cells
- Accumulates Ca$^{2+}$ in vascular smooth muscle cells
- Binds to LDL scavenger receptor
- Greater number of Apo-B containing particles

Framingham Offspring Study (n = 3,473) : Relationship of LDL Particles (LDL-P) & LDL Cholesterol (LDL-C) to Levels of HDL Cholesterol and Triglycerides


‘Lower HDL-C’ or ‘Higher TG’ associated with greater LDL-P
The Movement of Lipoproteins Particles is Gradient-driven

i.e. a ‘large concentration or number’ of LDL particles is most predictive of IHD
or better a ‘large concentration or number’ of all atherogenic particles (Chylomicron remnants, VLDL-remnants, IDL, LDL is most predictive of IHD
As the number of metabolic factors increased, the concentration of small cholesterol-depleted LDL-P increased, whereas the concentration of large cholesterol-enriched LDL-P decreased. These compositional changes in LDL particles translated into no change in LDL-C, but an increase in total LDL-P. Consistent with the increase in LDL-P, ApoB concentrations increased with increasing numbers of metabolic syndrome components.

Fruchart JC et al., *Am J Cardiol* 2008:102(suppl); 1K-34K.
LDL Particle Number May Be a Better Indicator of CHD Risk Than LDL-C

3,066 participants (mean age 51 yrs; 53% women), without CVD in Framingham Offspring cohort. The main outcome measure was incidence of first CVD event.

CVD event = recognized or unrecognized MI, angina pectoris, coronary insufficiency, CHD death, stroke, TIA, intermittent claudication, or CHF.

• LDL-P was more strongly correlated with the cardiovascular risk than LDL-C was.
• Differences in LDL-C had little effect on event-free survival within both the high LDL-P and low LDL-P participants.

Diabetes

CHD

Insulin Resistance (Metabolic) Syndrome Management

Hypertension

Dyslipidemia

Inflammation

Degrees of Glucose Intolerance

Coagulopathy Thrombosis

Diabetes

CHD

Obesity is an Early & Effective Therapeutic Target for Prevention of T2DM, Hypertension, Dyslipidemia and Coronary Heart Disease

Treatment: Diet, Exercise, Pharmacology Medical Surgery

In Lean and Obese: Treatment of Targeted Risk Factors

Optimal Treatment of Diabetes & CHD

Obesity

Degrees of Glucose Intolerance

Inflammation

Coagulopathy Thrombosis

Obesity is an Early & Effective Therapeutic Target for Prevention of T2DM, Hypertension, Dyslipidemia and Coronary Heart Disease

Treatment: Diet, Exercise, Pharmacology Medical Surgery

In Lean and Obese: Treatment of Targeted Risk Factors

Optimal Treatment of Diabetes & CHD
The Cholesterol Principle*: Criteria for LDL and ASCVD Causality
Supporting the Criticality of Apo B-associated Cholesterol Particle-Lowering

Apo B-containing lipoproteins that carry cholesterol [VLDL, VLDL remnants, CM remnants, IDL & Lp(a) and LDL], directly initiate, & cause progression of, ASCVD in all mammalian species.

>30 randomized trials, >200,000 participants, >30 000 ASCVD events, therapies that consistently reduce LDL-C reduces ASCVD events that are proportional to absolute LDL-C reduction

Monogenic lipid disorders, Prospective cohort studies, Mendelian randomization studies & Randomized Intervention trials all show Biological gradient

Biological gradient demonstrated in all >200 studies, >2 million participants, >20 million person-years F-U & >150,000 CV events

* formerly the ‘Cholesterol Hypothesis’

Unconfounded randomized evidence that LDL is associated with ASCVD, independent of other risk factors

Monogenic- & polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk.

