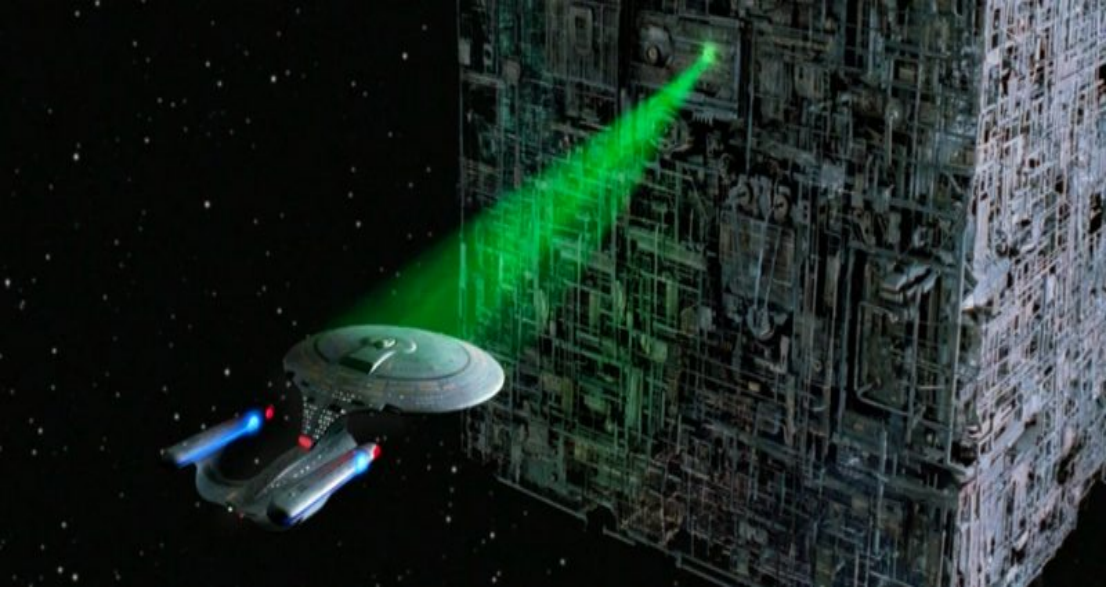

Hormones and the Heart: Is Resistance Futile?

Resistance is 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

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Faculty Disclosures*

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

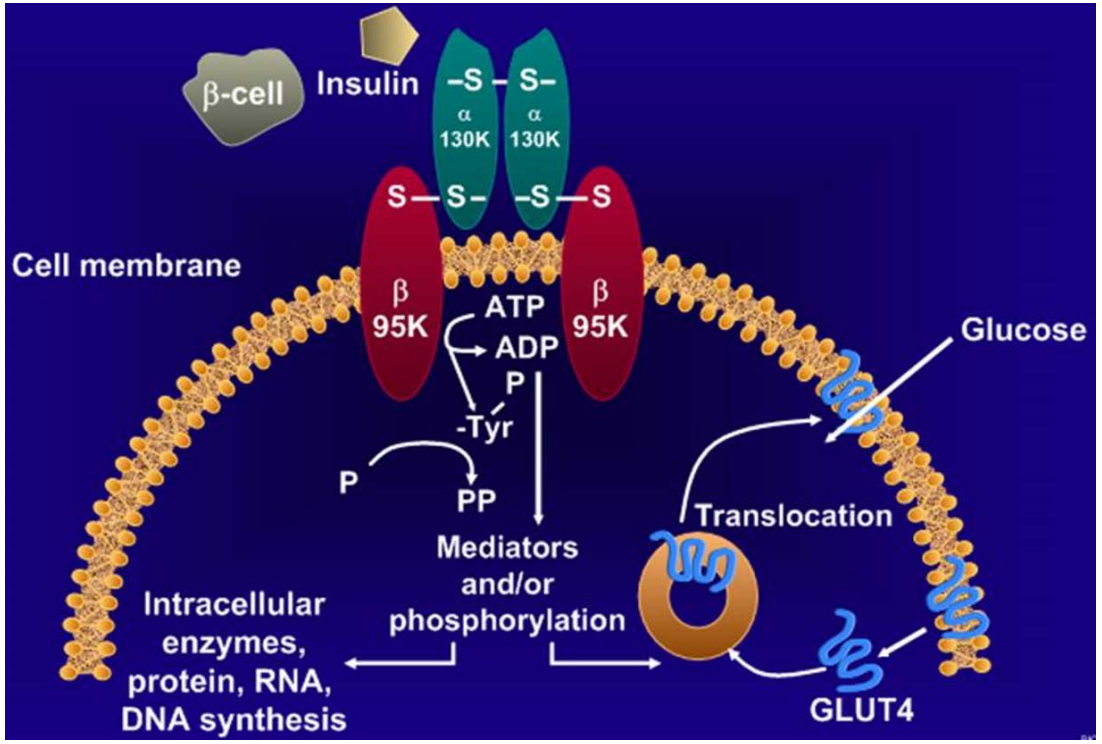
Speaker/Teaching Faculty	**Akcea Therapeutics/Ionis, Amgen, Janssen, Merck, Novo Nordisk**
Clinical Research Trial Site	**Amgen, Astra-Zeneca (Bristol Myers Squibb), Akcea Therapeutics/Ionis Pharmaceuticals, Boehringer-Ingelheim, Dexcom, GlaxoSmithKline, Lexicon, Mylan Pharma, Novo Nordisk, Sanofi-Regeneron.**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

Cellular Mechanisms of Insulin Action



What is 'Insulin Resistance' ?
- A patho-physiological state in which a normal amount of insulin produces subnormal cellular responses.

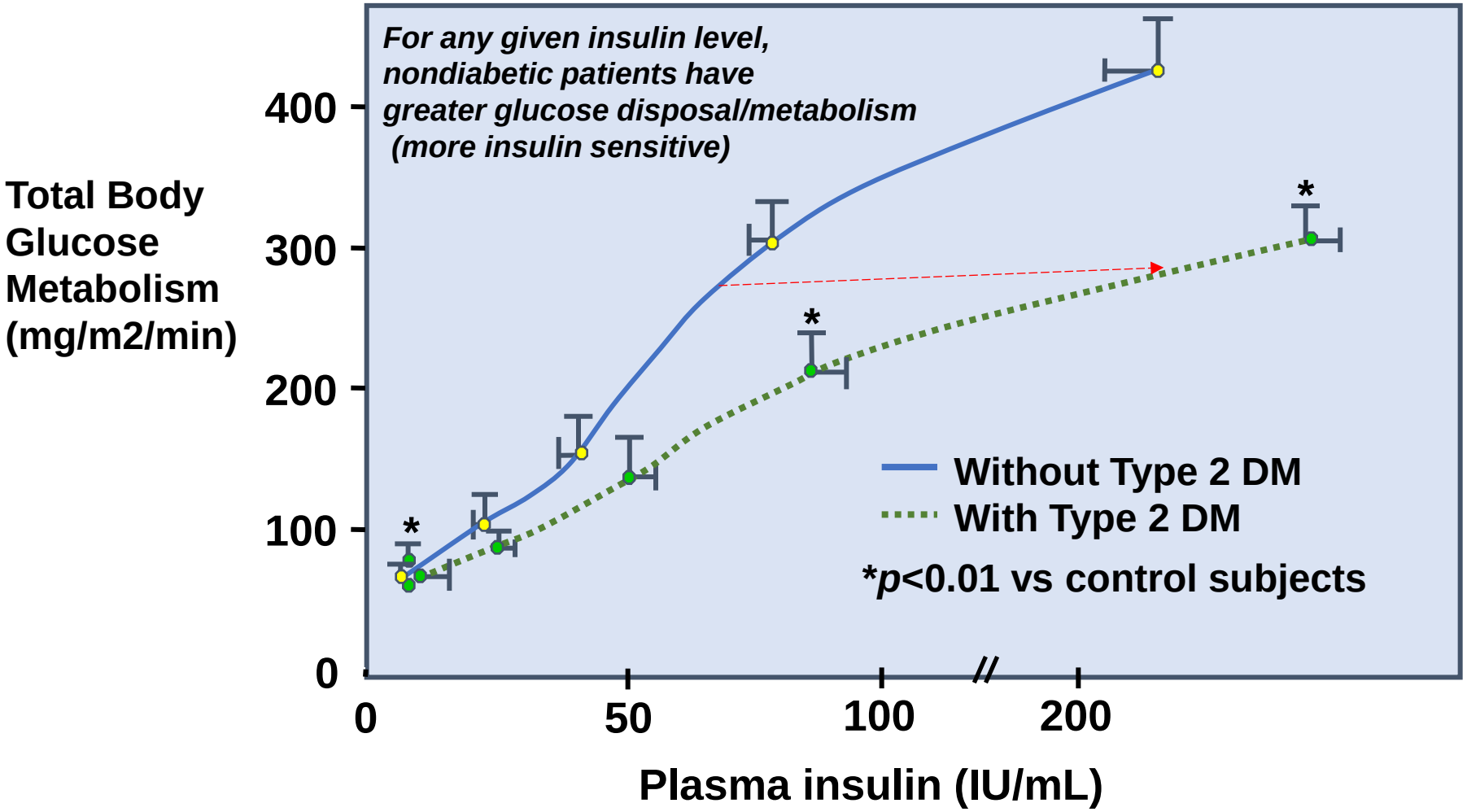
Kruszynska Y., Olesfsky JM. J Invest Med. 1996;44:413-428.

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)



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

Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, DeFronzo RA. *J Clin Invest* (1989) 84:205-213

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 → ↑↑ free fatty acids**
- **And, while not required, 'Syndrome X' was more common in overweight or obese individuals**

Reaven, Gerald M. Role of Insulin Resistance in Human Disease. *Diabetes* (1988) *37:1595-1607.*

Syndrome X-1988

Reaven's Syndrome

Insulin Resistance Syndrome 1988, 1991, 1992 –IDF, EGIR, AACE

Syndrome of Hyperinsulinemia

Metabolic Syndrome 1998, 1999, 2001, 2005-WHO, EGIR, NCEP, IDF

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)- Austrailia

Carbohydrate Intolerence, 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), Berkeley1988

Pattern B Dyslipidemia Phenotype, 1988

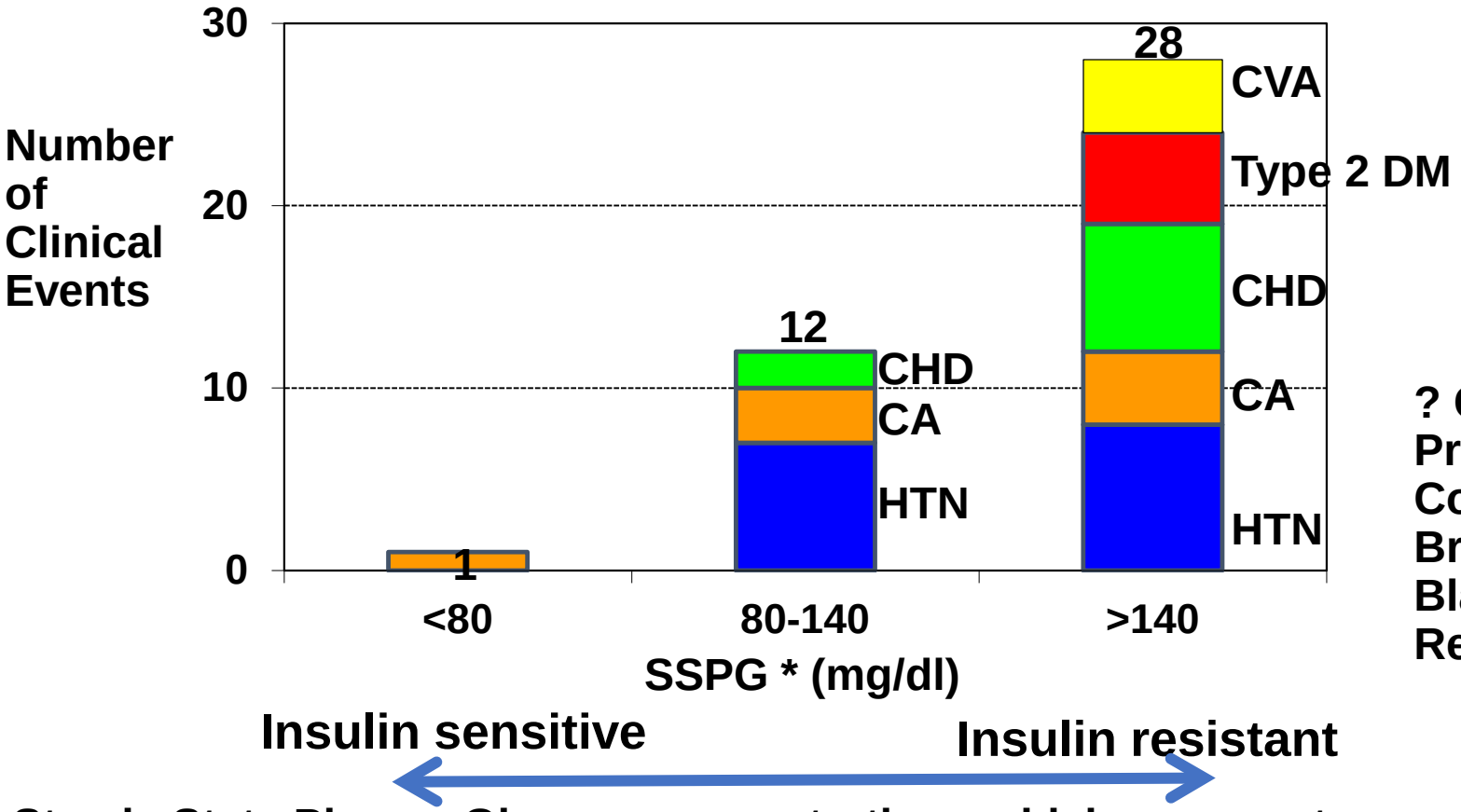
Atherogenic Dyslipidemia Syndrome

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



? CA: Prostate Colorectal, Breast, Bladder, Renal

*** 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**

Facchini FS, Hua N, Abbasi F, Reaven GM JCEM 2001;86:3574-3579.

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] → 'Cryptogenic' cirrhosis

Hypertension
Obesity
Sleep Apnea
Osteoarthritis
Dyslipidemia (TG, HDL)
Alzheimer's Disease
Gallbladder Disease

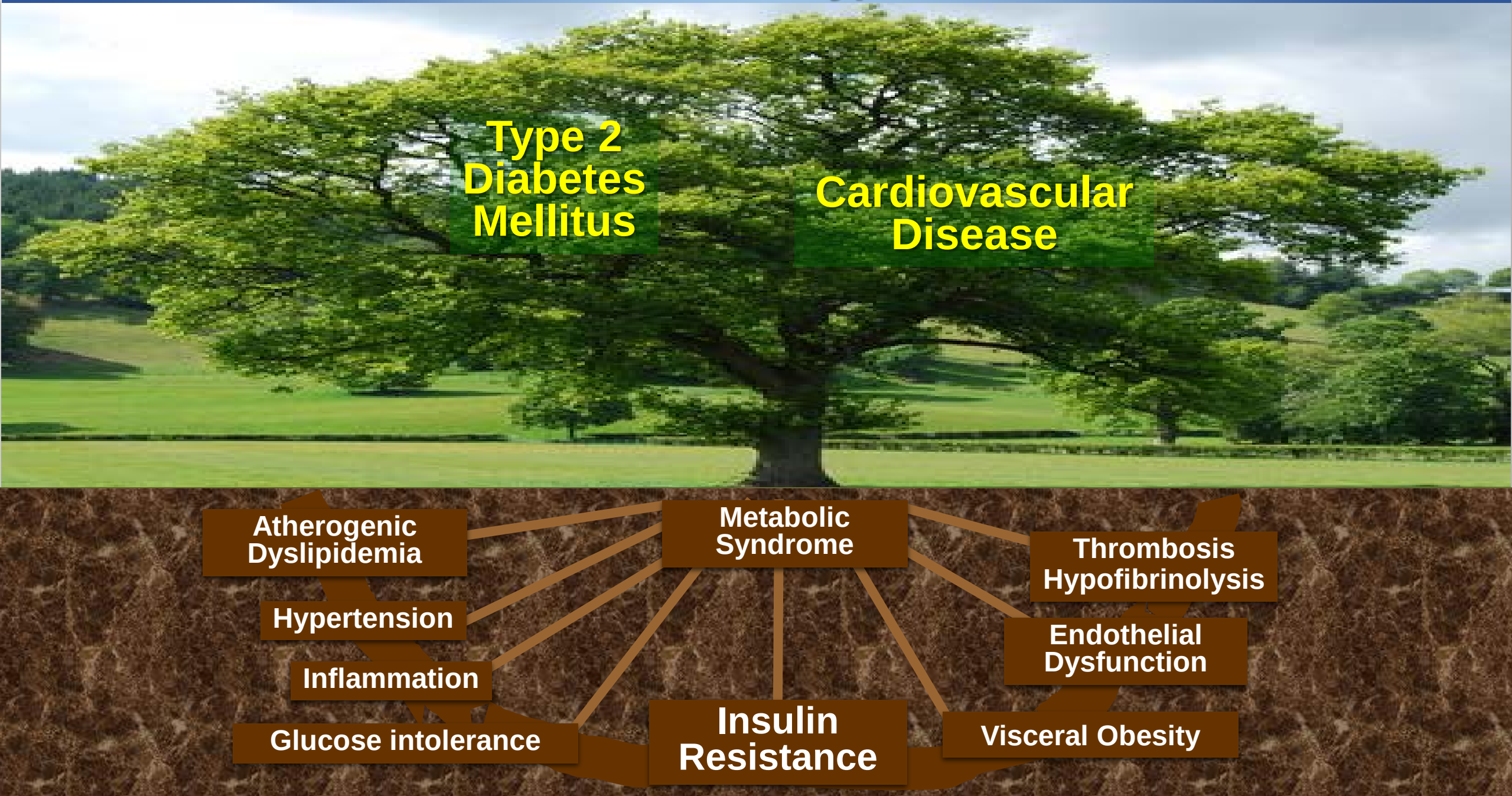
Cancer (certain)
– Breast
– Endometrial
– Prostate
– Renal
– Pancreatic

Hyperuricemia (Gout)

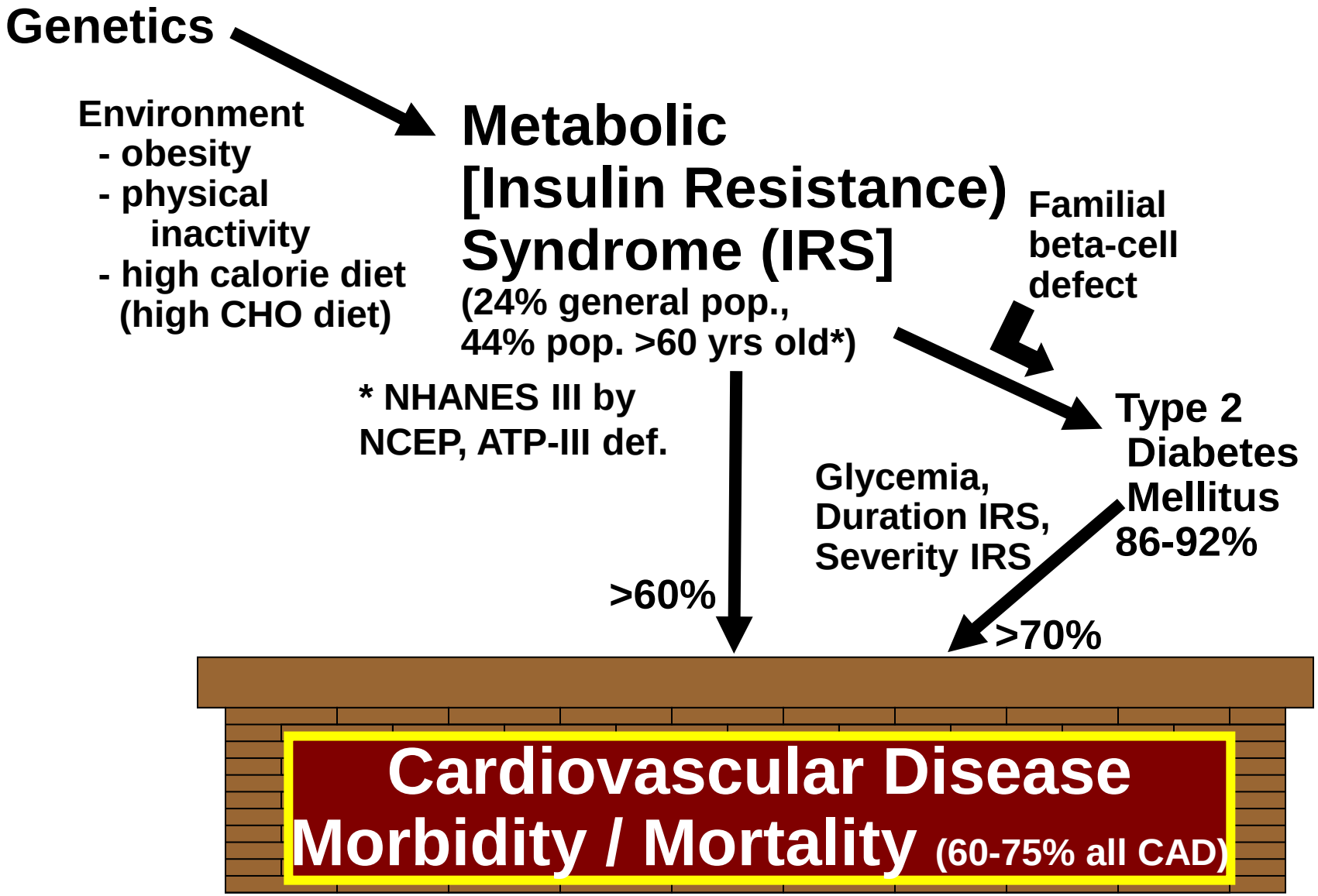
Acanthosis Nigricans

“Common Soil” Hypothesis

Stern MP. Diabetes. 1995;44(4):369-374.



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



NCEP-ATP III 2001 Guidelines: Clinical Identification of the Metabolic Syndrome

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

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

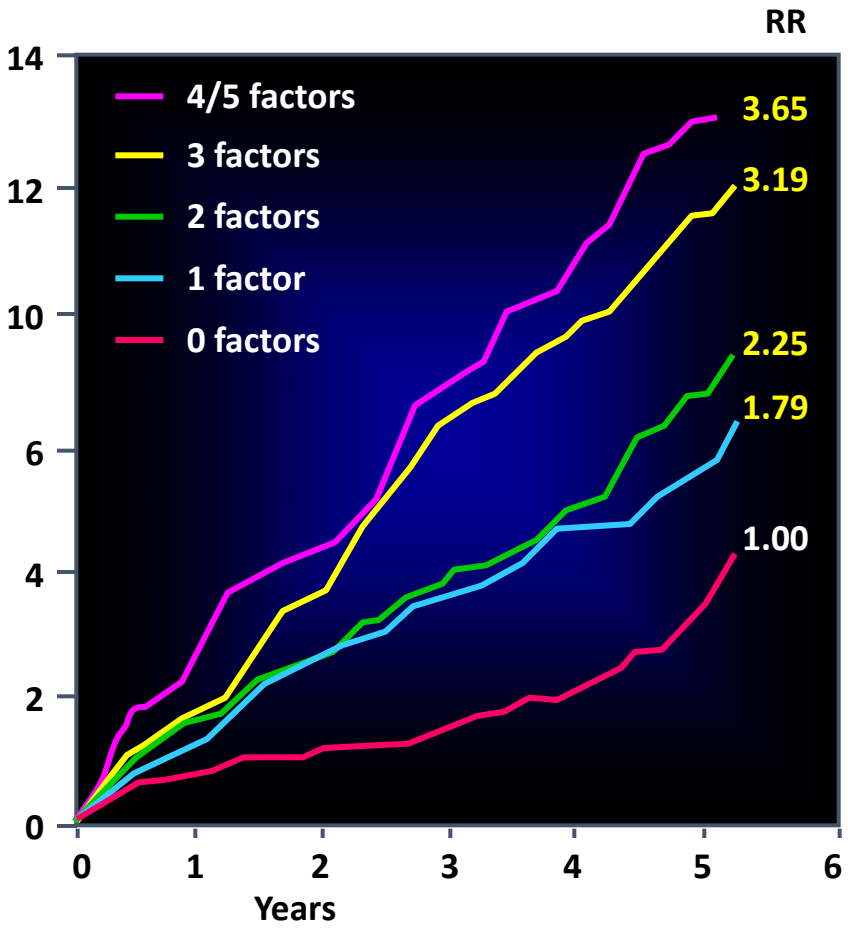
in Europids*, (& ethnic-specific levels in Chinese, Japanese and South Asians)

NCEP- Expert ATP III Report. JAMA. 2001;285(19):2486-2497.