Dose-dependent, log-linear assoc’n between the absolute magnitude of exposure to LDL & ASCVD risk

Monogenic lipid disorders & Mendelian randomization studies demonstrate that exposure to elevated LDL precedes ASCVD onset

Plausibility

Strength

Biological gradient

Temporal sequence

Specificity

Consistency

Coherence

Reduction in risk with intervention

Adapted from:
REACH Registry, n=45,227 patients: Risk of Ischemic Events (CV Death, MI, or Stroke) in Subsequent 4 Years of Follow-up in Out-Patients According to Baseline Risk Category

**Prior Clinical ASCVD**
- Diabetes
- No DM
- MultiVascular Beds
- No Multivascular Beds

**Subclinical ASCVD**
- Extreme Risk = 10-year MACE risk exceeding 30%

**Risk Factors Only**
- High Risk

* Stable coronary, cerebrovascular, or peripheral artery disease without prior MI or stroke events

Bhatt DL, Eagle KA, Ohman EM, for the REACH Registry Investigators. JAMA. 2010;304(12):1350-1357.
Cardiovascular Events in TNT According to Number of Metabolic Syndrome Components

FOURIER (n= 27,342, established CVD) : Cardiovascular Efficacy of Evolocumab by Metabolic Syndrome (MetSyn) Status

60% of FOURIER participants had MetSyn at baseline (mean age, 62 years; 28% women; 87% white; mean BMI, 31 kg/m²) Patients with MetSyn assigned evolocumab experienced a slightly lower mean reduction in LDL vs. those without MetSyn (58% vs. 61%; P < .00001 for both)

Deedwania P et al. presented at European Society of Cardiology (ESC) Congress, Munich, August 28, 2018

The higher the absolute risk, the greater the risk reduction, therefore identifying those at greatest risk distinguishes which patients can benefit most from (PCSK9i) therapy

Incidence of New Onset DM
- MetSyn 4.73%
+MetSyn 4.46%

CV death, MI, Stroke, hospital’n for UA, Coronary revasc.
FOURIER (Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk): Prespecified Analysis by Diabetes Status

N=27,564 patients, aged 40-85 years, Hx clinical ASCVD= (MI, nh-stroke, PAD) 40% Diabetes (DM); Background statin high-intensity (73%) or moderate-intensity.

3-Year Kaplan-Meier Cumulative Incidence Rates Recurrent ASCVD

NNT= Number Needed to Treat

Even Lower is Even Better

Beyond LDL, Triglyceride-rich Lipoprotein (TRL) Clearance Pathway (Lipoprotein Lipase) is Key to Reduced MI Risk

Triglyceride-Rich (Remnant) Lipoproteins and ASCVD: New Insights From Epidemiology, Genetics, and Biology

Like LDL, TGRLPs enter the arterial intima
Unlike LDL
• RLP intima retention > LDL
• Lipolysis produces
  – proinflammatory and pro-coagulant products
• Macrophages uptake RLPs
  – without modification
• RLP-C accumulation + low-grade chronic inflammation promote endothelial dysfunction and thrombosis

### Lipoprotein Cholesterol as a Function of Increasing Levels of Non-Fasting Triglycerides: Copenhagen General Population Study, [(n = 36,160) not on lipid lowering therapy]

<table>
<thead>
<tr>
<th>Non-Fasting Triglycerides</th>
<th>Lipoprotein Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;89</td>
<td>110.4</td>
</tr>
<tr>
<td>89-176</td>
<td>130</td>
</tr>
<tr>
<td>177-265</td>
<td>136.5</td>
</tr>
<tr>
<td>266-353</td>
<td>136.5</td>
</tr>
<tr>
<td>354-442</td>
<td>136.5</td>
</tr>
<tr>
<td>&gt;442</td>
<td>123</td>
</tr>
</tbody>
</table>

Nonfasting Remnant Cholesterol and LDL-C on a Continuous Scale and Risk for Myocardial Infarction, and All-Cause Mortality.

Hazard ratios (HR, blue line) with 95% confidence intervals (gold dashed lines) for endpoints as a function of remnant and LDL cholesterol by use of restricted cubic splines and adjusted. Nonfasting remnant cholesterol was calculated as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol. To convert cholesterol values from mmol/L to mg/dL, divide by 0.0259.

Varbo A, Freiberg JJ, Nordestgaard BG. Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90,000 Individuals from the General Population. Clinical Chemistry 2015;61(3)533-543.
Triglycerides (TG) and TG-Rich Lipoprotein (TGRL) remnants are in the Causal Pathway for CVD and Treatment May Result in CV Benefit

<table>
<thead>
<tr>
<th>Epidemiological Data</th>
<th>Genetic Data</th>
<th>Clinical Data</th>
<th>Outcomes Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated TG correlates with elevated CV risk</td>
<td>TG/TG-rich lipoproteins are in the causal pathway of CVD</td>
<td>Reducing TG in certain subgroups reduces CV risk</td>
<td>No studies completed dedicated to ↑ TG (&gt;2 mmol/L, &gt;180 mg/dL)</td>
</tr>
<tr>
<td>Kasai 2013 (meta)</td>
<td>Van Iperen 2016</td>
<td>Jun 2010 (meta)</td>
<td>Does pharmacological lowering of TG in prospectively enrolled statin-treated patients with elevated TG reduce CV risk?</td>
</tr>
<tr>
<td>Di Angelantonio (ERFC 2009; meta)</td>
<td>Crosby 2014</td>
<td>AIM-HIGH (Guyton 2013; subgroup)</td>
<td></td>
</tr>
<tr>
<td>Women’s Health (Bansal 2007)</td>
<td>Thomsen 2014</td>
<td>FIELD (Scott 2009; subgroup)</td>
<td></td>
</tr>
<tr>
<td>Asia Pacific Cohort (Patel 2004)</td>
<td>Do 2013</td>
<td>JELIS (Saito 2008; subgroup)</td>
<td></td>
</tr>
<tr>
<td>Austin 1998 (meta)</td>
<td>Willer (GLGC) 2013</td>
<td>BIP (Haim 2006; subgroups)</td>
<td></td>
</tr>
<tr>
<td>Copenhagen Male, Jeppesen 1998</td>
<td>Varbo (Circ) 2013</td>
<td>HHS (Manninen 1992; subgroup)</td>
<td></td>
</tr>
<tr>
<td>Framingham Heart (Castelli 1986, 1992)</td>
<td>Schunkert 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Teslovich 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pollin 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wittrup 1999</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes Data
Does pharmacological lowering of TG in prospectively enrolled statin-treated patients with elevated TG reduce CV risk?

- REDUCE-IT (EPA, icosapent ethyl, active, Started 11/2011, Completion 12/2017 25% RRR CV Events)
- STRENGTH (EPA/DHA, omega-3-carboxylic acid), not recruiting, active, PEP 1st MACE, Started: 10/2014, Completion: 11/2019
- PROMINENT (SPPARM in T2DM, Pemafibrate; recruiting)
- Other products in the planning: Synthesis inhibitors of Apo CIII, ANGPTL3.
REDUCE-IT cardiovascular (CV) outcomes study of VASCEPA (icosapent ethyl) capsules

Design overview: Enrolled adult patients with LDL-C between 41-100 mg/dL (median baseline 75 mg/dL) on statin therapy and with various CV risk factors: persistent elevated TGs [150-499 mg/dL (median baseline 216 mg/dL)] and either established CVD (secondary prevention) or DM & at least one other CV risk factor (primary prevention)
Randomized 8,179 pts on a 1:1 basis to statin plus VASCEPA 4g/day or statin plus placebo and compared the incidence of MACE (median F-U 4.9 years
Global trial conducted based on a special protocol assessment agreement with the FDA with statistical power based on 1,612 primary endpoint events

Pre-specified primary composite endpoint in the intent-to-treat population:
• Showed ~25% reduction (P <0.001) in the Primary Endpoint, a 5-point composite of MACE.
  • 5-point composite endpoint = CV death, nonfatal MI, including silent MI, nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization
• Secondary endpoints (multiple) also robust efficacy.