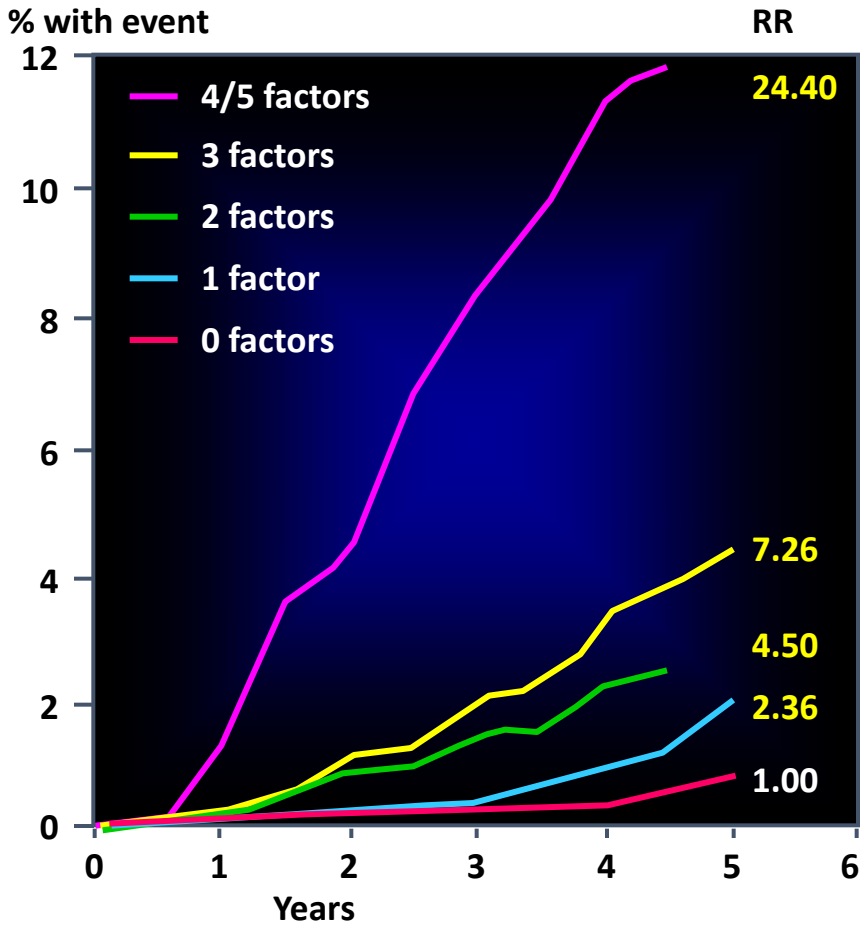
*IDF) Global Consensus Statement: Worldwide Definition of the Metabolic Syndrome 2005

WOSCOPS: Metabolic Syndrome as a Predictor of CHD and Diabetes

CHD Death/Non-fatal MI

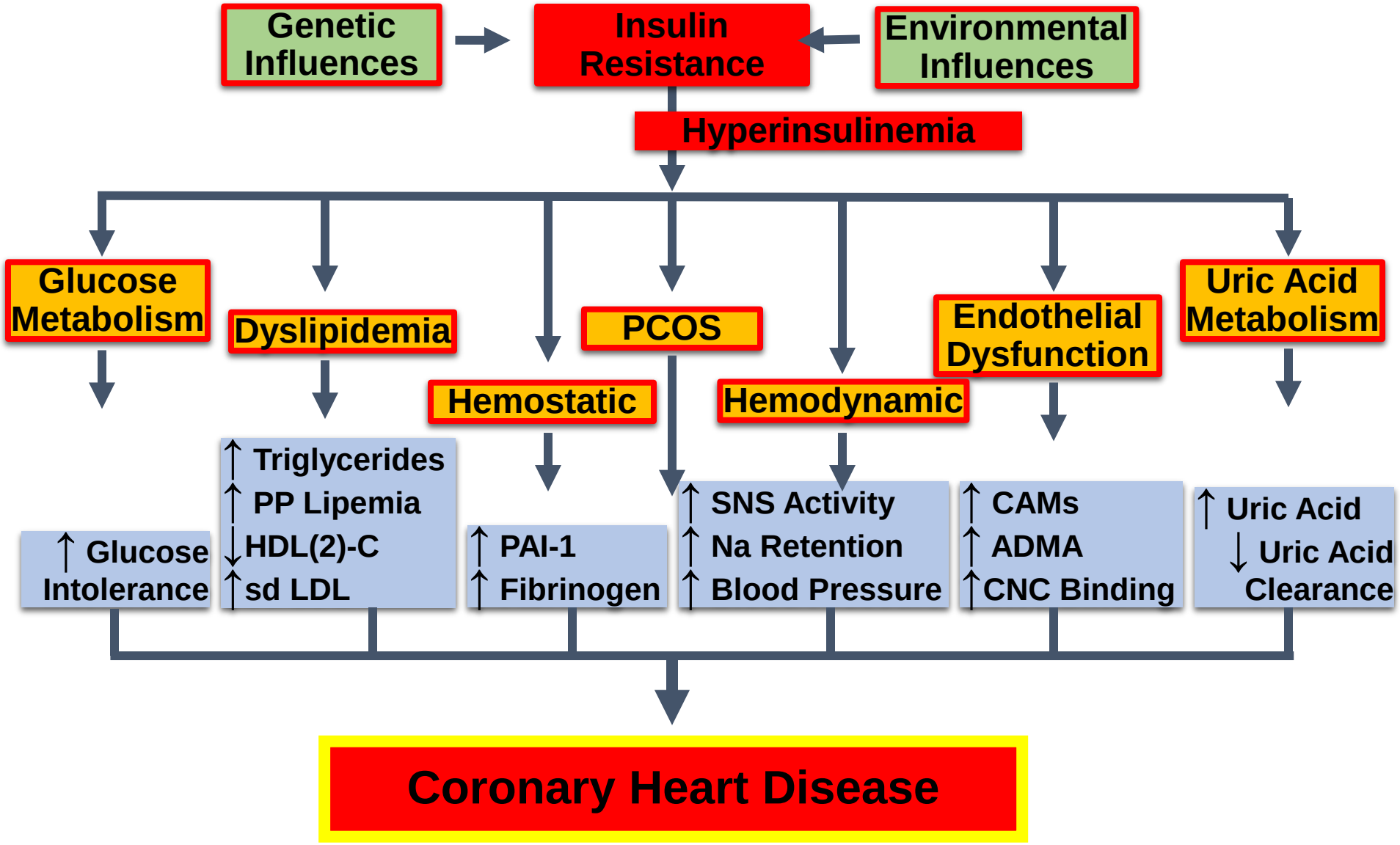


Onset of New DM



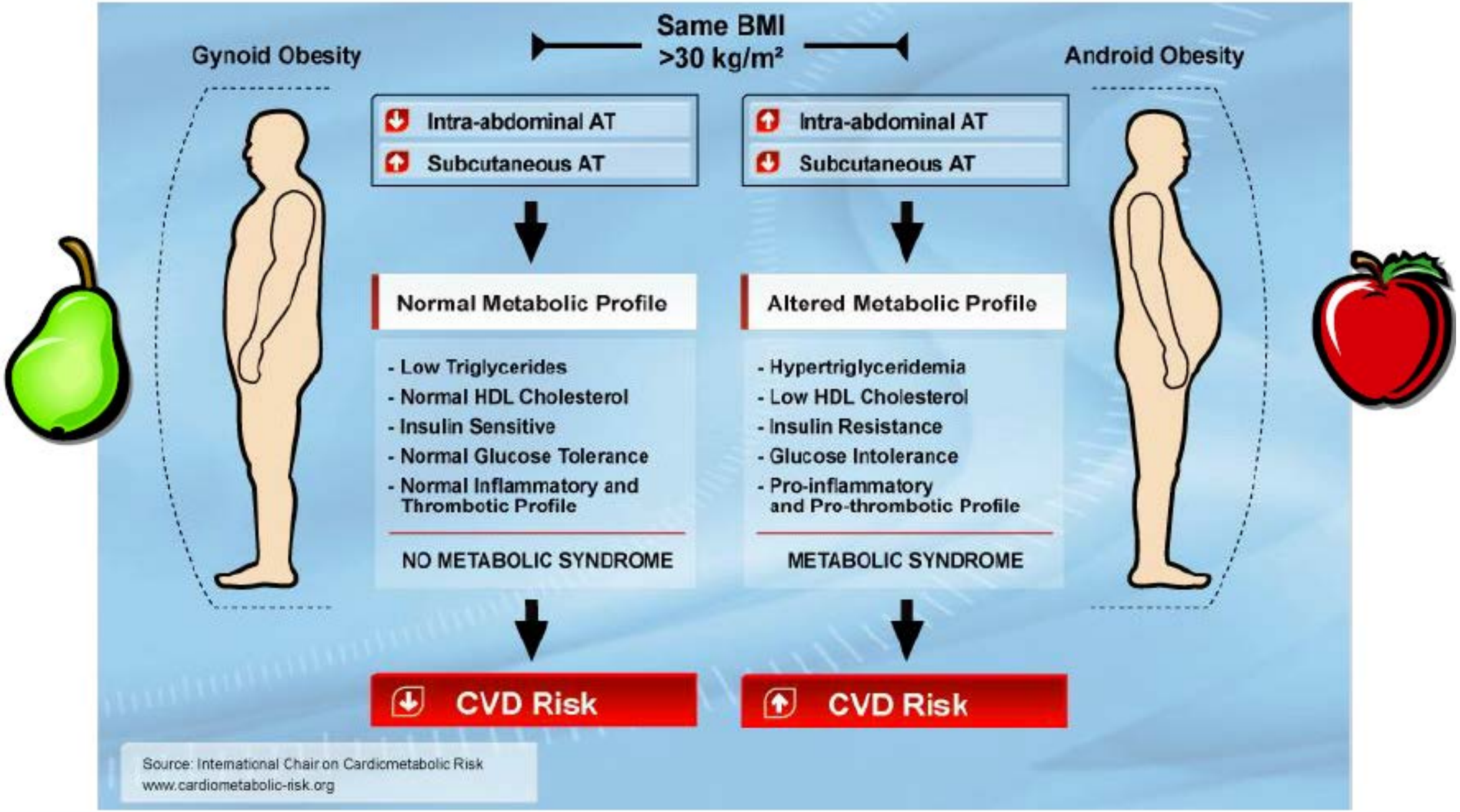
Sattar N, Gaw A, Scherbakova O, et al., Circulation. 2003;108(4):414-419

Proposed Role of Insulin Resistance and Compensatory Hyperinsulinemia in 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



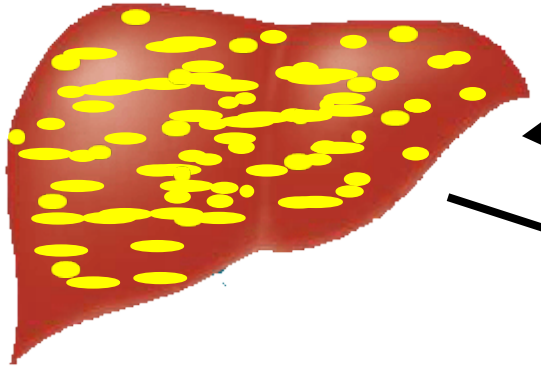
Role of Insulin Resistance and Visceral Fat in Atherogenesis

Overnutrition,
Malnutrition,
Sedentary state

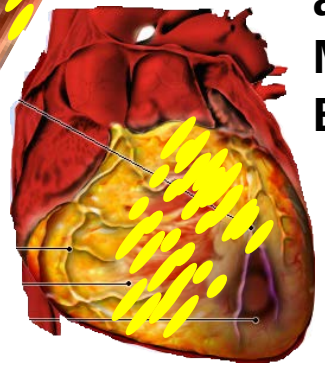
Abdominal obesity

Genetics

Fatty Liver
NAFLD, NASH



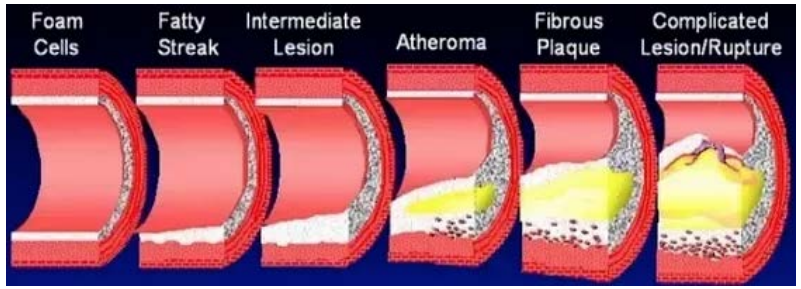
Macrophages
Endocrine, Paracrine, Autocrine
Inflammatory signals
Fatty acids
(Lipotoxicity)



TG content
in Skeletal
and Heart
Muscle &
Epicardium

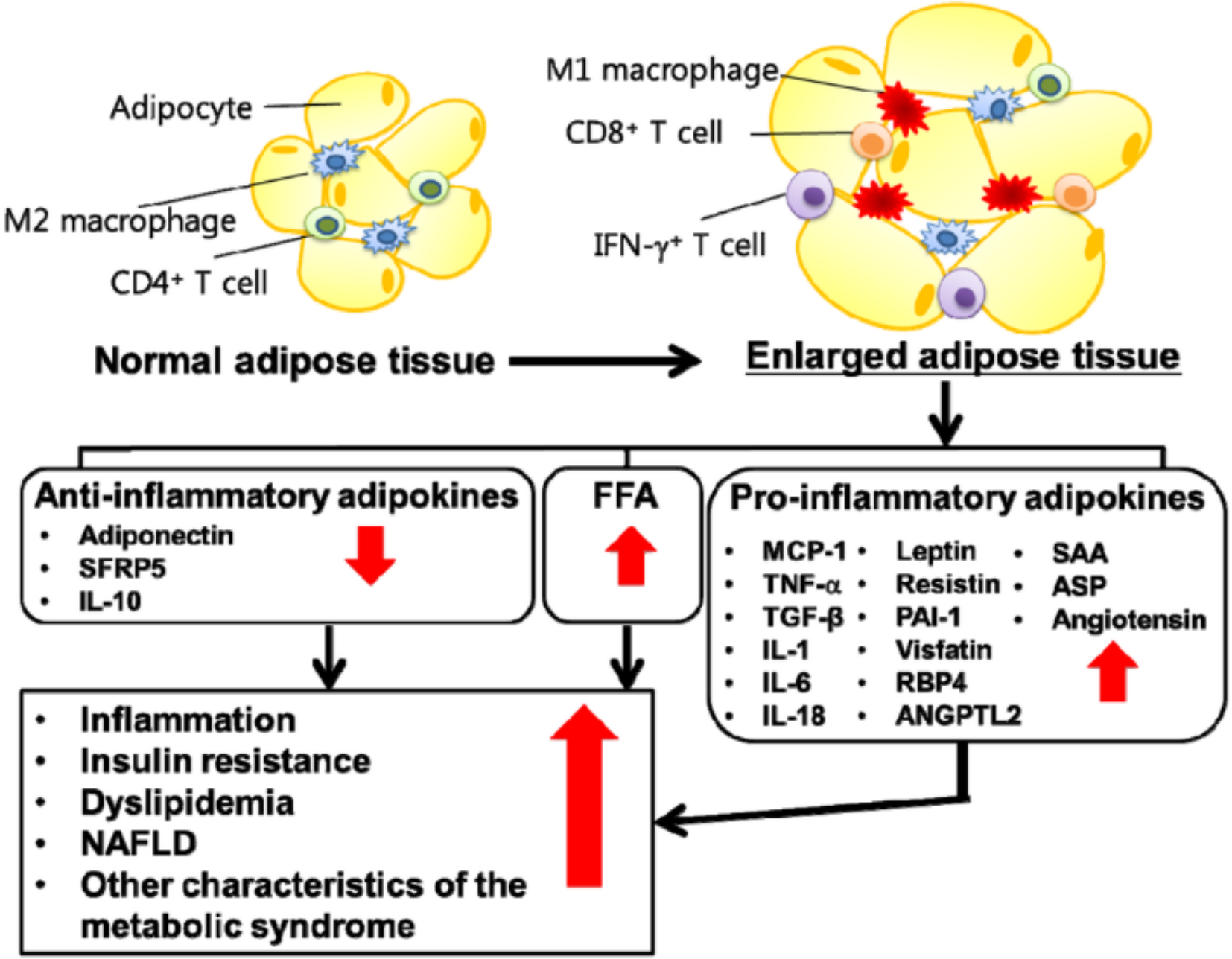
Insulin Resistance
hyperinsulinemia

Hypertension, Dyslipidemia, Hyperglycemia



Adapted from de Luca C & Olefsky JM.
Nat Med. 2006;12:41-42.
Lau DCW, Dhillon B, Yan H
Am J Physiol Heart Circ Physiol.
2005;288:H2031-2041.

Insulin Resistance Inspired by Obesity



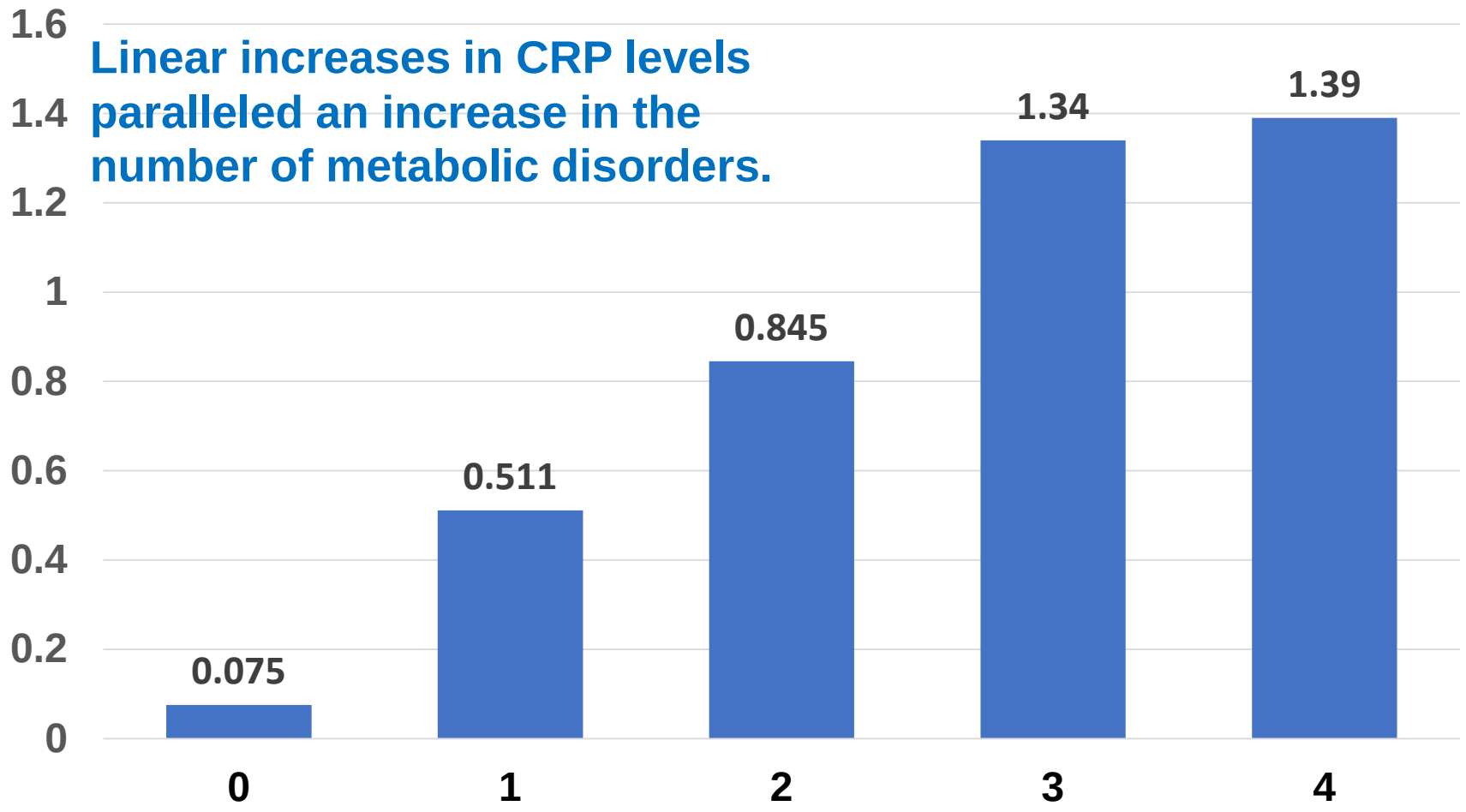
Monocyte chemotactic protein (MCP)-1, Tumor necrosis factor (TNF)-α, Interlukin (IL)-1, IL-6 and IL-8, have been reported to promote insulin resistance

Jung UJ, Choi M-S. Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease. Int. J. Mol. Sci. 2014;15(4):6184-6223.