•Safety: VASCEPA well tolerated with a safety profile consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labelling.
•The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups
•FDA has not reviewed and opined on a new drug application related to the REDUCE-IT data. FDA has thus not determined whether to approve VASCEPA for use to reduce the risk of major adverse cardiovascular events in the REDUCE-IT patient population*
Thiazolidinediones (TZD): Nuclear Transcription Factors

TZD

PPARγ

↑ FFA uptake + storage
↑ Insulin sensitivity
↑ Adiponectin

Gene transcription
Gene suppression

RNA

Inflammatory cytokines
NF-κB
Adhesion molecules
Pioglitazone Decrease Visceral Fat and Increases Subcutaneous Fat: The “Abdominal Obesity” Factor is Improved

Case: Male/59 years old

Baseline

Pioglitazone for 16 weeks

MRI Assessment

Subcutaneous Fat Area: 144.3 cm²
Visceral Fat Area: 140.0 cm²
Body Weight: 67.4 kg
FPG: 184 mg/dl
HbA₁c: 7.3 %

Subcutaneous Fat Area: 204.7 cm²
Visceral Fat Area: 105.1 cm²
Body Weight: 69.2 kg
FPG: 117 mg/dl
HbA₁c: 6.5 %

4-month changes
+ 42%
- 25%

Consistent Effect of Thiazoladinediones (troglitazone, pioglitazone, rosiglitazone) on Fat Topography / Magnetic Resonance Imaging

Bays H, Mandarino L, and Defronzo RA J Clin Endocrinol Metab 2004;89:463-478
## Prevention of Type 2 Diabetes Mellitus
### Results of Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Intervention</th>
<th>N in arm, Duration yrs</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish DPS</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>265 3</td>
<td>-58%</td>
</tr>
<tr>
<td>US DPP</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>1,079 4</td>
<td>-58%</td>
</tr>
<tr>
<td>Da Qing DPP</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>192 6</td>
<td>-58%</td>
</tr>
<tr>
<td>US DPP</td>
<td>IGT</td>
<td>Metformin</td>
<td>1,073 4</td>
<td>-31%</td>
</tr>
<tr>
<td>IDPP</td>
<td>IGT</td>
<td>Metformin</td>
<td>133 3</td>
<td>-26%</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>IGT</td>
<td>Acarbose</td>
<td>714 3.3</td>
<td>-25%</td>
</tr>
<tr>
<td>XENDOS</td>
<td>IGT</td>
<td>Orlistat</td>
<td>1,650 4</td>
<td>-45%</td>
</tr>
<tr>
<td>TRIPOD</td>
<td>Prior GDM</td>
<td>Troglitazone</td>
<td>235 3</td>
<td>-55%</td>
</tr>
<tr>
<td>US DPP</td>
<td>IGT</td>
<td>Troglitazone</td>
<td>585 1.5</td>
<td>-75%</td>
</tr>
<tr>
<td>PIPOD</td>
<td>Prior GDM</td>
<td>Pioglitazone</td>
<td>230 3.5</td>
<td>-55%</td>
</tr>
<tr>
<td>DREAM</td>
<td>IFG &amp;/or IGT</td>
<td>Rosiglitazone</td>
<td>2,635 5</td>
<td>-62%</td>
</tr>
<tr>
<td>CANOE</td>
<td>IGT</td>
<td>Rosi2/Met500</td>
<td>207 3.9</td>
<td>-66%</td>
</tr>
<tr>
<td>ACT-NOW</td>
<td>IGT, [2/3,IFG]</td>
<td>Pioglitazone</td>
<td>602 2.4</td>
<td>-72%</td>
</tr>
</tbody>
</table>

DeFronzo RA et al. NEJM. 2011;364(12):1104-1115
Yusuf et al. Lancet. 2006;368:1096-1105
Ziinman B et. al. Lancet 2010; 376: 103–11
Buchanan TA et al. Diabetes. 2002;51:2796-2803
Chiasson JL et al. Lancet. 2002;359:2072-2077
Thiazoladinediones: Risk Reduction
Human Cardiovascular Markers/Surrogates

Favorable Reductions in:
- Insulin resistance
- Insulinemia
- Glycemia
- Free fatty acid release
- Triglycerides and VLDL particle size
- Apo B / LDL ratio
- TChol / HDL ratio
- Systolic and diastolic blood pressure
- Peripheral vascular resistance
- Endothelial dysfunction*
- Microalbuminuria
- Intra-abdominal, muscle, hepatic and pancreatic fat
- Inflammatory factors: Fibrinogen, hs-CRP, IL-6, TNF-a, WBC count, MCP-1, MMP9
- Vascular Markers: VCAM-1, SMC proliferation, Monocyte migration
- Platelet aggregation
- Coagulation factors: PAI-1, fibrinogen

Favorable Increases in:
- Beta-cell responsiveness
- Beta-cell longevity/durability
- Insulin sensitivity (peripheral)
- HDL-C
- HDL particle size
- LDL particle size
- Cardiac output, stroke volume
- Nitric oxide synthesis
- Brachial artery reactivity*
- Adiponectin

Favorable Changes in
Cardiovascular Risks

Not so favorable increases in
- Peripheral / Subcutaneous fat deposition
Carotid Intima-Media THICkness (CIMT) in Atherosclerosis Using PioglitazOne (CHICAGO)


Over an 18 month treatment period in patients with Type 2 DM pioglitazone slowed progression of CIMT compared to glimepiride
"It should be noted that in both DREAM and ACT NOW, cessation of TZD therapy was associated with return of diabetes incidence rates similar to those observed in the placebo group."


3,554 Consecutive pts. + Diabetes evaluated, after successful stent placement for angiographic outcome at 6 mos & for clinical outcomes at 1 yr

<table>
<thead>
<tr>
<th></th>
<th>Diabetes n=715</th>
<th>No Diabetes n=2,839</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis (%)</td>
<td>37.5</td>
<td>28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death (%)</td>
<td>5.7</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death &amp; Non-fatal MI (%)</td>
<td>8</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Repeat PTCA (%)</td>
<td>21.1</td>
<td>15.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Post-stent, compared with pts. without diabetes, pts with diabetes had significantly higher rates of cardiac mortality & combined cardiac death/nonfatal MI & need for repeat PTCA.

No distinction among non-diabetics as to presence or absence of insulin resistance.

Neointimal Hyperplasia After Coronary Stenting: Effect of adding Pioglitazone (30mg/day) to Conventional Anti-Diabetic Therapy* in Type 2 DM

* Conventional antidiabetic therapy (insulin, sulfonylurea, or acarbose) was continued in both groups.

IVUS immediately after stent implantation and 6 months later.

NI [neointimal (tissue proliferation) index] (%) after implantation of a coronary stent

-47% RRR

(P<0.0001).

The stent area (SA), lumen area (LA), neointimal area (NA = SA - LA), and neointimal index (NI = NA/SA x 100%)
Thiazolidinediones on Discharge after Drug Eluding Stent Implantation Decreases 1-Year Mortality

1,719 diabetic patients underwent PCI with DES implantation between 2001 and 2010 (Washington Hospital Center, Washington, DC) divided into 2 groups; Controls vs. TZDs (pioglitazone or rosiglitazone) given on discharge (n=376): The ‘Control’ group was not prescribed TZDs (n=1343). Pt. F/U 3 years for clinical events such as cardiac death, MI, need for revascularization, sub acute stent thrombosis and all cause mortality.

Primary Outcome = composite outcome of death & Q wave MI at 1 yr.
Secondary Outcome = MACE= Death, MI and TVR (target vessel revascularization)

Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) Trial: Primary End-Point (Plaque Volume Changes)

Primary Outcome
* All-cause mortality, stroke, MI, ACS, coronary or peripheral revascularization, & amputation
*Unadjusted

Placebo (572 events)

10% Relative Risk Reduction
HR* 0.84 (0.72–0.98)
p = 0.027

Pioglitazone (514 events)

Pioglitazone (301 events)

Secondary Outcome
3-Point MACE=
All-cause mortality, MI (excluding silent MI), stroke

Placebo (358 events)

16% RRR
HR* 0.84 (0.72–0.98)
p = 0.027

Recruited participants with extensive macrovascular disease defined by ≥1 criteria: MI or stroke ≤ 6 mos., PTCA or CABG, ACS ≤ 3 mos. or objective evidence of CAD or obstructive PAD.

This 3-point MACE sub-analysis was not prespecified and therefore remains "exploratory."