‘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*

Mean Values, log ultrasensitive CRP



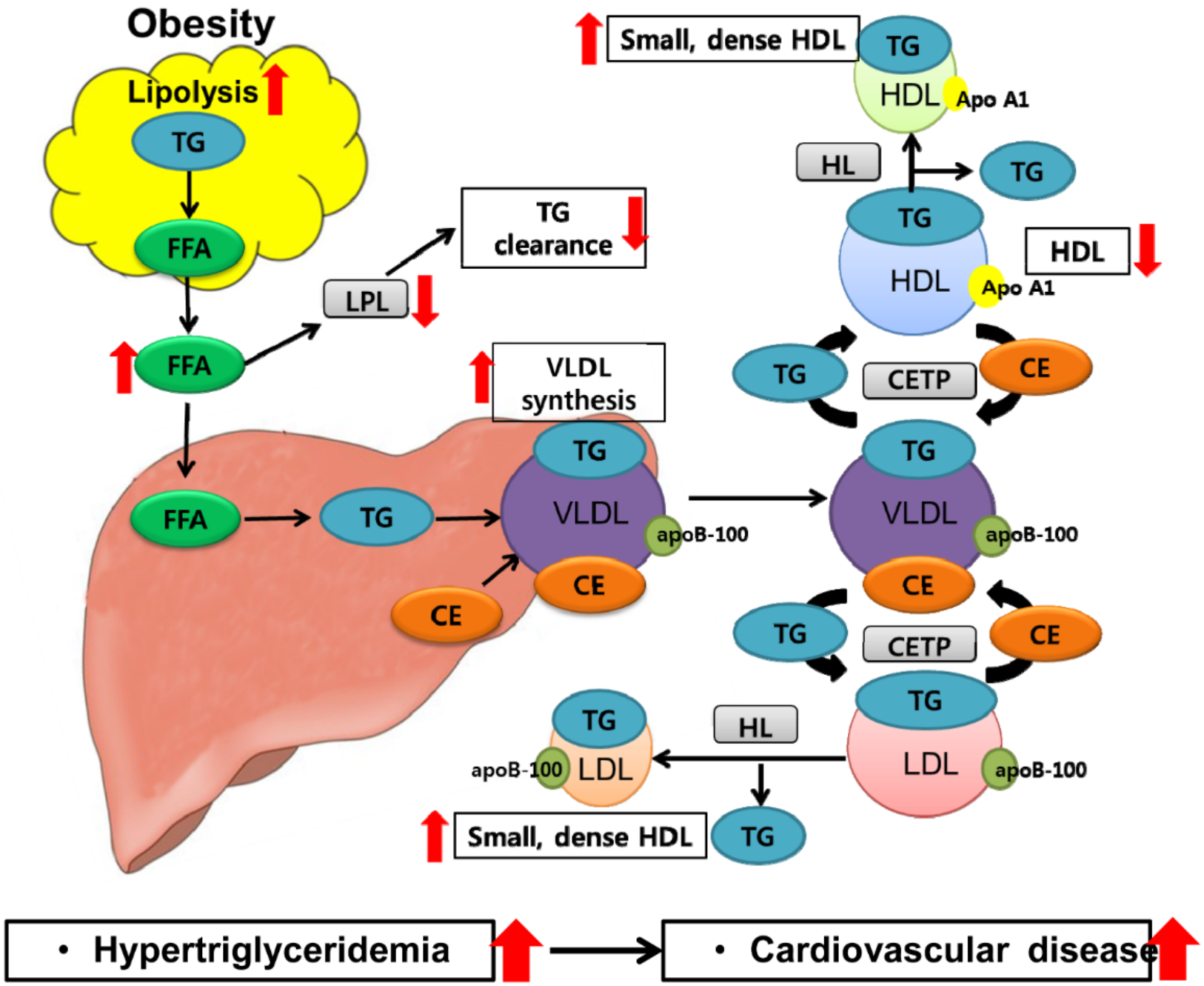
<u>*Metabolic Disorders</u>
(Highest tertiles of):

- **Dyslipidemia (TG)**
- **Upper-body obesity (BMI)**
- **Insulin resistance**
- **Hypertension**

Festa A, D'Agostino R Jr, Howard G, Mykkänan L, Tracy RP, Haffner SM. Circulation 102:42 -47, 2000.

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

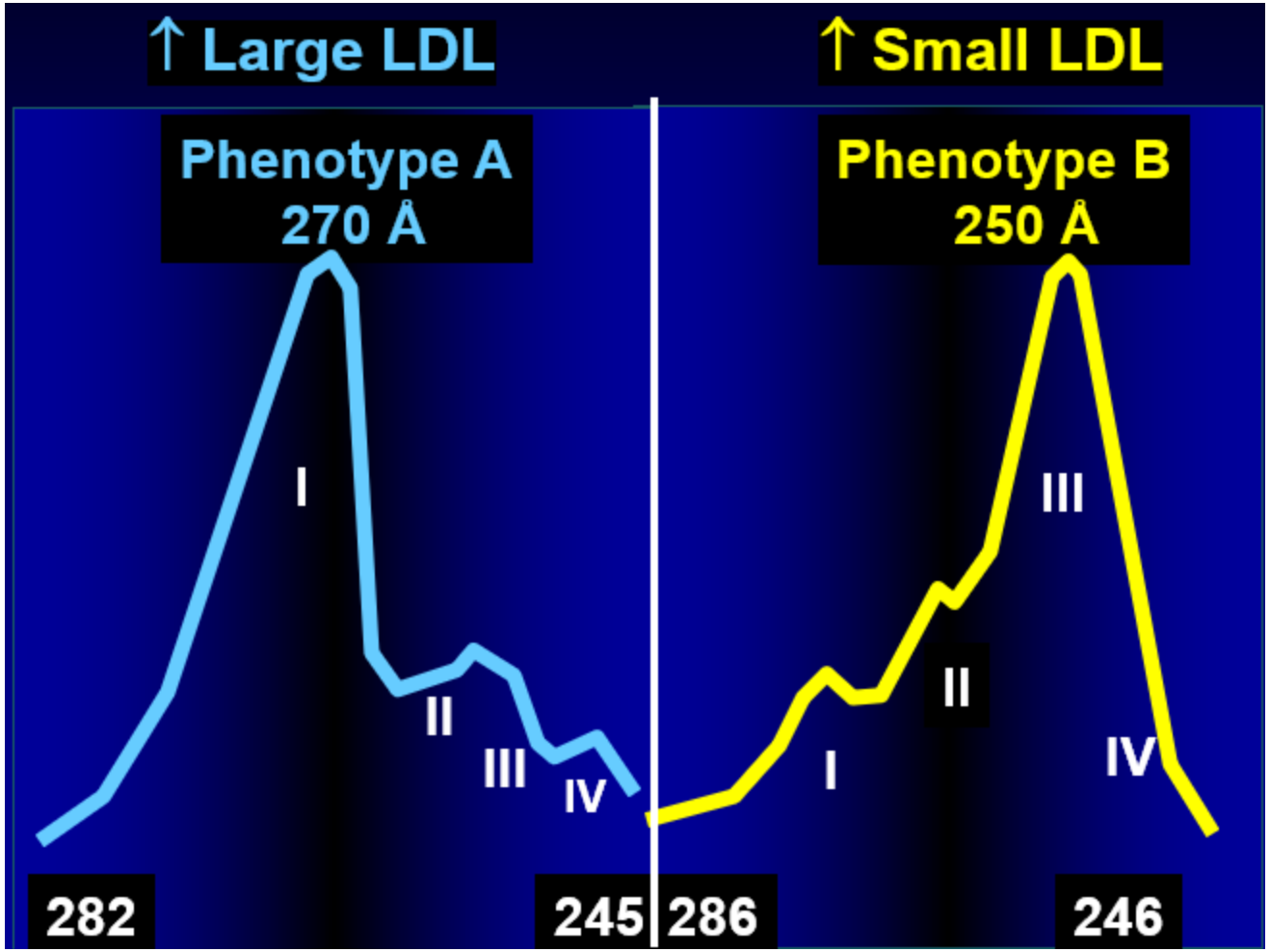
Resistance to insulin-stimulated suppression of adipose tissue lipolysis →
↑↑↑free fatty acids



Jung UJ, Choi M-S. Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease. Int. J. Mol. Sci. 2014;15(4):6184-6223.

LDL Fractionation via Gradient Gel Electrophoresis

↓TG
↓VLDL
↓VLDL1
↓IDL
↓Apo B
↑HDL
↑HDL2
↓HDL3
↑Apo A-1
↓Apo CIII
↓LDL/HDL
↓TChol/HDL
↓TG/HDL
↓Non-HDL
↓Non-HDL/HDL
↓ApoB/ApoA-1



↑TG
↑VLDL
↑VLDL1
↑IDL
↑Apo B
↓HDL
↓HDL2
↑HDL3
↓Apo A-1
↑Apo CIII
↑LDL/HDL
↑TChol/HDL
↑TG/HDL
↑Non-HDL
↑Non-HDL/HDL
↑ApoB/ApoA-1

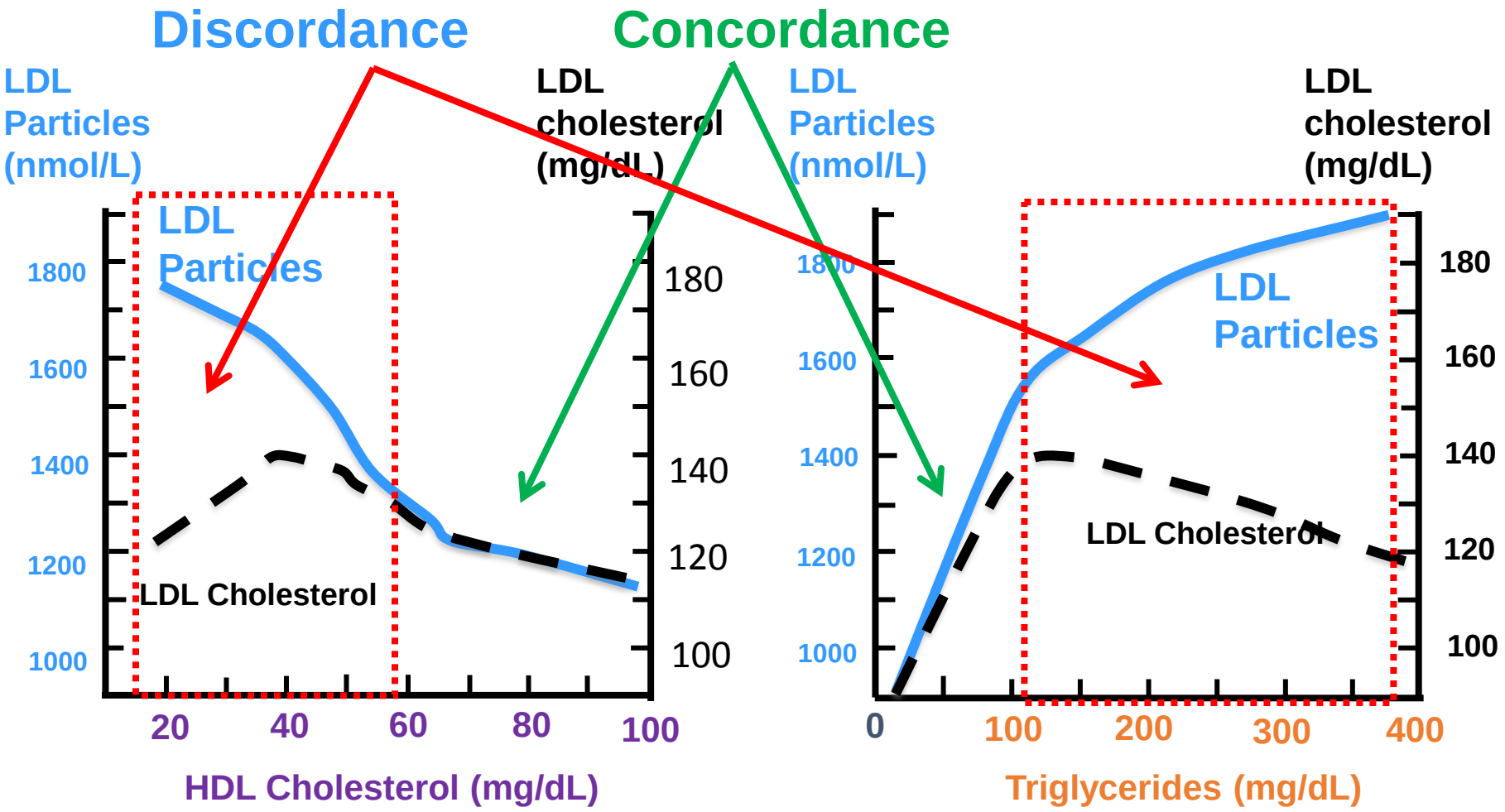
Adapted from Austin M et al. Am J Med (1990)

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

Sniderman AD et al. *Ann Intern Med*. 2001;135:447-59.

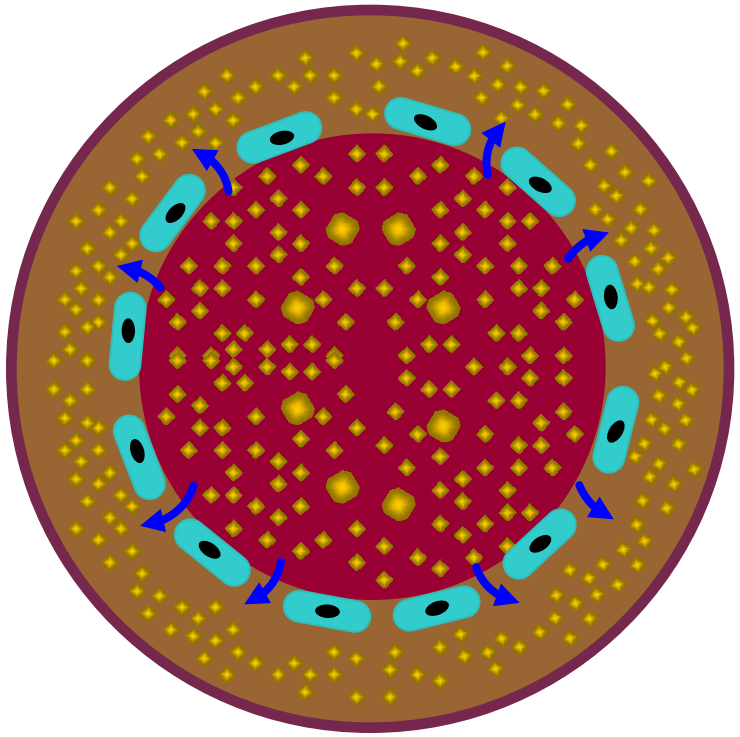
Framingham Offspring Study (n = 3,473) : Relationship of LDL Particles (LDL-P) & LDL Cholesterol (LDL-C) to Levels of HDL Cholesterol and Triglycerides



'Lower HDL-C' or 'Higher TG' associated with greater LDL-P

Cromwell WC and Otvos JD. Curr. Athero. Reports 2004;6:381-387

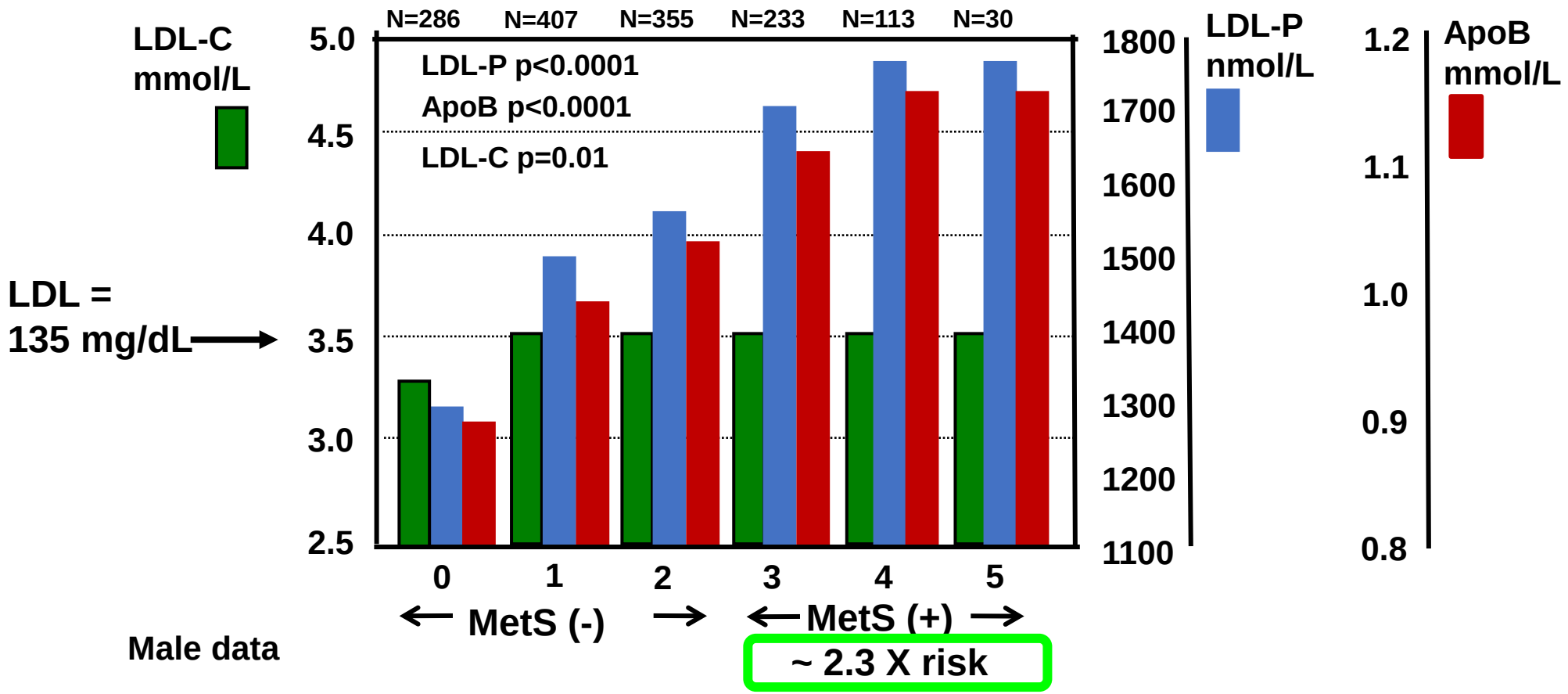
The Movement of Lipoproteins Particles is Gradient-driven



i.e. a 'large concentration or number' of LDL particles is most predictive of IHD

or better a 'large concentration or number' of <u>all</u> atherogenic particles (Chylomicron remnants, VLDL-remnants, IDL, LDL is most predictive of IHD

Framingham Offspring Study (FOS): LDL-C, LDL-P, Apo B with Increasing Number of Metabolic Syndrome Features

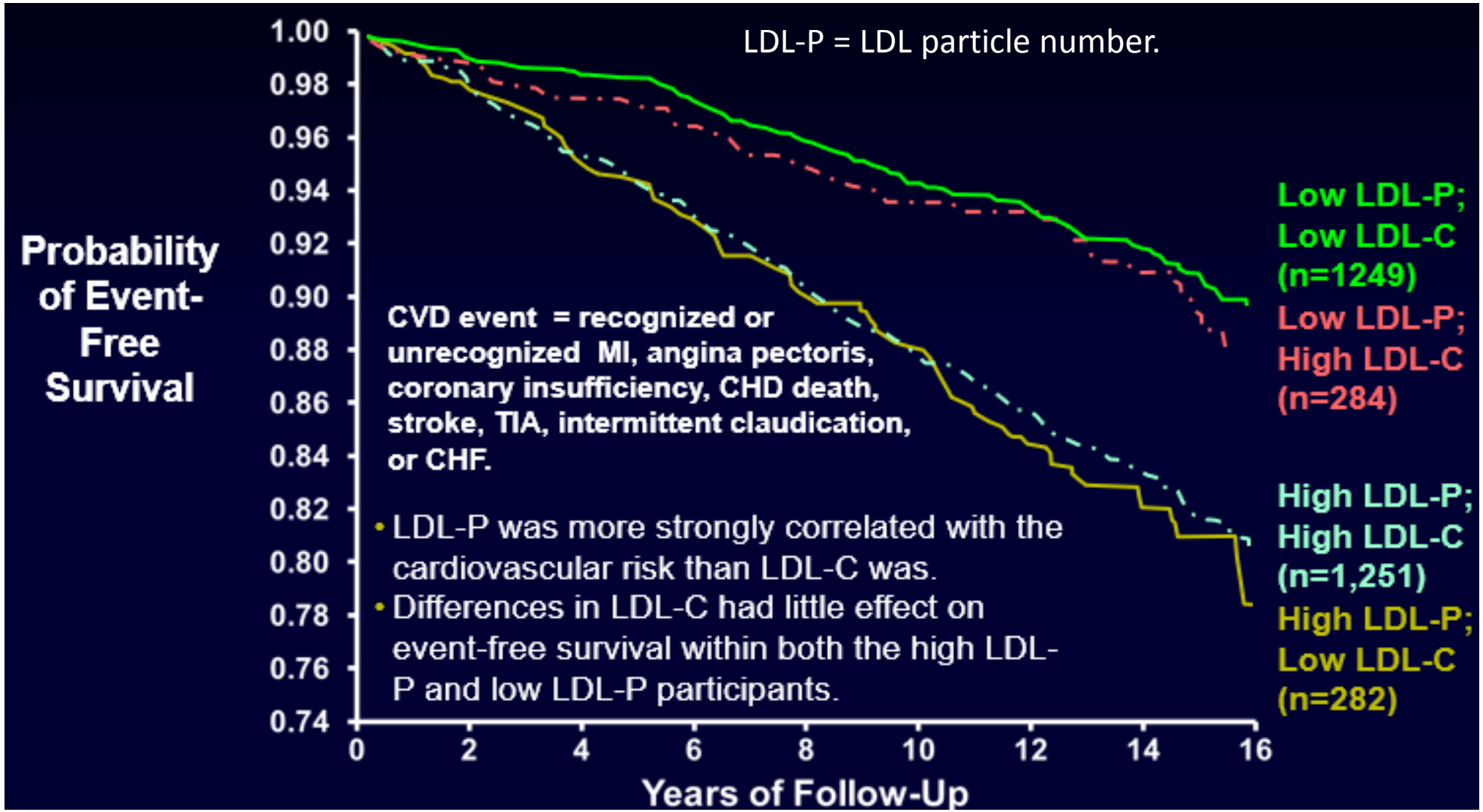


As the number of metabolic factors increased, the concentration of small cholesterol-depleted LDL-P increased, whereas the concentration of large cholesterol-enriched LDL-P decreased. These compositional changes in LDL particles translated into no change in LDL-C, but an increase in total LDL-P. Consistent 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.
Rosenson R, et al. Atherosclerosis 2010;213:1–7.

LDL Particle Number May Be a Better Indicator of CHD Risk Than LDL-C

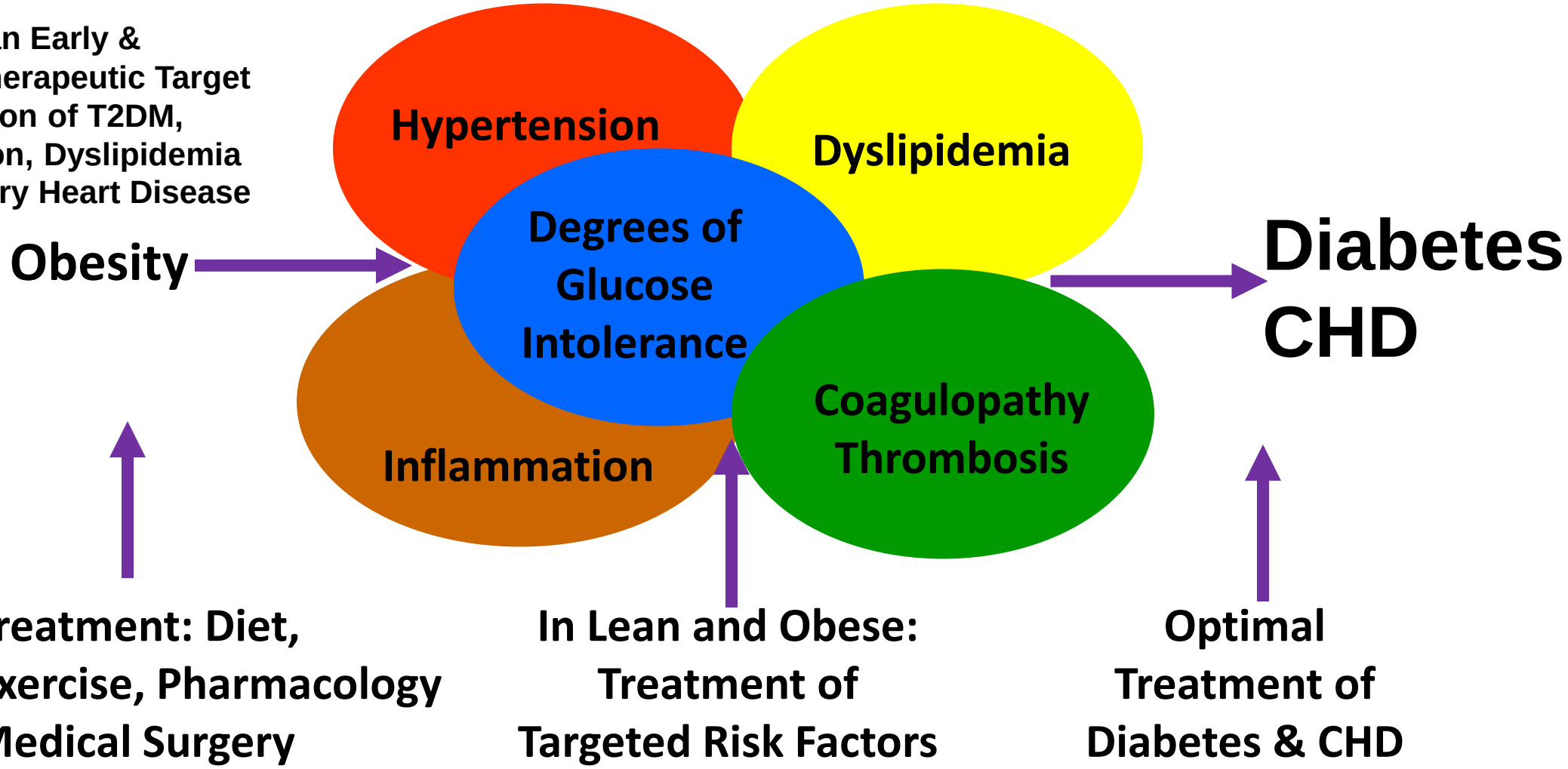
3,066 participants (mean age 51 yrs; 53% women), without CVD in Framingham Offspring cohort. The main outcome measure was incidence of first CVD event.



Cromwell WC et al. *J Clin Lipidol*. 2007;1(6):583–592.

Insulin Resistance (Metabolic) Syndrome Management

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



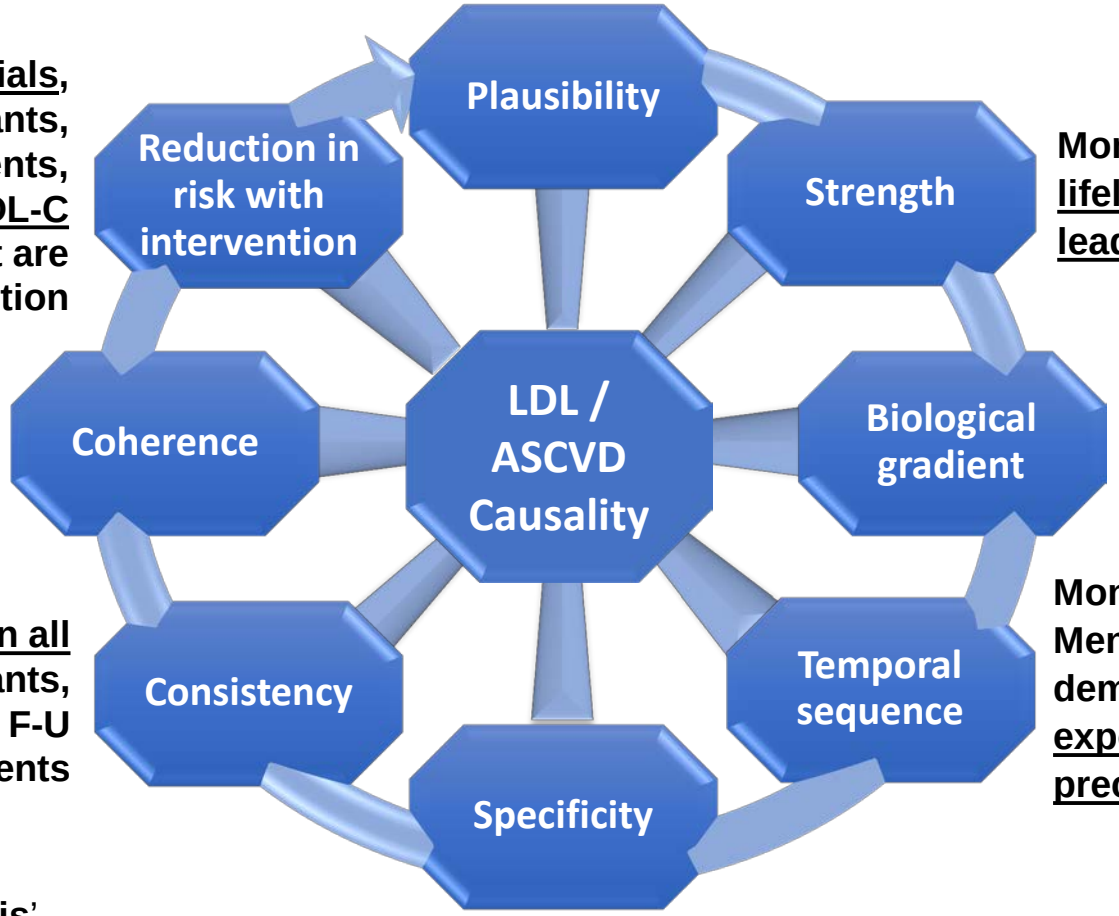
The Cholesterol Principle*: Criteria for LDL and ASCVD Causality Supporting the Criticality of Apo B-associated Cholesterol Particle-Lowering

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



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

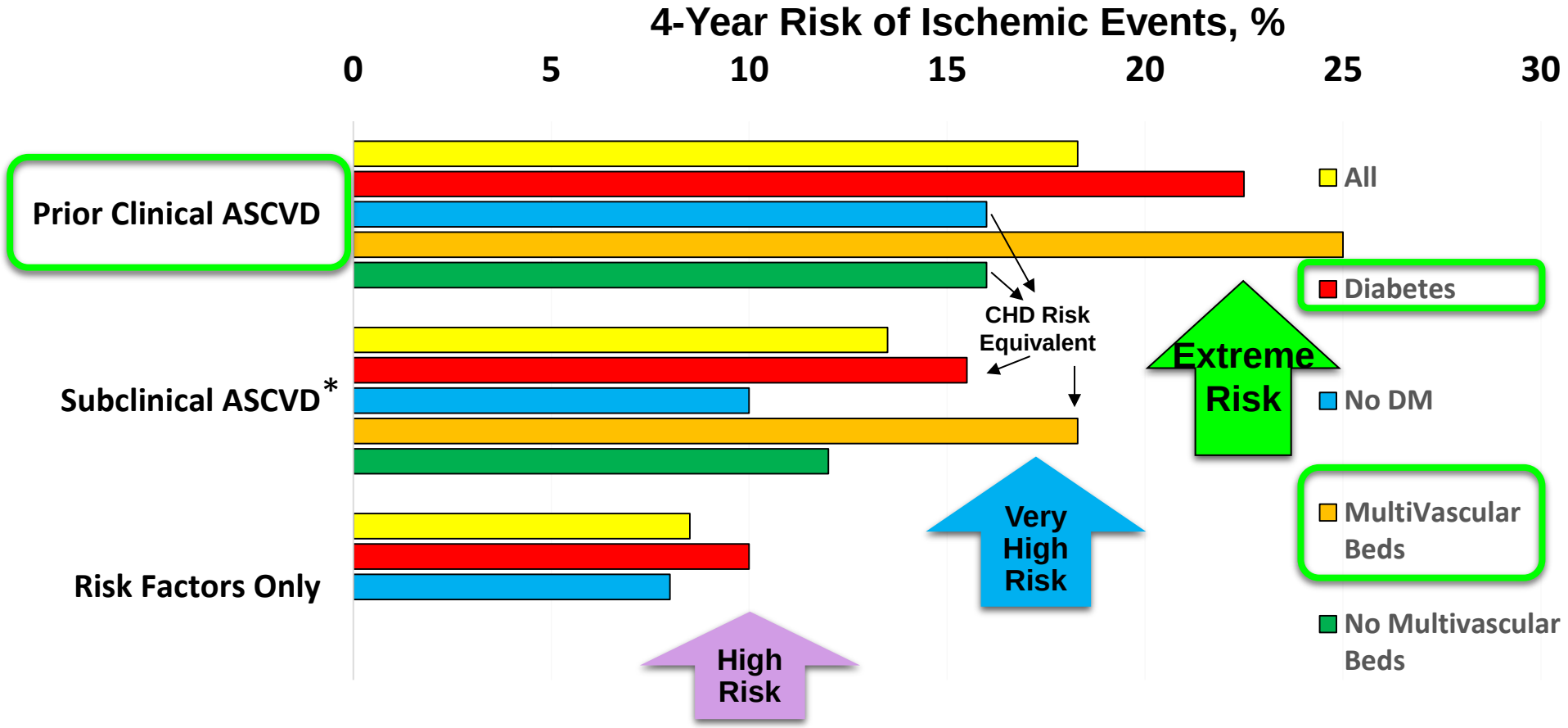
*** formerly the 'Cholesterol Hypothesis'**

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

Adapted from:
Ference BA, Ginsberg HN, Graham I et al.
Eur Heart J. 2017;38(32):2459-2472.

PDR

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

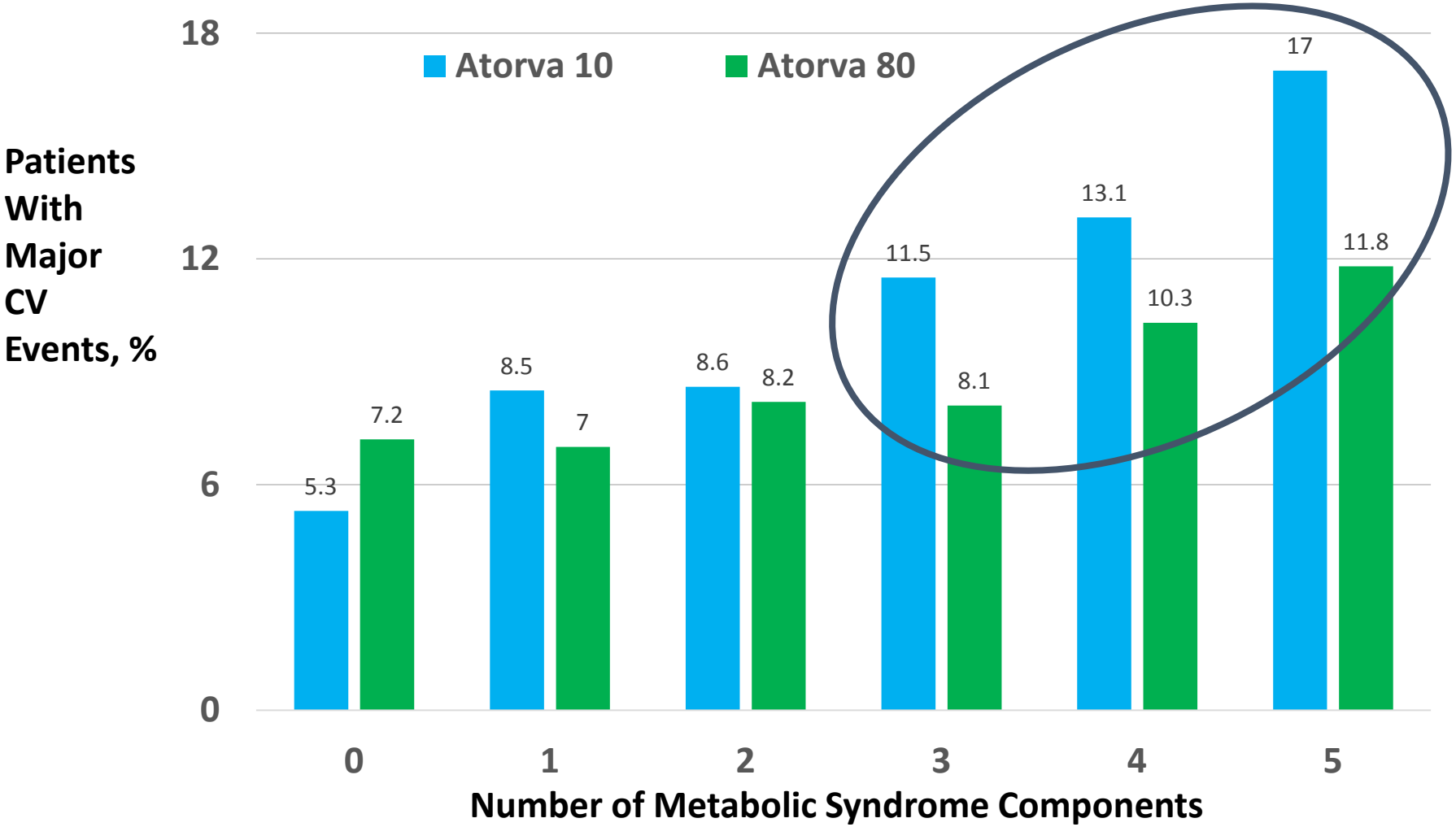


* Stable coronary, cerebrovascular, or peripheral artery disease without prior MI or stroke events

Bhatt DL, Eagle KA, Ohman EM, for the REACH Registry Investigators. JAMA. 2010;304(12):1350-1357.

Extreme Risk = 10-year MACE risk exceeding 30%

Cardiovascular Events in TNT According to Number of Metabolic Syndrome Components

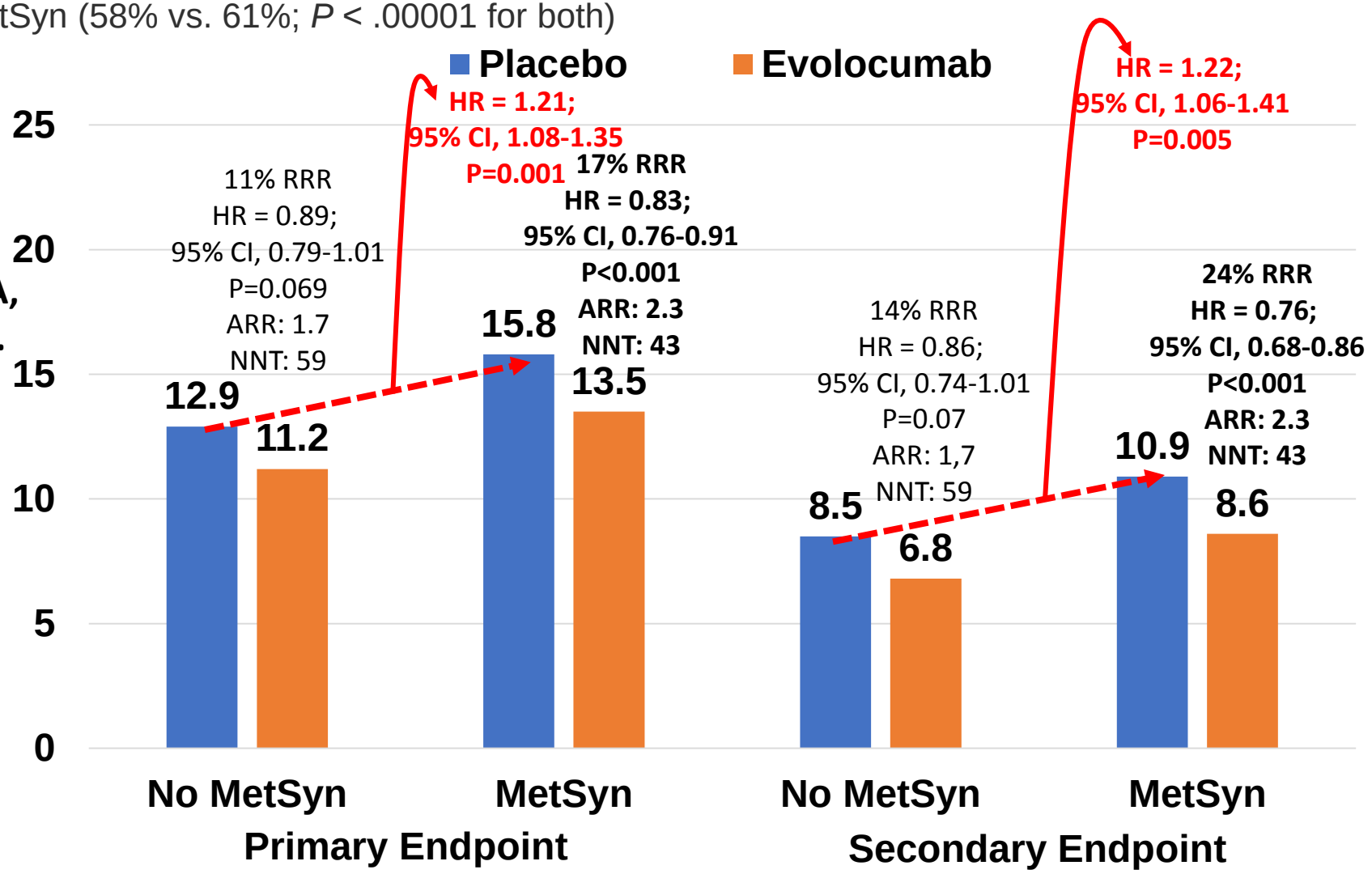


Deedwania P, Barter P, Carmena R, Fruchart J-C, Grundy SM, Haffner S, Kastelein JJP, LaRosa JC, Schachner H, Shepherd J, Waters DD. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. The Lancet. 2006;368(9539):919–928.

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)

CV death, MI, Stroke, hospital'n for UA, Coronary revasc.



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

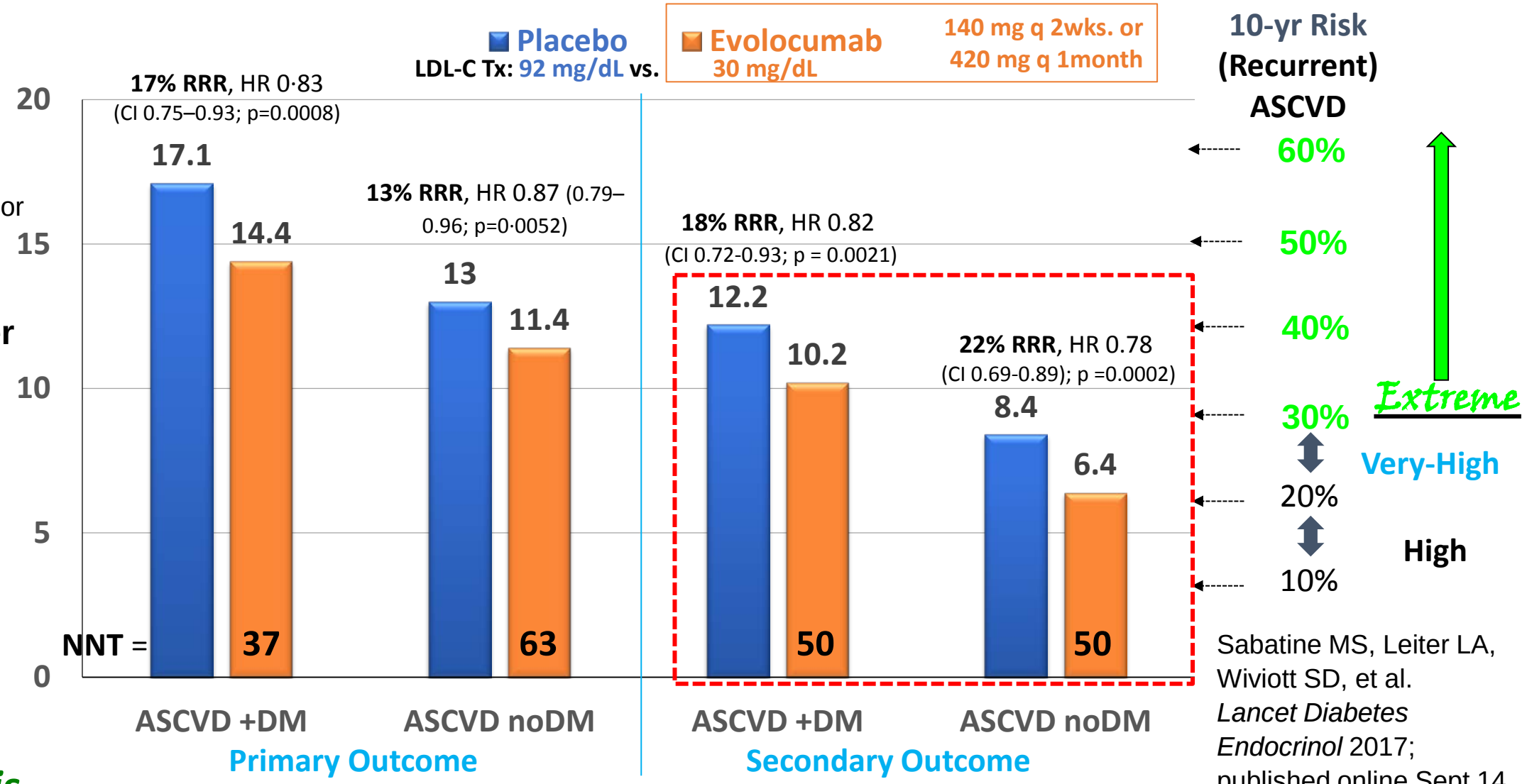
Incidence of New Onset DM
- MetSyn 4.73%
+MetSyn 4.46%

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

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

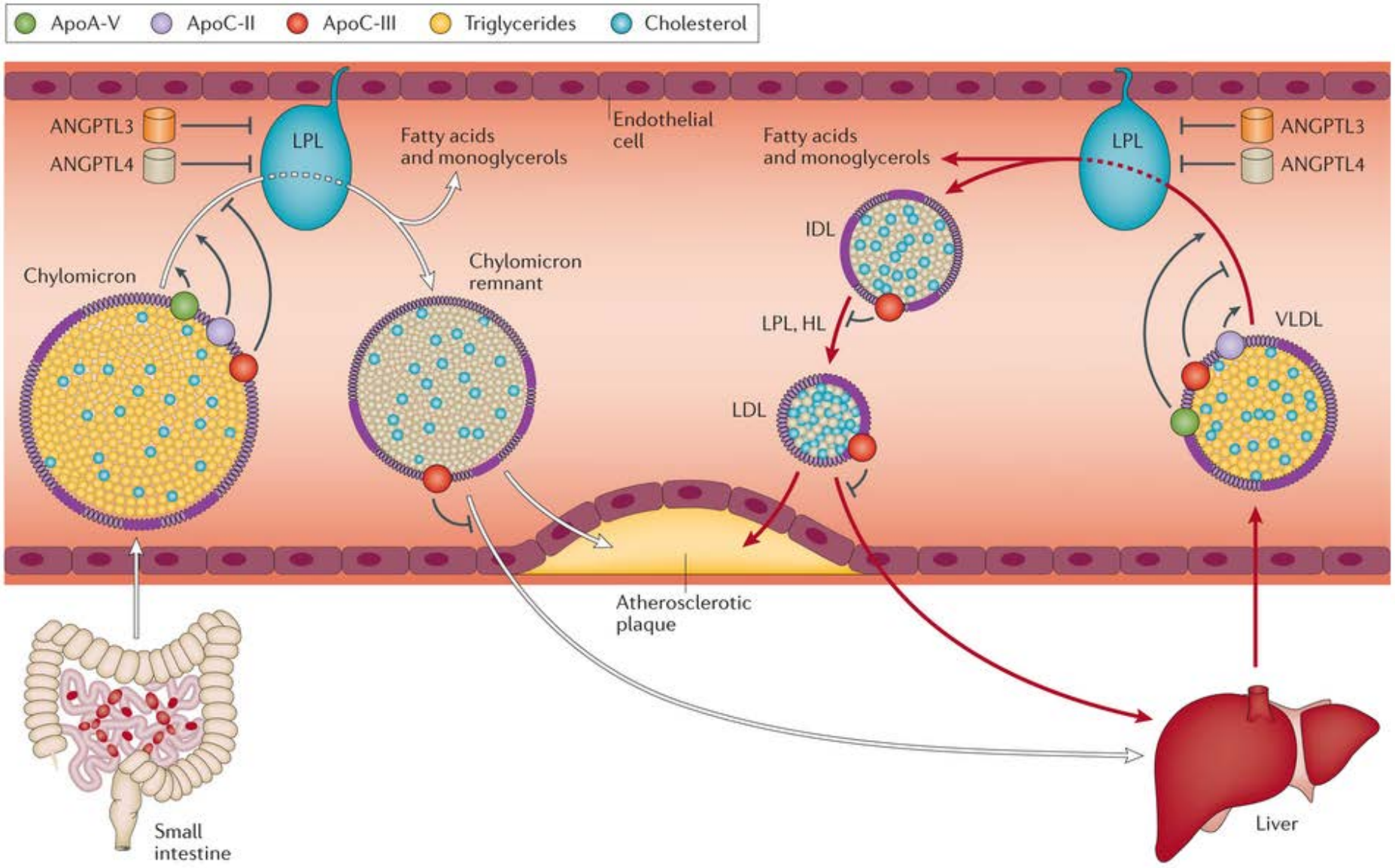


NNT= Number Needed to Treat

Even Lower is Even Better

Sabatine MS, Leiter LA, Wiviott SD, et al. *Lancet Diabetes Endocrinol* 2017; published online Sept 14. http://dx.doi.org/10.1016/S2213-8587(17)30313-3