PROACTIVE: Time to Permanent Insulin Use

Pioglitazone use resulted in a 3-year 53% reduced risk of requiring insulin.

Pioglitazone’s Effect on Recurrent MI in Patients with Previous MI

Kaplan-Meier Event Rate

Pioglitazone (65 / 1230)
Placebo (88 / 1215)

HR 0.72, 95 % CI 0.52 - 0.99, p-Value 0.045

Erdmann E. et al. JACC 2007; 49: 1772-1780
PROACTIVE: Pioglitazone’s Effect on Recurrent Stroke in Patients with Previous Stroke: Kaplan-Meier Event Rate

Insulin Resistance Intervention after Stroke (IRIS) Trial: Primary Outcome

Among insulin resistant, non-diabetic patients with a recent ischemic stroke or TIA, to determine if the TZD, pioglitazone, compared with placebo, reduces risk for Stroke or MI.

TZDs (Pioglitazone): Weighing Benefit vs. Risk

Optimists, Hopeful, Cheerleaders, Enthusiasts

- Insulin sensitization
- Beta Cell Preservation
- Improved dyslipidemia
- Reduced Visceral Fat
- Reduced Inflammation
- Reduced atherosclerosis
- Low risk Hypoglycemia
- Reduced MI, Stroke, Mortality

Pessimists, Naysayers, Skeptics, Cynics

- Weight gain
- Edema
- Macular edema???
- Reduced atherosclerosis
- CHF
- Fractures
- Bladder CA???

Increased Subcutaneous Fat
Central Insulin Resistance

Kaplan-Meier Curve– Bromocriptine Quick-Release (QR) Safety Trial:
Cumulative Percent Composite CVD Endpoint (52 week duration)
(n=3,723, mean age 60 yrs, 57% male, 68% Caucasian, 17% AA, 1% Hispanic, 1% Asian)

Baseline pre-existing composite event hx:
39.3% Placebo
33.3% Bromocriptine QR;
Enrolled pts. on ≤2 antidiabetic meds: met, SU, alpha α-glucosidase inhibitor and/or insulin

Cumulative Percent Composite* CVD Endpoint

![Graph showing Kaplan-Meier curve with event rates and time intervals.]

<table>
<thead>
<tr>
<th>Adv. Events</th>
<th>Bromocriptine-QR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>32.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Headache</td>
<td>11.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.8</td>
<td>5.1</td>
</tr>
</tbody>
</table>

RRR=42%
HR 0.58; 95% CI 0.35-0.96

0.8 mg tabs titrated to 4.8 mg or maximally tolerated dose

Bromocriptine-QR
37 events/2,054 (1.8%)


*MI, Stroke, unstable angina hospitalization, CHF hospitalization, or coronary revasc.
Management of Insulin Resistance is **Not** Futile, But Requires Global Cardio-Metabolic Risk Management

Insulin Resistance

- **Hypertension**
- **Dyslipidemia**
- **Inflammation**
- **Coagulopathy & Thrombosis**

**Obesity**

- **Degrees of Glucose Intolerance**

**Treatment:** Diet, Exercise, Pharmacology, Medical Surgery

- **In Lean and Obese:** Treatment of Targeted Risk Factors
- **Optimal Treatment of Diabetes & CHD**

Obesity is an Early & Effective Therapeutic Target for Prevention of T2DM, Hypertension, Dyslipidemia and Coronary Heart Disease
Thank you
Classical Lifestyle and Pharmaceutical Treatments for Insulin Resistance

- Reduced Calories, for weight loss and maintenance.
- ‘Low-Glycemic-Index’ foods [reduced simple sugars diets, increased fiber (esp. foods containing fiber)]
- Low Fat, without increasing simple CHOs
- High protein, without increasing saturated fat
- Vegetarian diets, without high glycemic index (simple CHOs)
- Trial proven compositions: Mediterranean, Dash
- Physical Activity/Exercise: Resistance Training Combined with Aerobic Training Improves Insulin Sensitivity. 15 minutes of high-intensity exercise, three days a week
- Reduce stress: Yoga, meditation relax patients.
- Good Sleep habits: Deep, restorative sleep, also called slow-wave sleep
Physical Activity Persistence Influences Obesity, Insulin Resistance, and Diabetes

- Insulin action is greater in physically active than sedentary individuals.\(^1\)
- A single exercise session can increase insulin-stimulated glucose uptake in previously sedentary adults.\(^2\)
- A single bout of moderate intensity exercise can increase glucose uptake by skeletal muscle at least 40\%.\(^3\)
- The benefits of exercise dissipate ~48 to 72 h from last exercise session.\(^4\)
- Cessation of exercise even in trained persons is associated with a marked and rapid decrease in insulin sensitivity.\(^5\)
- Exercise with or without weight loss improves insulin sensitivity.\(^6\)
- The long-term impact of exercise training on insulin sensitivity is mediated and magnified by diminished body weight and/or adiposity.\(^7,8\)

## Preferred/Approved Weight Loss Medications in Patients with Obesity (especially if Hypertension)

<table>
<thead>
<tr>
<th>Preference</th>
<th>Obesity Medication</th>
<th>Medication References &amp; Notes</th>
<th>Clinical Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Phentermine/Topiramate ER</td>
<td>BP decreased by 3.2/1.1 mmHg placebo subtracted (1)</td>
<td>Monitor heart rate</td>
</tr>
<tr>
<td>1st</td>
<td>Liraglutide 3 mg</td>
<td>BP decreased by 2.8/0.9 mmHg placebo subtracted (21)</td>
<td>Monitor heart rate</td>
</tr>
<tr>
<td>1st</td>
<td>Orlistat</td>
<td>BP decreased by 2.1/1.0 mmHg placebo subtracted at 1 year (12)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Lorcaserin</td>
<td>BP decreased by 0.6/0.5 mmHg placebo subtracted at 1 year (15)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>Naltrexone ER / Bupropion ER</td>
<td><strong>Contraindicated if BP is uncontrolled.</strong> No change from baseline despite weight loss (17) or decrements less than observed in placebo (SBP -1.3 vs 3.0; DBP 1.4 vs 2.8) despite greater weight loss with drug (19).</td>
<td><strong>Contraindicated if BP is uncontrolled.</strong> BP lowering is not commensurate with degree of weight loss. Monitor heart rate and BP</td>
</tr>
</tbody>
</table>
Direct Meta-Analysis: Likelihood of Discontinuation Commonly Recommended Weight Loss drugs Due to Adverse Events

Common Adverse Events

- **Liraglutide 3.0 mg**: GI AEs, hypoglycemia if on hypoglycemic agents for diabetes, headache
- **Naltrexone ER/bupropion ER**: GI AEs, headache
- **Phentermine/topiramate ER**: parasthesia, dizziness, distorted taste, insomnia, constipation, dry mouth
- **Lorcaserin BID**: hypoglycemia, headache, fatigue
- **Orlistat**: abdominal pain/discomfort, oily spotting / stool, fecal urgency

---

*a Selected common (defined as incidence > 5%) AEs are noted; refer to medication package inserts and cited references for complete information*

4. ADA. *Diabetes Care* 2017;40(suppl 1):S57-S63.
Weight Loss Recidivism with Lifestyle and Pharmacology

• 53% of Americans are currently attempting weight loss and
• 25% are battling weight maintenance,
• Initial weight reduction is challenging,
• Maintenance of weight loss (when it does occur) is even more problematic.
• Weight lost recidivism is the norm (>90%).
• Only 6% maintain weight loss of at least 5% after 6 years.
• This phenomenon has been repeatedly observed, with estimates showing that nearly 1/3 of weight loss is regained in 1st year following any weight loss intervention.

In Obesity, Biology Protects Against Weight Loss and Maintains a High Body Weight

Incidence of Type 2 Diabetes Mellitus After Bariatric Surgery: A Population-based Matched Cohort Study, at 7-Year Follow-up

Cardiovascular Events After Bariatric Surgery in SOS [Swedish Obese Subjects] (n=670) With Type 2 Diabetes

345 surgically treated subjects and the 262 matched controls that had type 2 diabetes