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



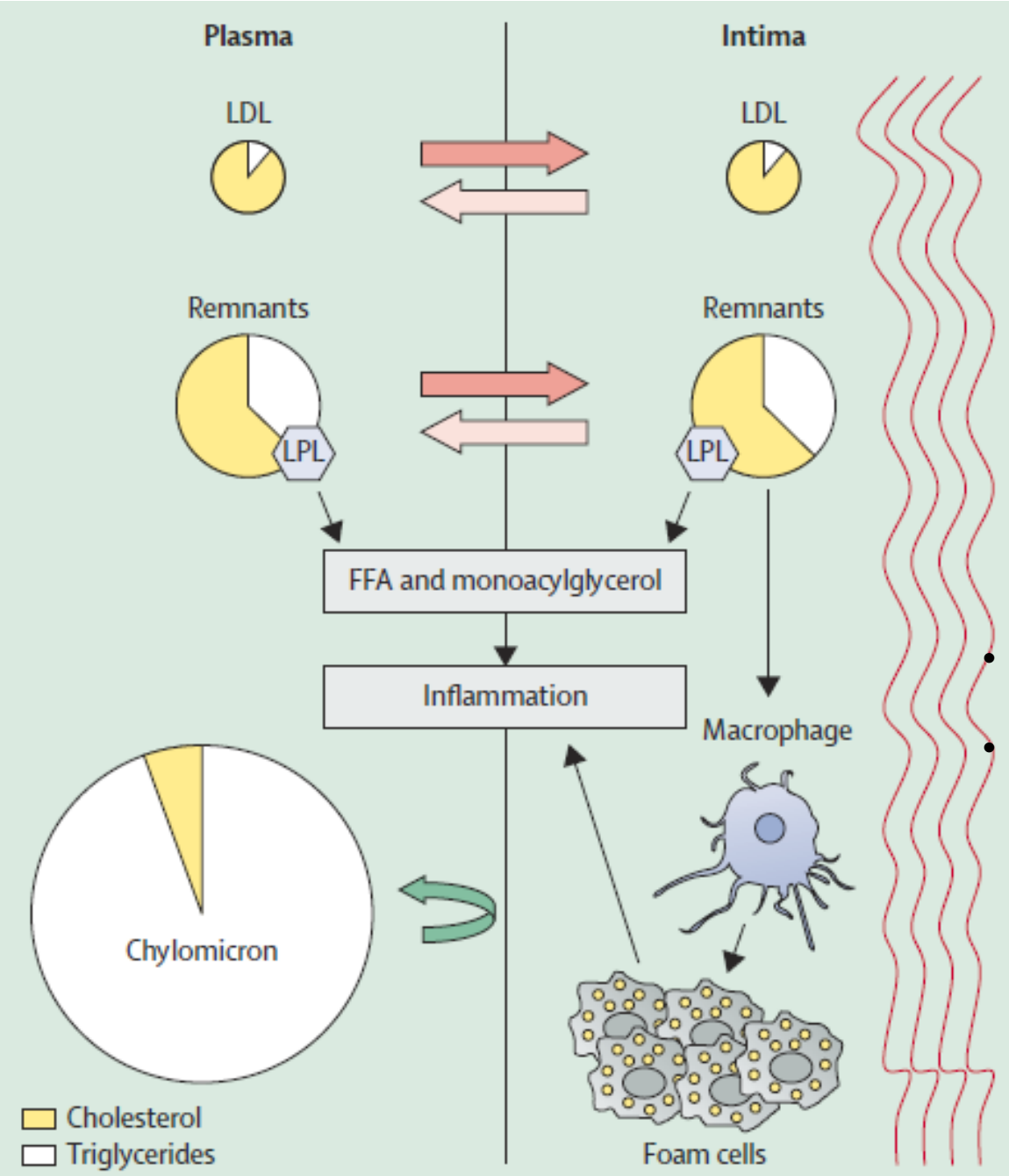
Khera AV, Kathiresan S. Nature Reviews Genetics 2017;18:331–344.

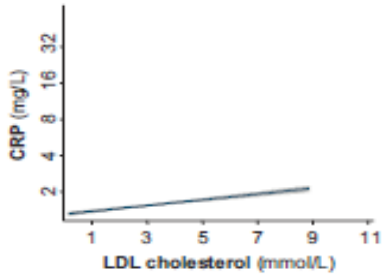
doi:10.1038/nrg.2016.160 (2017)

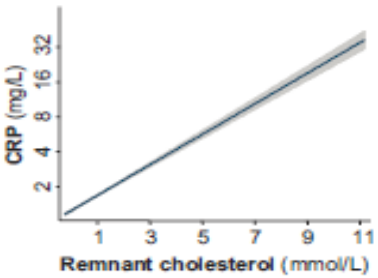
Triglyceride-Rich (Remnant) Lipoproteins and ASCVD: New Insights From Epidemiology, Genetics, and Biology

FFA, free fatty acids;
LDL, low-density lipoprotein;
LPL, lipoprotein lipase.

Nordestgaard BG. *Circ Res*. 2016;118:547-563;
Nordestgaard & Varbo. *Lancet*. 2014;384:626-635.



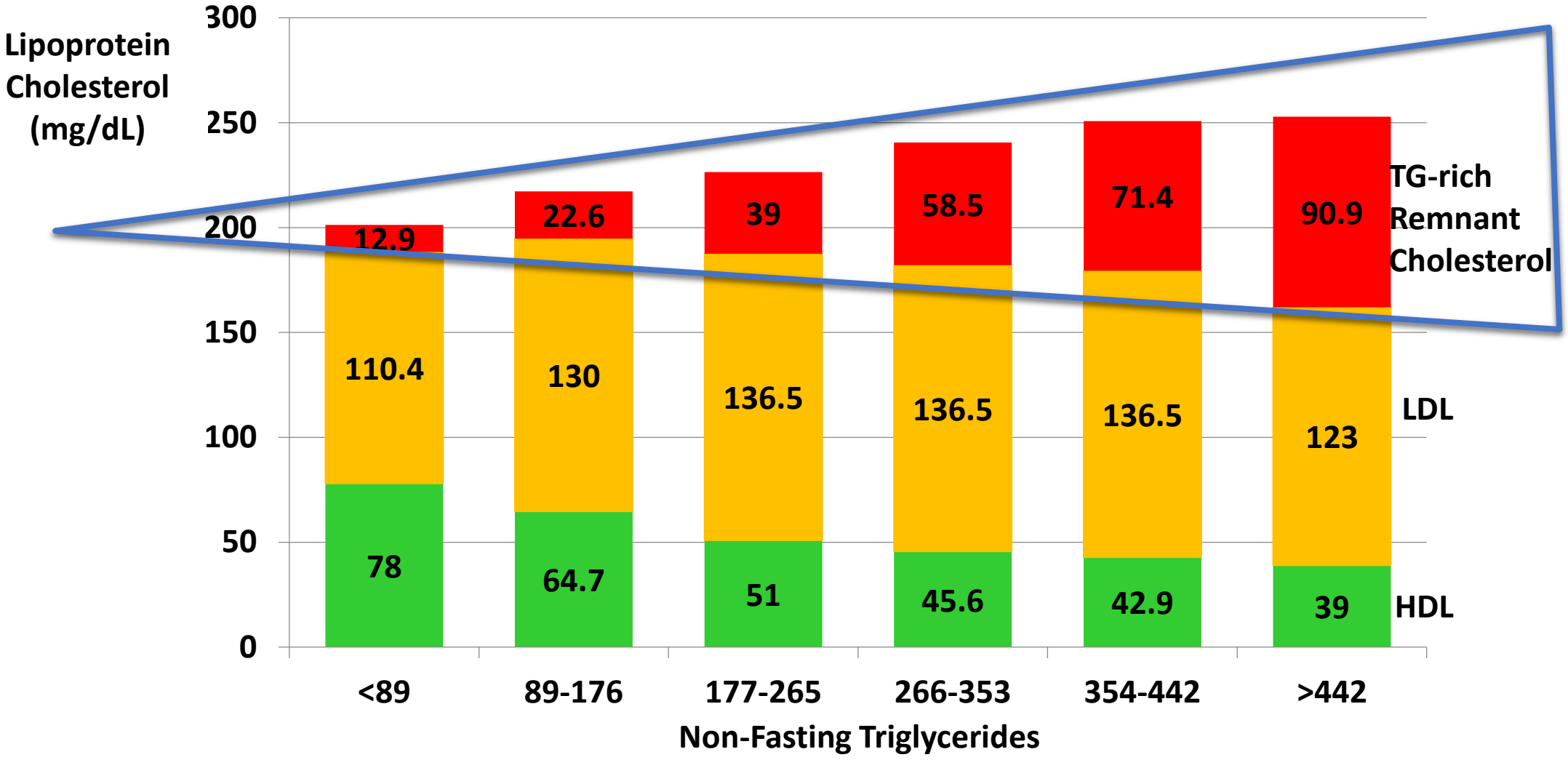




RLPs Deposit Cholesterol and Induce Inflammation

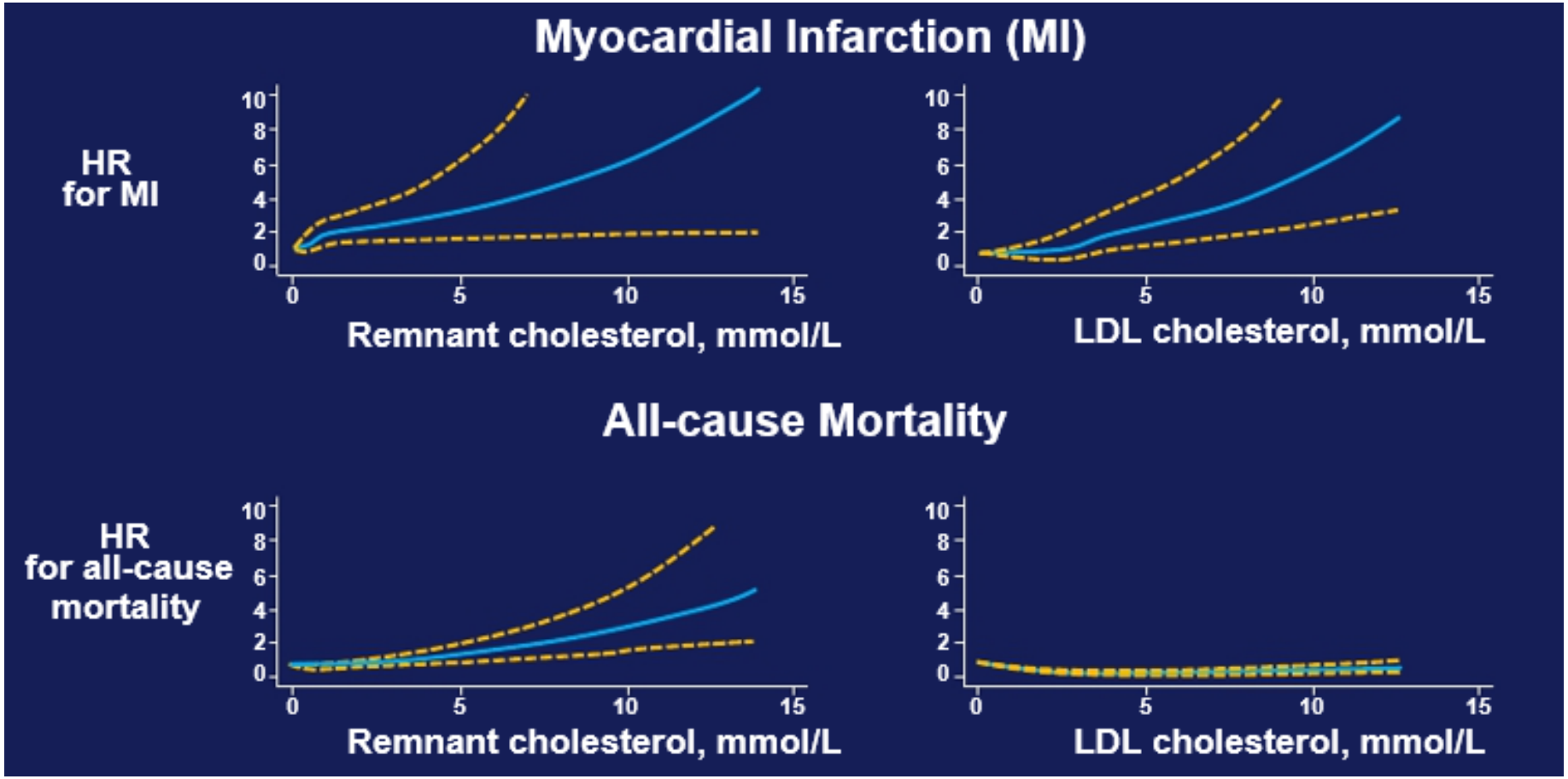
- **Like LDL, TGRLPs enter the arterial intima**
- **Unlike LDL**
  - **RLP intima retention > LDL**
  - **Lipolysis produces**
    - **proinflammatory and**
    - **pro-coagulant products**
  - **Macrophages uptake RLPs**
    - **without modification**
  - **RLP-C accumulation + low-grade chronic inflammation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



Chapman MJ, Ginsberg HN, Amarenco P et al. European Heart Journal 2011;32(11): 1345–1361

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



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

Epidemiological Data

Elevated TG correlates with elevated CV risk

- Kasai 2013 (meta)
- Sarwar 2007, 2010 (metas)
- Di Angelantonio (ERFC 2009; meta)
- Copenhagen General Population (Langsted 2008, 2011)
- Copenhagen City Heart (Nordestgaard 2007, Freiberg 2008, Langsted 2011)
- Women's Health (Bansal 2007)
- Asia Pacific Cohort (Patel 2004)
- Austin 1998 (meta)
- COLTS, Miller 1998
- Copenhagen Male, Jeppesen 1998
- Hokanson 1996 (meta)
- PROCAM (Assman 1992, 1996)
- Framingham Heart (Castelli 1986, 1992)

Genetic Data

TG/TG-rich lipoproteins are in the causal pathway of CVD

- Van Iperen 2016
- Do 2015
- Crosby 2014
- Jørgensen 2014
- Holmes 2014
- Thomsen 2014
- Do 2013
- Willer (GLGC) 2013
- Jørgensen 2013
- Varbo (Circ) 2013
- Varbo (JACC) 2013
- Johannsen 2012
- Schunkert 2011
- Teslovich 2010
- Pollin 2008
- Wittrup 1999

Clinical Data

Reducing TG in certain subgroups reduces CV risk

- Jun 2010 (meta)
- ACCORD-Lipid (Ginsberg 2010; subgroup)
- AIM-HIGH (Guyton 2013; subgroup)
- PROVE-IT (Miller 2008)
- IDEAL & TNT (Faergeman 2009)
- FIELD (Scott 2009; subgroup)
- JELIS (Saito 2008; subgroup)
- BIP (Haim 2006; subgroups)
- VA-HIT (Rubins 1999)
- HHS (Manninen 1992; subgroup)
- Stockholm Ischaemic Heart Dis. Sec. Prev. (Carlson 1988)

Outcomes Data

No studies completed dedicated to ↑ TG (>2 mmol/L, >180 mg/dL)

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:

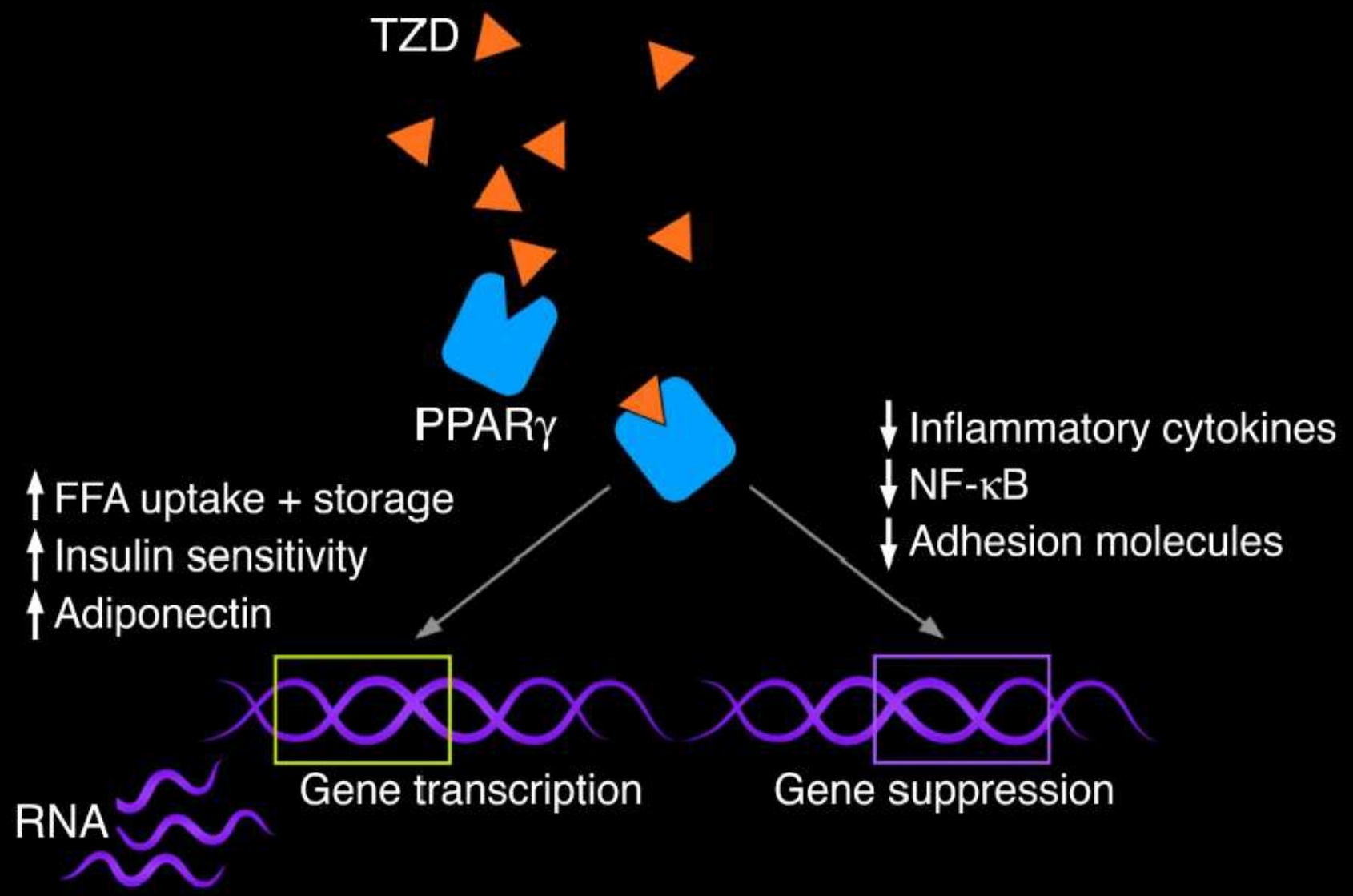
- **Showed ~25% reduction (P <0.001) in the Primary Endpoint, a 5-point composite of MACE.**
  - **5-point composite endpoint = CV death, nonfatal MI, including silent MI, nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization**
- **Secondary endpoints (multiple) also 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*

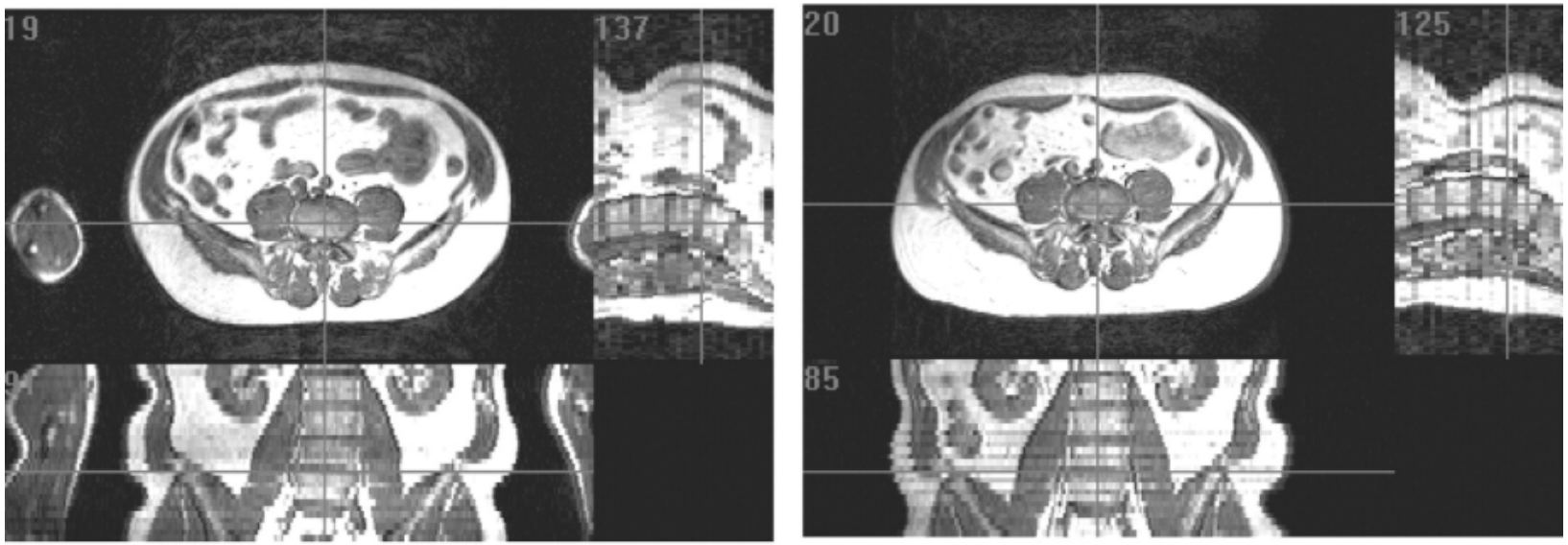
Thiazolidinediones (TZD): Nuclear Transcription Factors



Pioglitazone Decrease Visceral Fat and Increases Subcutaneous Fat: The "Abdominal Obesity" Factor is Improved

Case: Male/59 years old

Baseline | **Pioglitazone for 16 weeks**

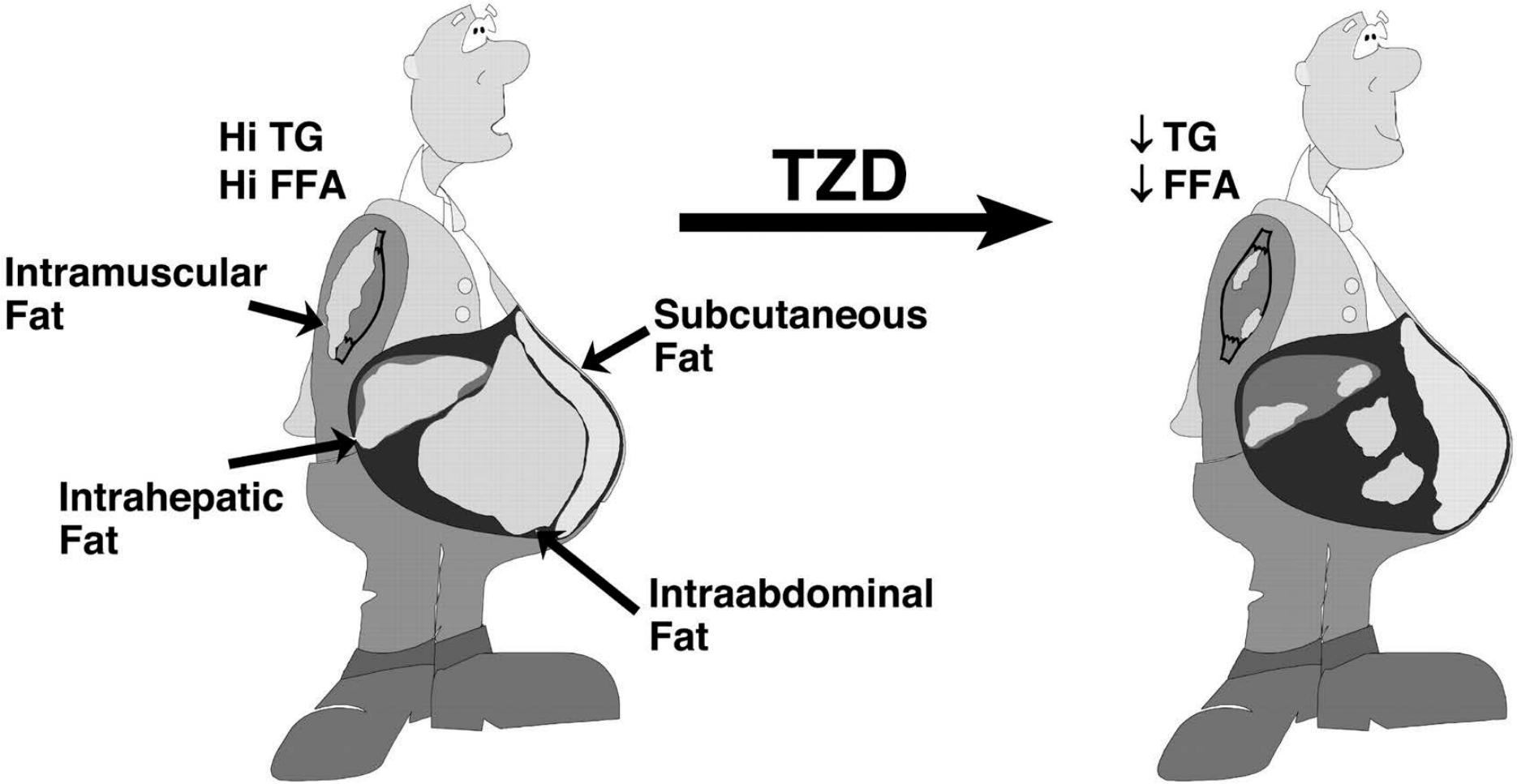


MRI Assessment

Baseline	Pioglitazone for 16 weeks	4-month changes
Subcutaneous Fat Area: 144.3 cm^2	Subcutaneous Fat Area: 204.7 cm^2	+ 42%
Visceral Fat Area:140.0 cm^2	Visceral Fat Area:105.1 cm^2	- 25%
Body Weight: 67.4 kg	Body Weight: 69.2 kg	
FPG: 184 mg/dl	FPG: 117 mg/dl	
HbA_{1c}: 7.3 %	HbA_{1c}: 6.5 %	

Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA. J Clin Endocrinol Metab. 2002 Jun;87(6):2784-91et al: JCEM 2002, 87, 2784-2791.

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

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

DeFronzo RA et NEJM. 2011;364(12):1104-1115
Xiang et al: *Diabetes* 55:517-522, 2006
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
Knowler WC et al. *N Engl J Med*. 2002;346:393-403
Torgerson JS et al. *Diabetes Care*. 2004;27:155-161
Toumilehto J et al. *N Engl J* Med. 2001;344:1343-1350

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:

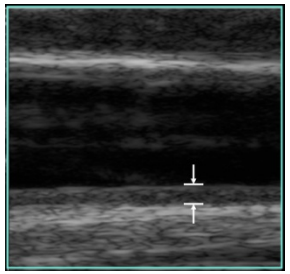
Beta-cell responsiveness
Beta-cell longevity/durability
Insulin sensitivity (peripheral)
HDL-C
HDL particle size
LDL particle size
Cardiac output, stroke volume
Nitric oxide synthesis
Brachial artery reactivity*
Adiponectin

Not so favorable increases in

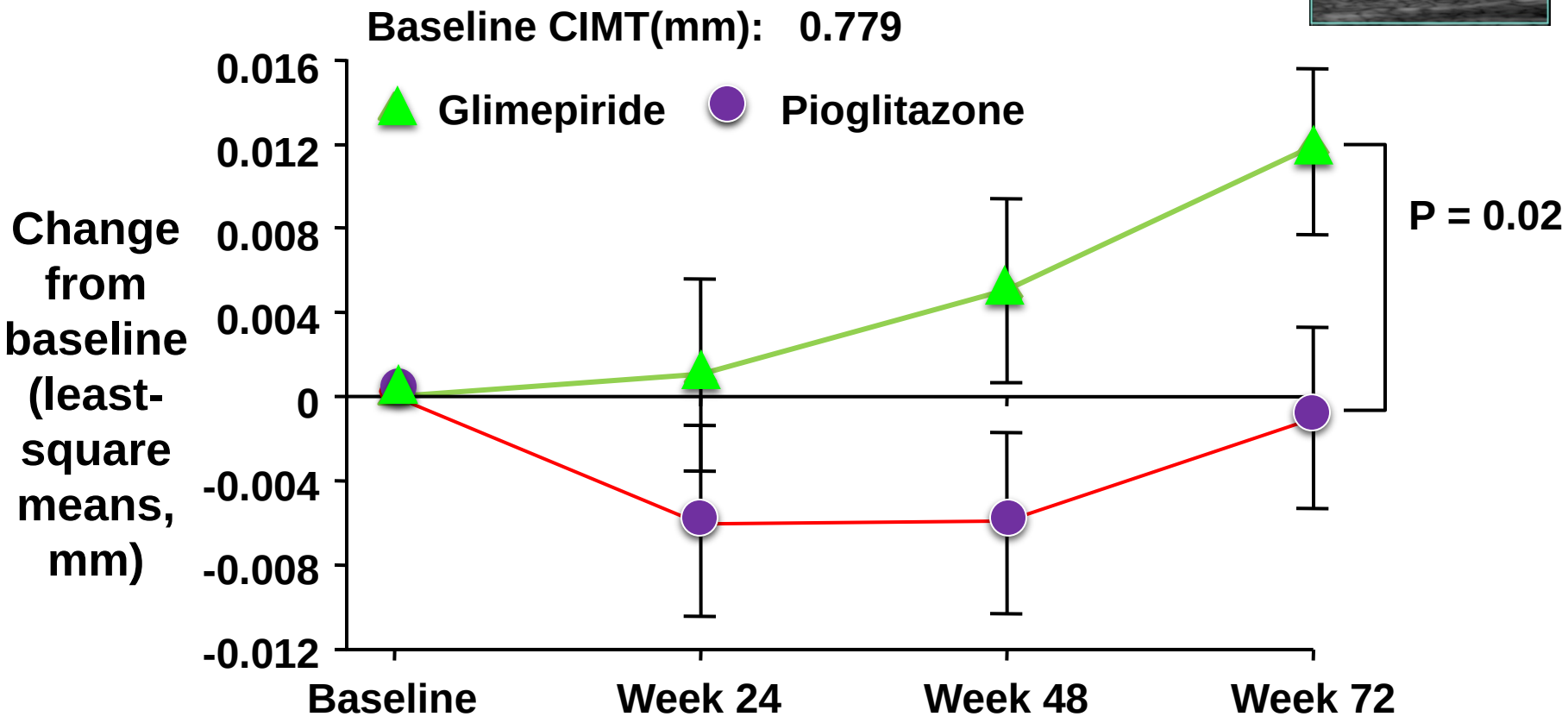
Peripheral / Subcutaneous fat deposition

Favorable Changes in Cardiovascular Risks

Carotid Intima-Media THICkness (CIMT) in Atherosclerosis Using PioGlitazOne (CHICAGO)



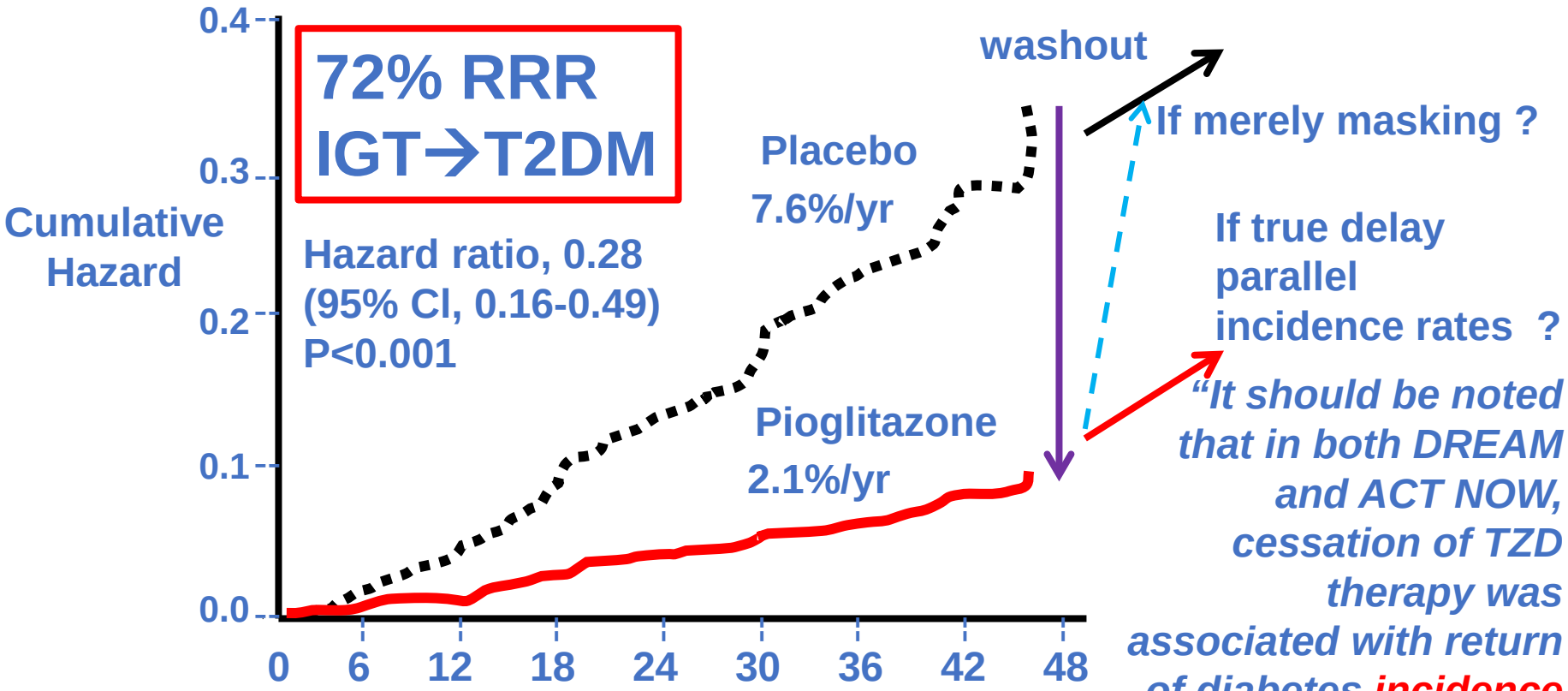
Treatment effect on posterior wall CIMT



Over an 18 month treatment period in patients with Type 2 DM pioglitazone slowed progression of CIMT compared to glimepiride

Mazzone T, et al. *JAMA*. 2006;296(21):2572-2581

Actos Now for Prevention of Diabetes (Act Now): Kaplan-Meier Plot of Hazard Ratios for Time to Development of Diabetes (n=602)



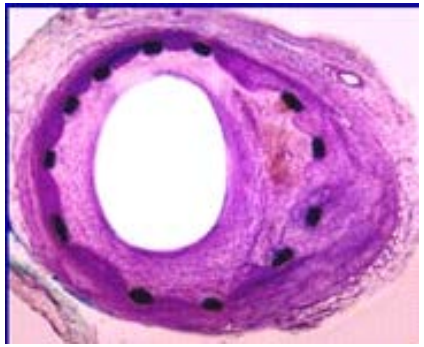
No. at Risk								
Placebo	299	259	228	204	191	134	83	17
Pioglitazone	303	262	244	228	218	140	87	24

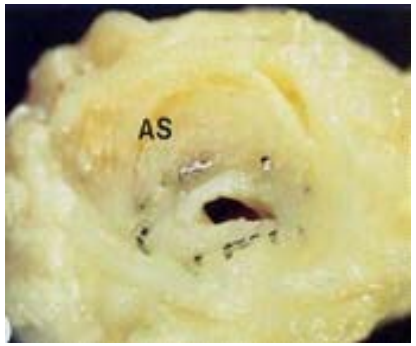
"It should be noted that in both DREAM and ACT NOW, cessation of TZD therapy was associated with return of diabetes incidence rates similar to those observed in the placebo group."

Defronzo R A, Abdul-Ghani M,Diabetes Care 34(Suppl. 2):S202–S209, 2011

DeFronzo RA, Tripathy, D, Schwenke DC, et al. N Engl J Med 2011;364:1104-1115

Stenting: Clinical & Angiographic Outcomes





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

	Diabetes n=715	No Diabetes n=2,839	p value
Restenosis (%)	37.5	28.8	<0.001
Death (%)	5.7	2.9	<0.001
Death & Non-fatal MI (%)	8	4.6	<0.001
Repeat PTCA (%)	21.1	15.6	<0.001

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

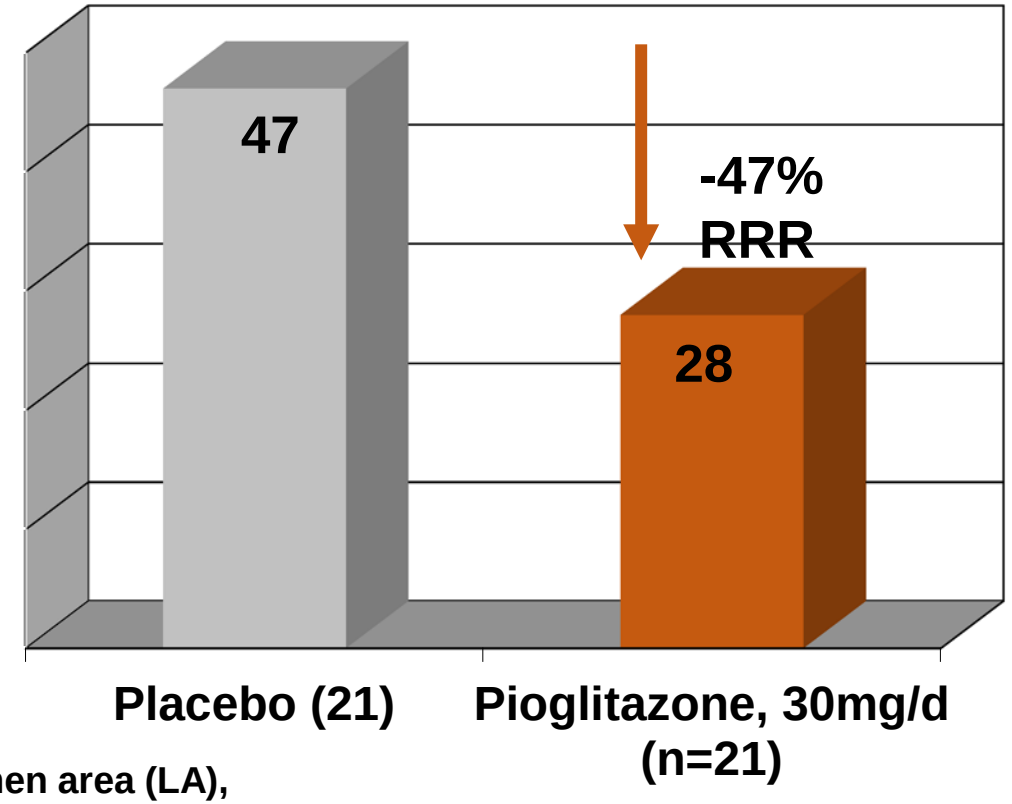
Elezi S et al. *J Am Coll Cardiol*. 1998;32:1866-1873

Neointimal Hyperplasia After Coronary Stenting: Effect of adding Pioglitazone (30mg/day) to Conventional Anti-DiabeticTherapy* 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



(*P*<0.0001).

The stent area (SA), lumen area (LA), neointimal area (NA = SA - LA), and neointimal index (NI = NA/SA x 100%)

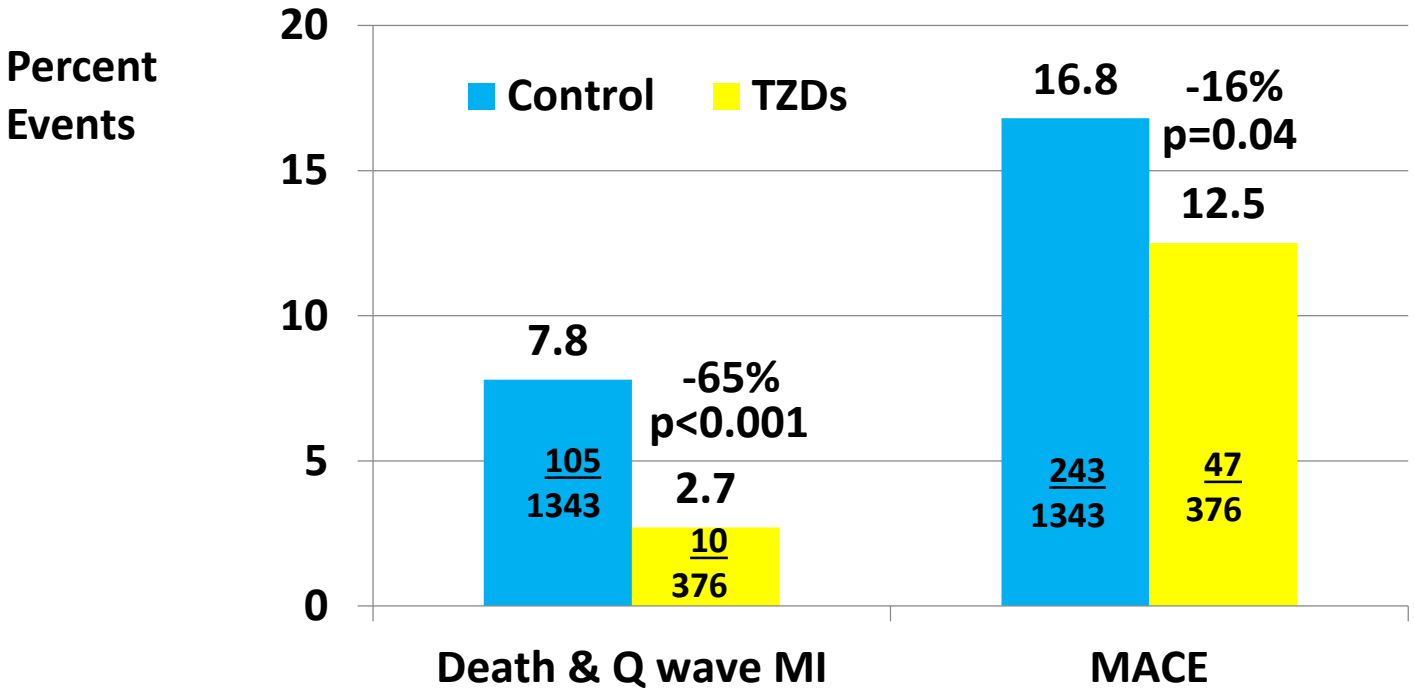
Takagi T et al. *Am Heart J*. 2003;146:1-8

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.

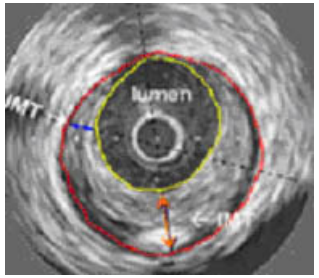
Primary Outcome = composite outcome of death & Q wave MI at 1 yr.

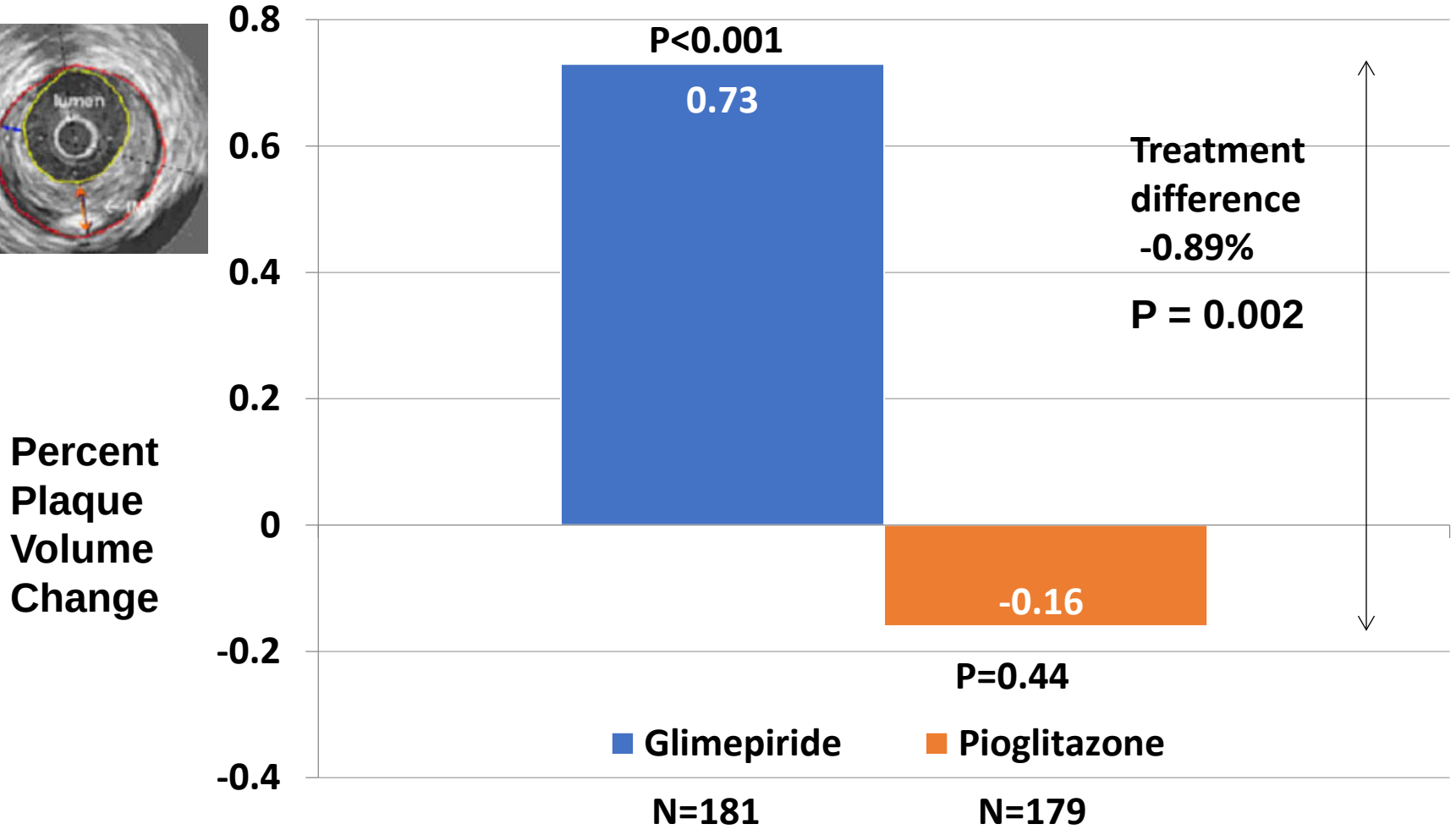
Secondary Outcome = MACE= Death, MI and TVR (target vessel revascularization)



Patel DB, et al. J Am Coll Cardiol. 2011;57(14_Suppl_S):E1826.

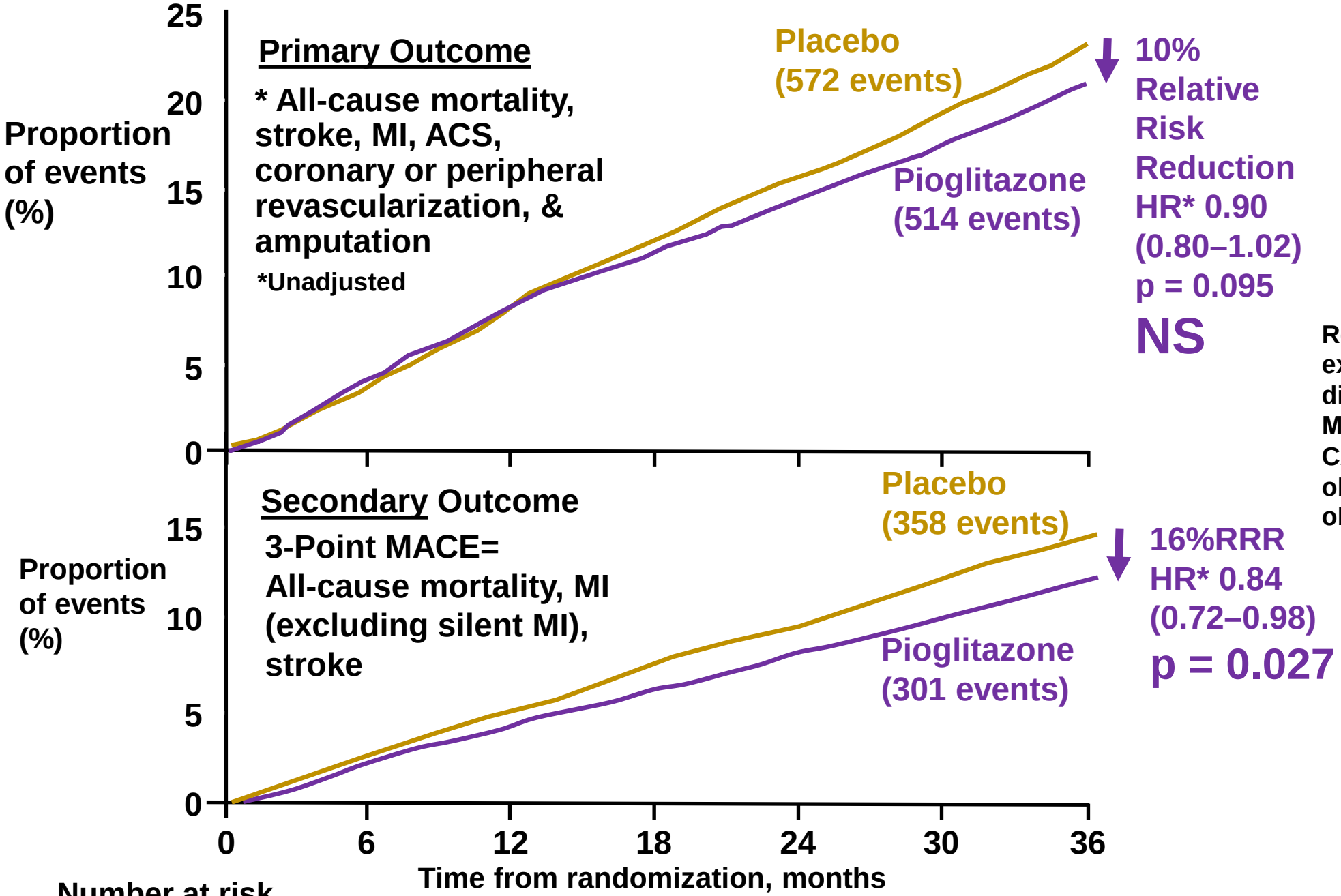
Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) Trial: Primary End-Point (Plaque Volume Changes)





Nissen SE, et al. *2008;299(13):1561-1573*

PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROactive)

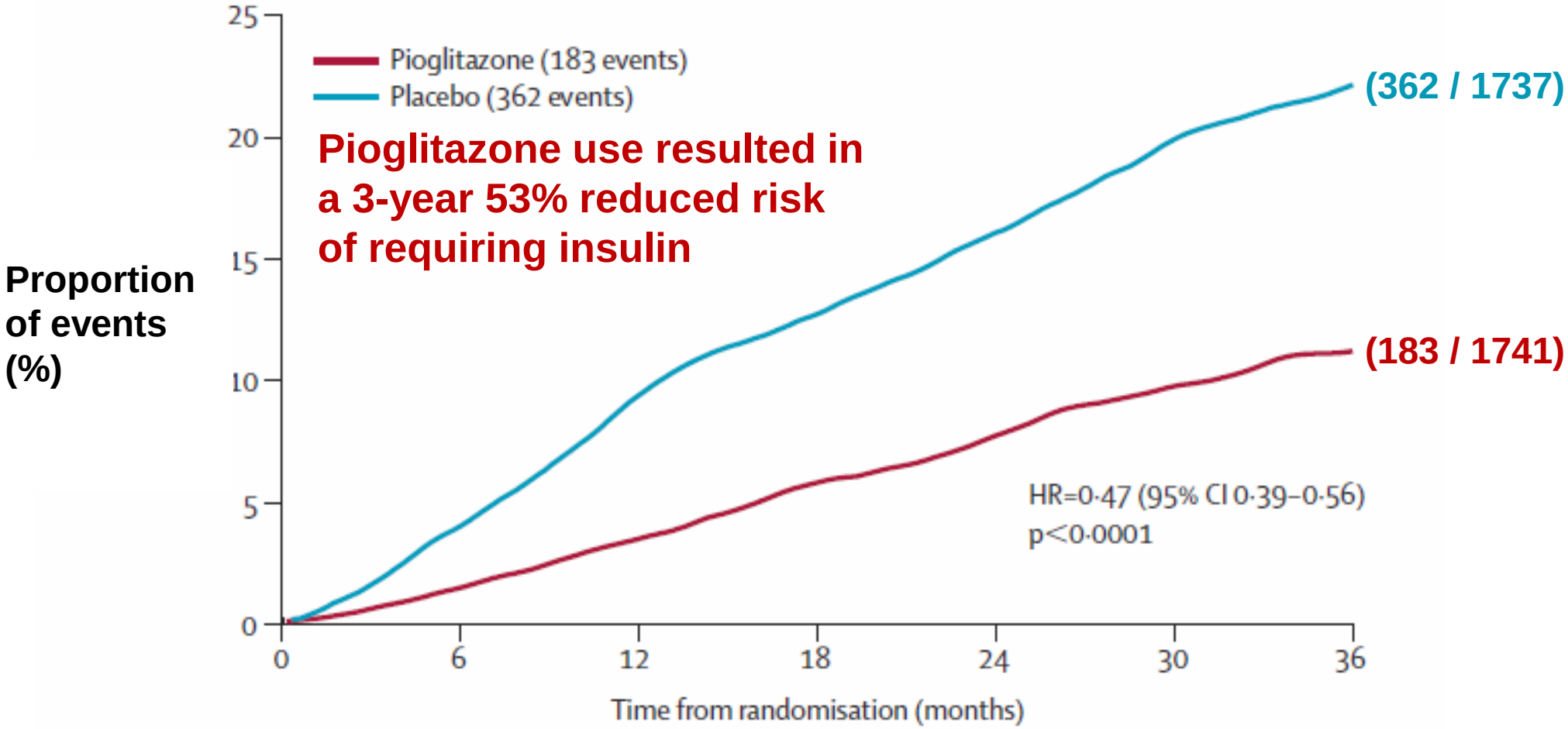


Recruited participants with extensive macrovascular disease defined by ≥1 criteria: MI or stroke ≤ 6 mos., PTCA or CABG, ACS ≤ 3 mos. or objective evidence of CAD or obstructive PAD.

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

Dormandy JA, et al. *Lancet*. 2005;366:1279-89.

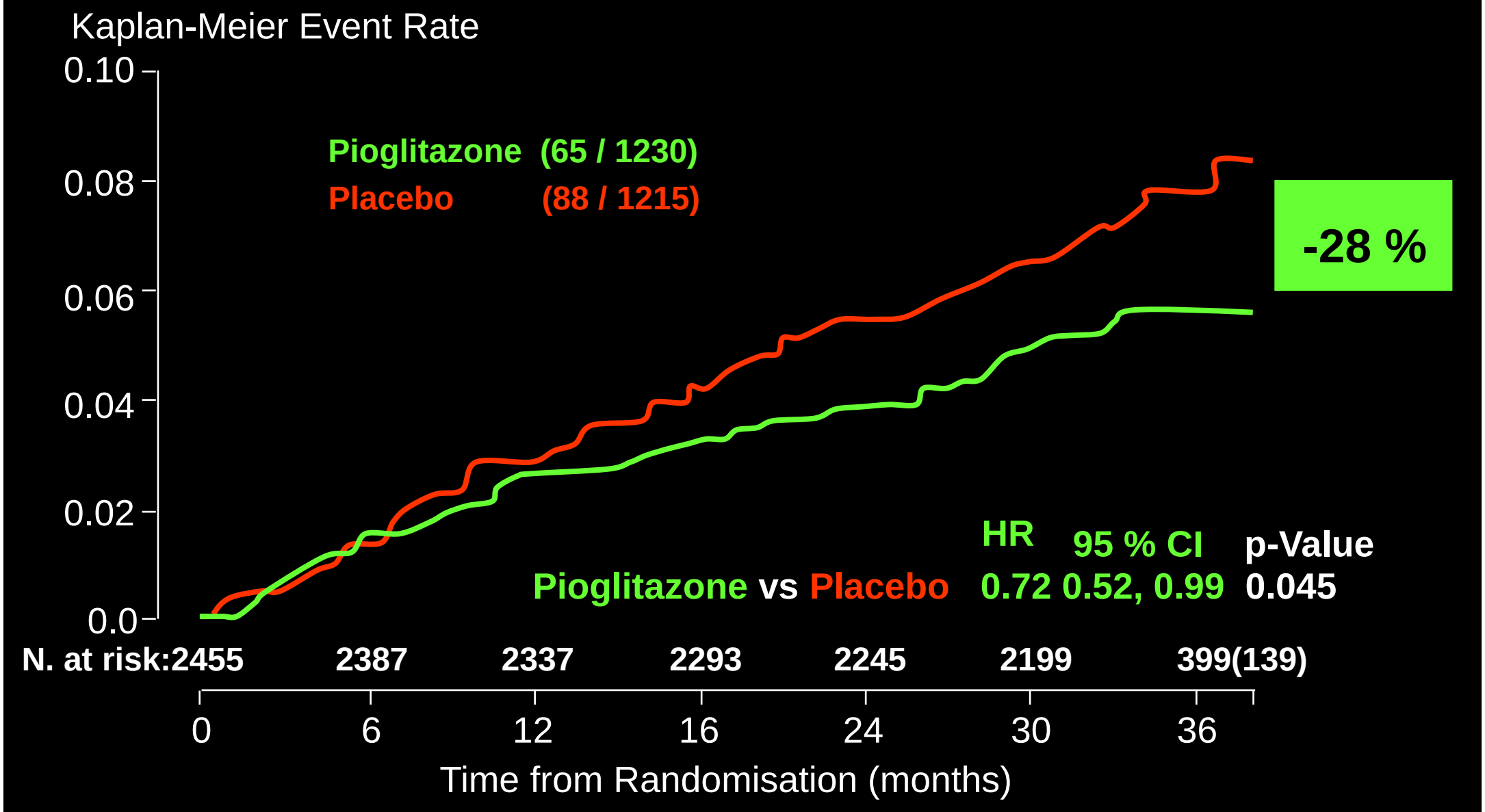
PROACTIVE: Time to Permanent Insulin Use



Numbers at risk						
Pioglitazone	1700	1654	1603	1554	1499	244
Placebo	1646	1544	1472	1401	1325	202

Dormandy JA, Charbonnel B, Eckland DJA, et al. Lancet 2005;366:1279-1289)

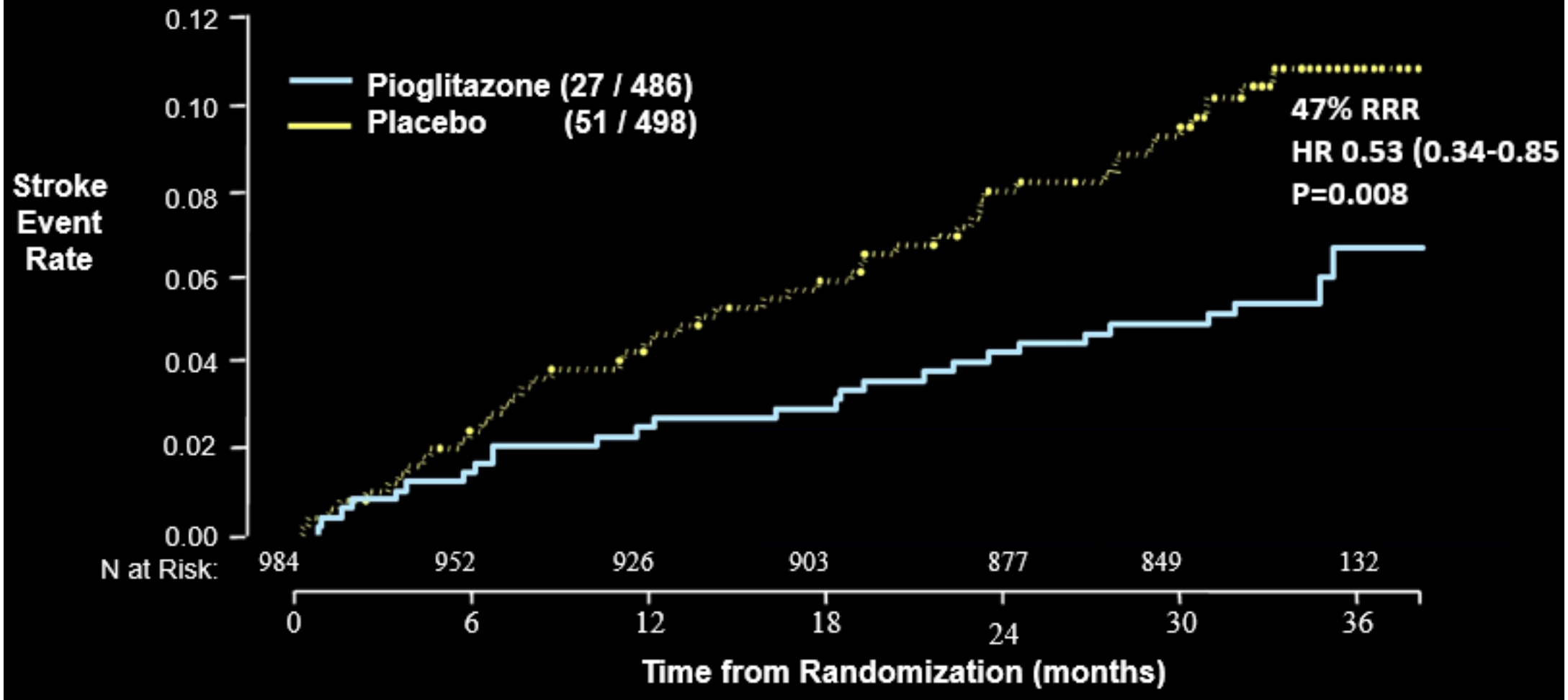
Pioglitazone's Effect on Recurrent MI in Patients with Previous MI



proactive-results.com

Erdmann E. et al. JACC 2007; 49: 1772-1780

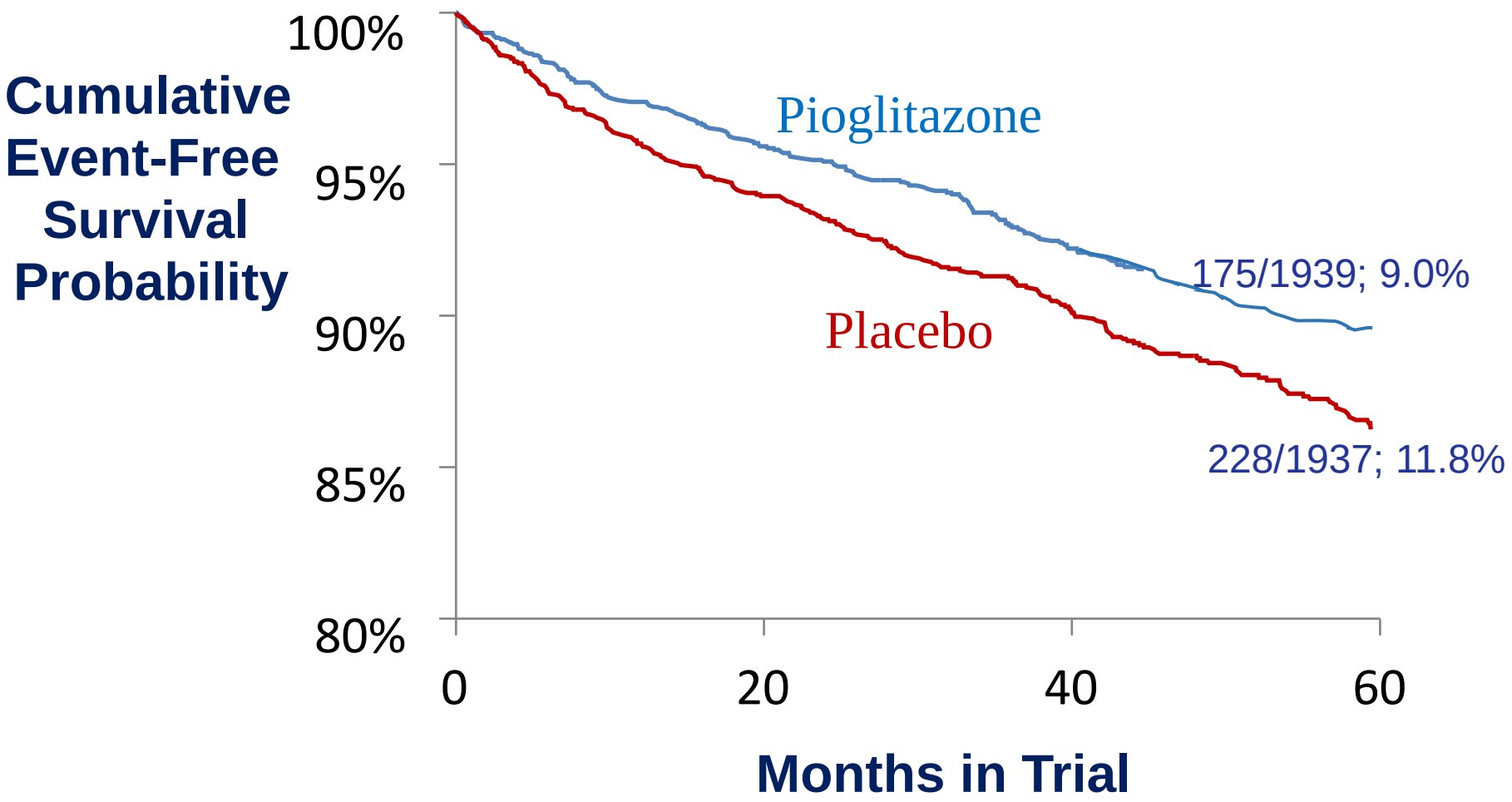
PROACTIVE: Pioglitazone's Effect on Recurrent Stroke in Patients with Previous Stroke: Kaplan-Meier Event Rate



Wilcox R, Bousser MG, Betteridge DJ, et al. Stroke. 2007;38:865-873.

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

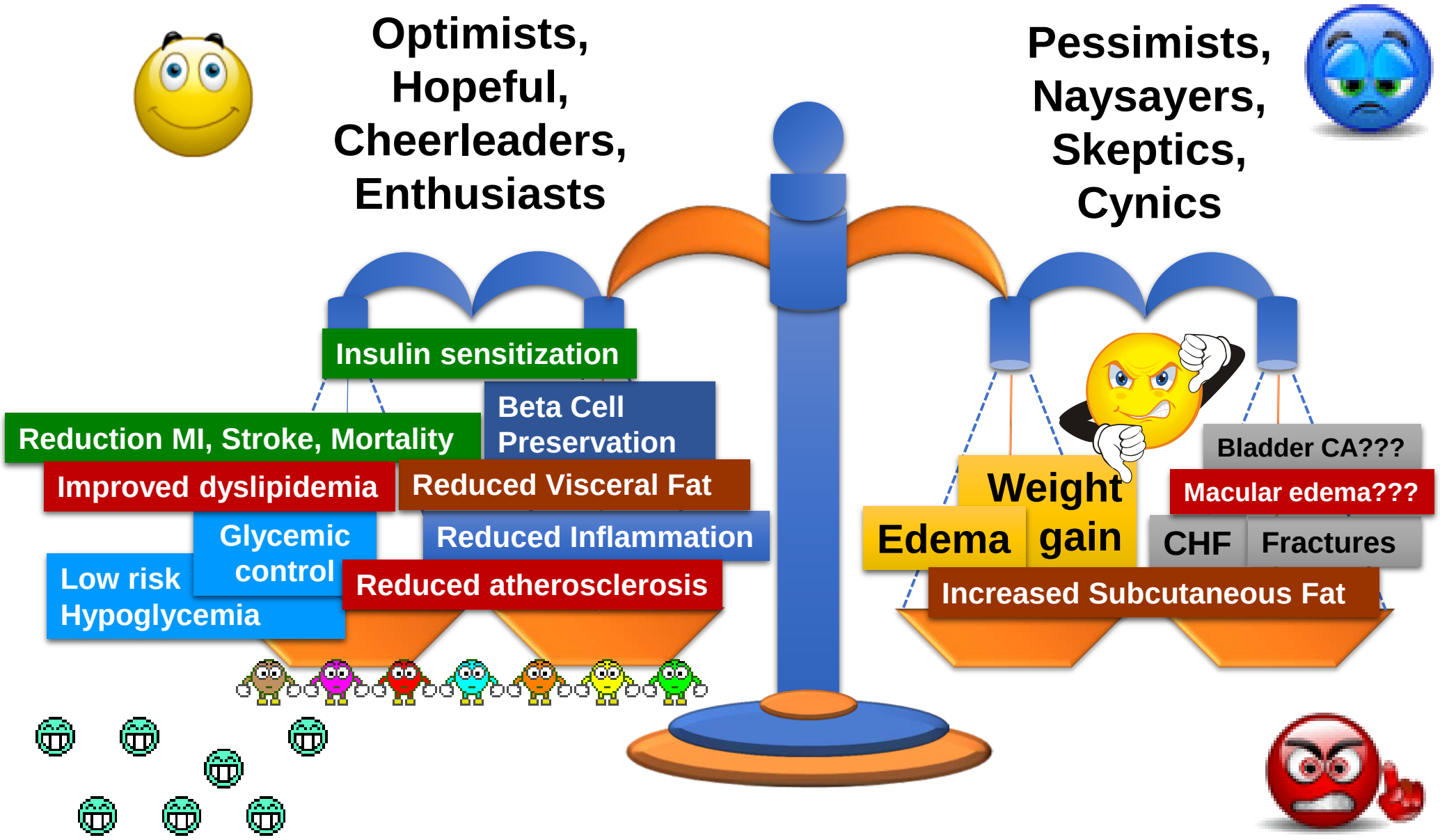
Among insulin resistant, non-diabetic patients with a recent ischemic stroke or TIA, to determine if the TZD, pioglitazone, compared with placebo, reduces risk for Stroke or MI.



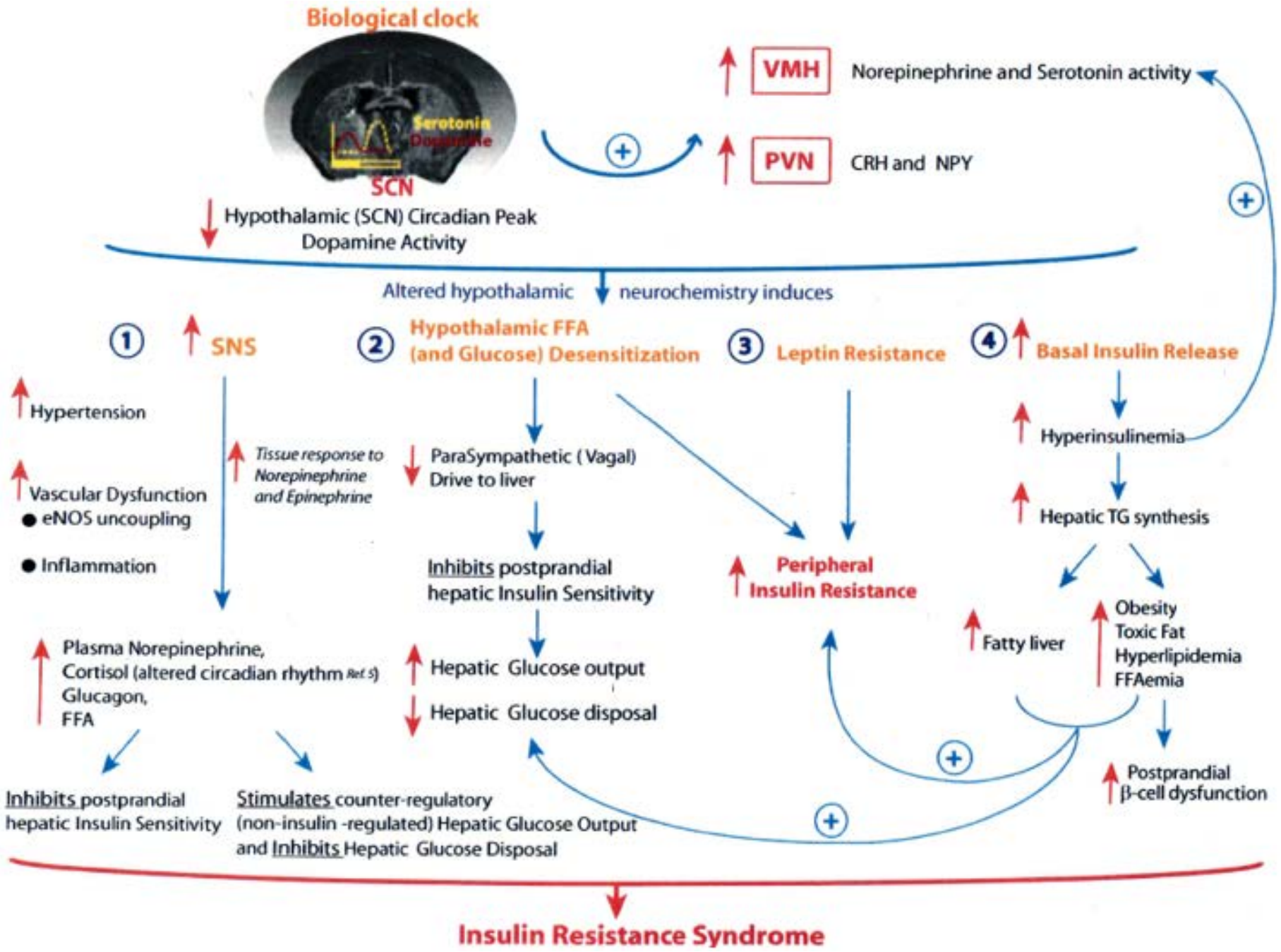
24% RRR
HR, 0.76;
95% CI, 0.62 to 0.93;
P=0.007
ARR 2.8%
NNT =36

Kernan WN, Viscoli CM, Furie KL et al. for the IRIS Trial Investigators. N Engl J Med 2016; 374:1321-1331

TZDs (Pioglitazone): Weighing Benefit vs. Risk



Central Insulin Resistance



Cincotta AH et al. Amer J Physiol Regula Integr Comp. 2000;278(2):R435-444.
Luo S, et al. Diabetologia. 2008;51:[suppl 1]S59.
Liang Y Metabolism. 1999;48(10):1287-1289.
Zhang Y et al. Diabetes. 2013;62(suppl 1):A525.
Hansen B, Shaffrir E, Cincotta AH. Hypothalamic role in the insulin resistance syndrome. In Insulin Resistance Syndrome. Hansen B, Shaffrir E, Eds. London, Taylor and Francis, 2002, p. 271–312.

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

***MI, Stroke, unstable angina hospitalization, CHF hospitalization, or coronary revasc.**

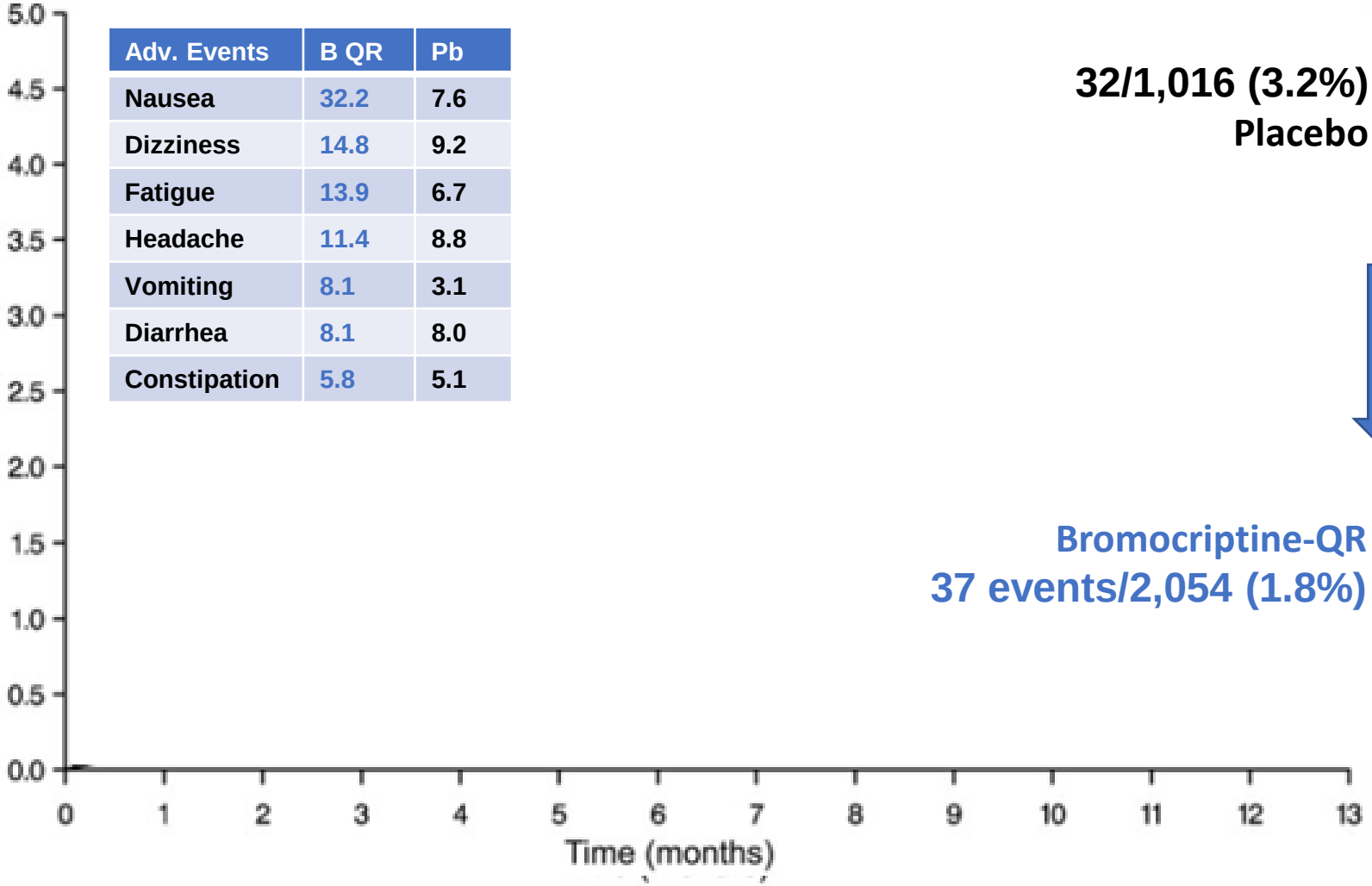
Adv. Events	B QR	Pb
Nausea	32.2	7.6
Dizziness	14.8	9.2
Fatigue	13.9	6.7
Headache	11.4	8.8
Vomiting	8.1	3.1
Diarrhea	8.1	8.0
Constipation	5.8	5.1

32/1,016 (3.2%)
Placebo

0.8 mg tabs titrated to 4.8 mg or maximally tolerated dose

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

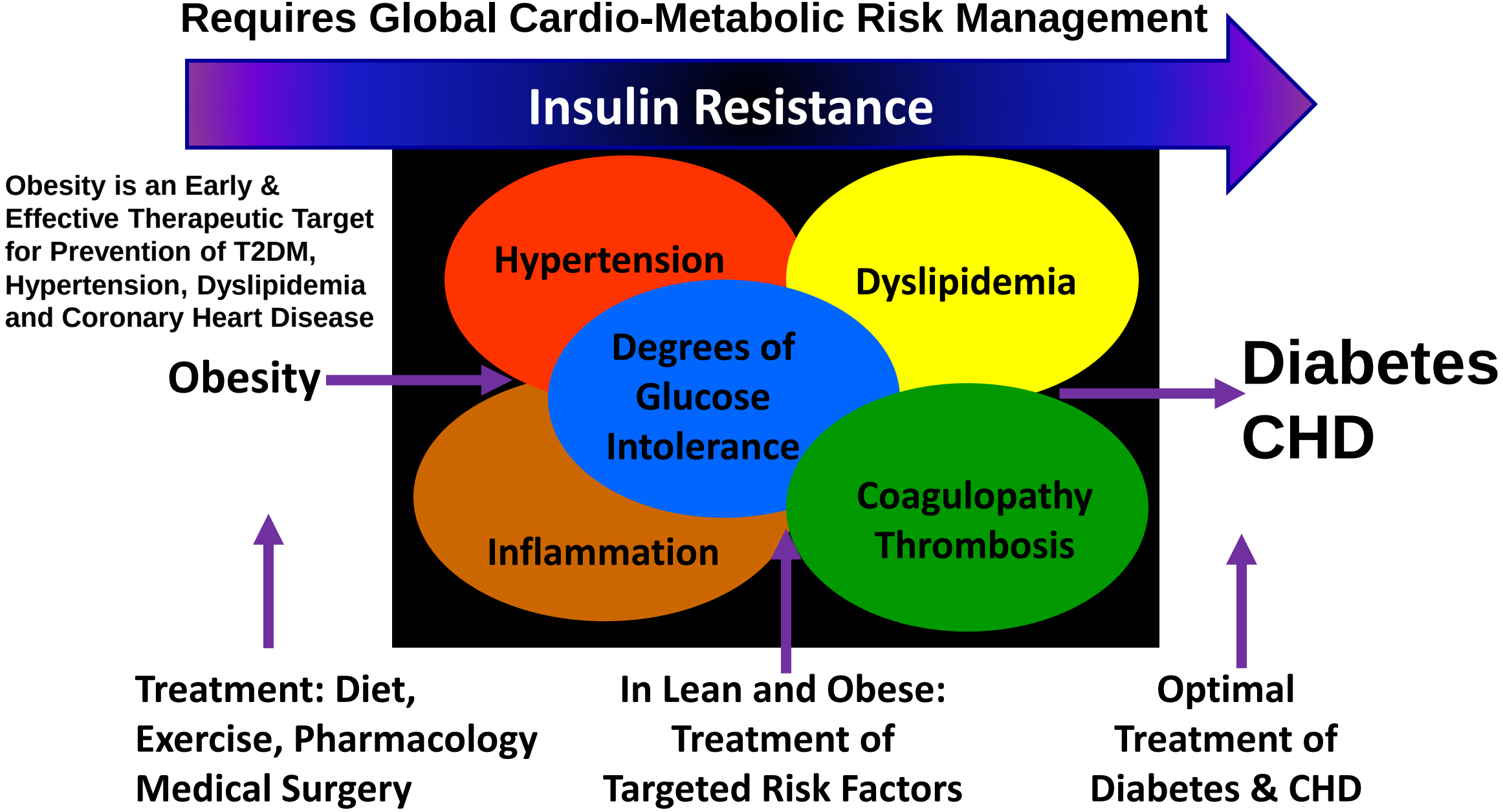
Bromocriptine-QR
37 events/2,054 (1.8%)



Number at risk				
Bromocriptine-QR	2054	1822	1691	1453
Placebo	1016	950	898	793

Gaziano JM, Cincotta AH, O'Connor CM, Diabetes Care. 2010;33(7):1503-1508.

Management of Insulin Resistance is Not Futile, But Requires Global Cardio-Metabolic Risk Management



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

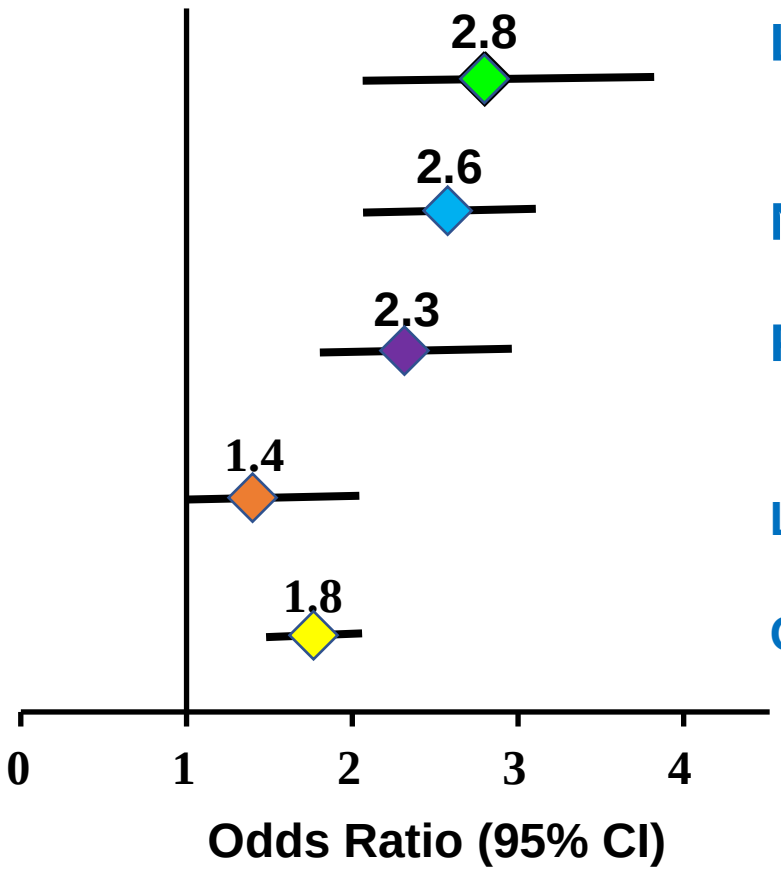
- **Insulin action is greater in physically active than sedentary individuals.[1]**
- **A single exercise session can increase insulin-stimulated glucose uptake in previously sedentary adults.[2]**
- **A single bout of moderate intensity exercise can increase glucose uptake by skeletal muscle at least 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]**

1. Björntorp P, Fahlen M, Grimby G. Metabolism. 1972;21:1037-1044.
2. Devlin JT, Hirshman M, Horton ED, et al. Diabetes. 1987;36:434-439.
3. Perseghin G, Price TB, Petersen KF, et al. N Engl J Med. 1996;335:1357-1362.
4. King DS, Baldus PJ, Sharp RL, et al. J Appl Physiol 1995;78:17-22.
5. Burstein R, Polychronakos C, Toews CJ, et al. Diabetes 1985;34:756–760.
6. Duncan GE, Perri MG, Theriaque DW, et al. Diabetes Care 2003;26:557-562.
7. Pate RR, Pratt M, Blair SN, et al. JAMA. 1995;273:402-407.
8. Blair SN, Kohl HW 3rd, Barlow CE, et al. JAMA. 1995;273:1093–1098.

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

Preference	Obesity Medication	Medication References & Notes	Clinical Monitoring
1st	**Phentermine/ Topiramate ER**	BP decreased by 3.2/1.1 mmHg placebo subtracted (1)	Monitor heart rate
1st	**Liraglutide 3 mg**	BP decreased by 2.8/0.9 mmHg placebo subtracted (21)	Monitor heart rate
1st	**Orlistat**	BP decreased by 2.1/1.0 mmHg placebo subtracted at 1 year (12)	
2nd	**Lorcaserin**	BP decreased by 0.6/0.5 mmHg placebo subtracted at 1 year (15)	
3rd	**Naltrexone ER / Bupropion ER**	**Contraindicated if BP is uncontrolled.** 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).	**Contraindicated if BP is uncontrolled.** BP lowering is not commensurate with degree of weight loss. Monitor heart rate and BP

Direct Meta-Analysis: Likelihood of Discontinuation Commonly Recommended Weight Loss drugs Due to Adverse Events[1]



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

Common Adverse Events[2-4,a]

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

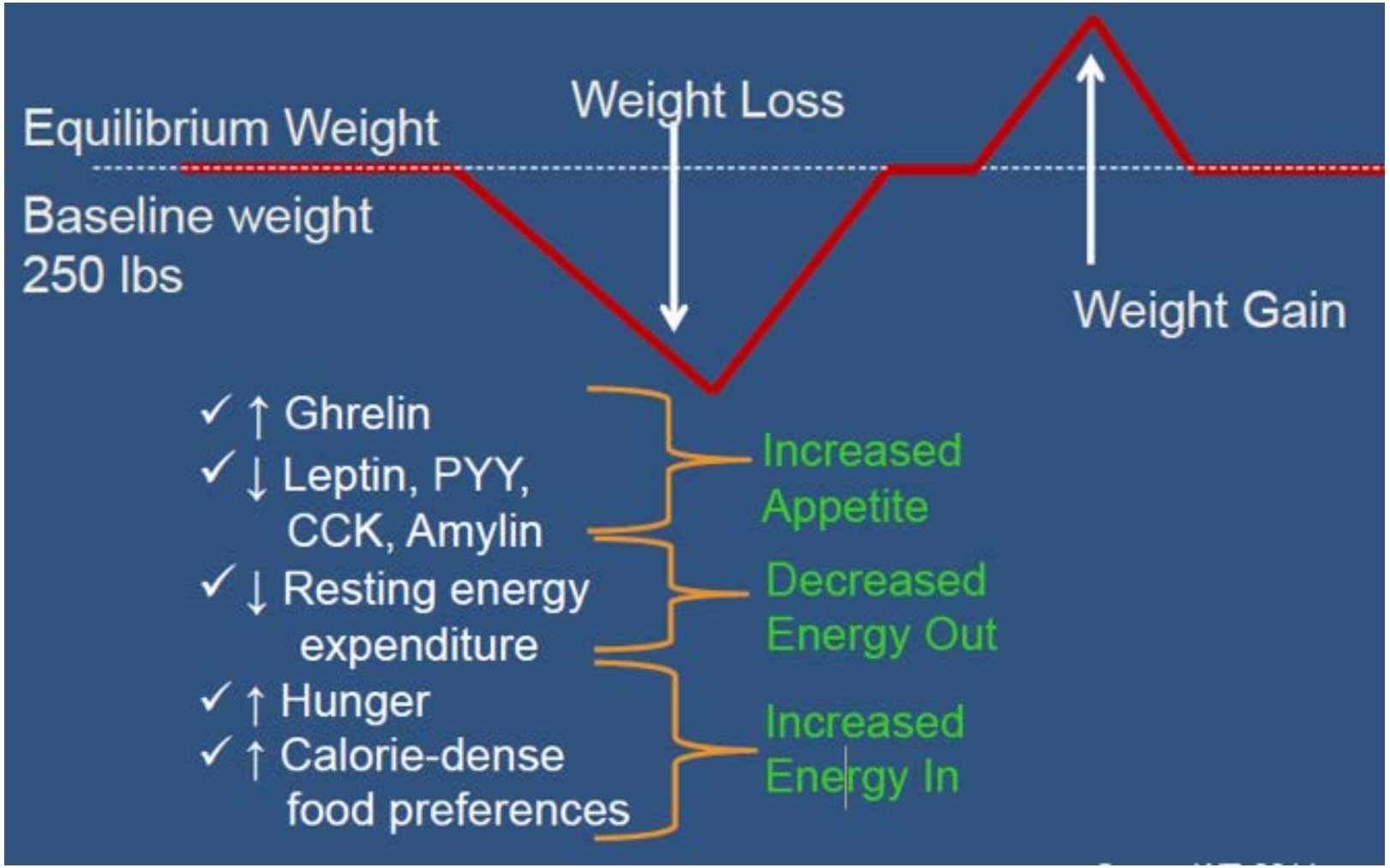
1. Khera R, et al. *JAMA*. 2016;315:2424-2434;
2. Drugs@FDA: FDA approved drug products. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;
3. Garvey WT, et al. *Endocr Pract*.2016;22:842-884;
4. ADA. *Diabetes Care* 2017;40(suppl 1):S57-S63.

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.**

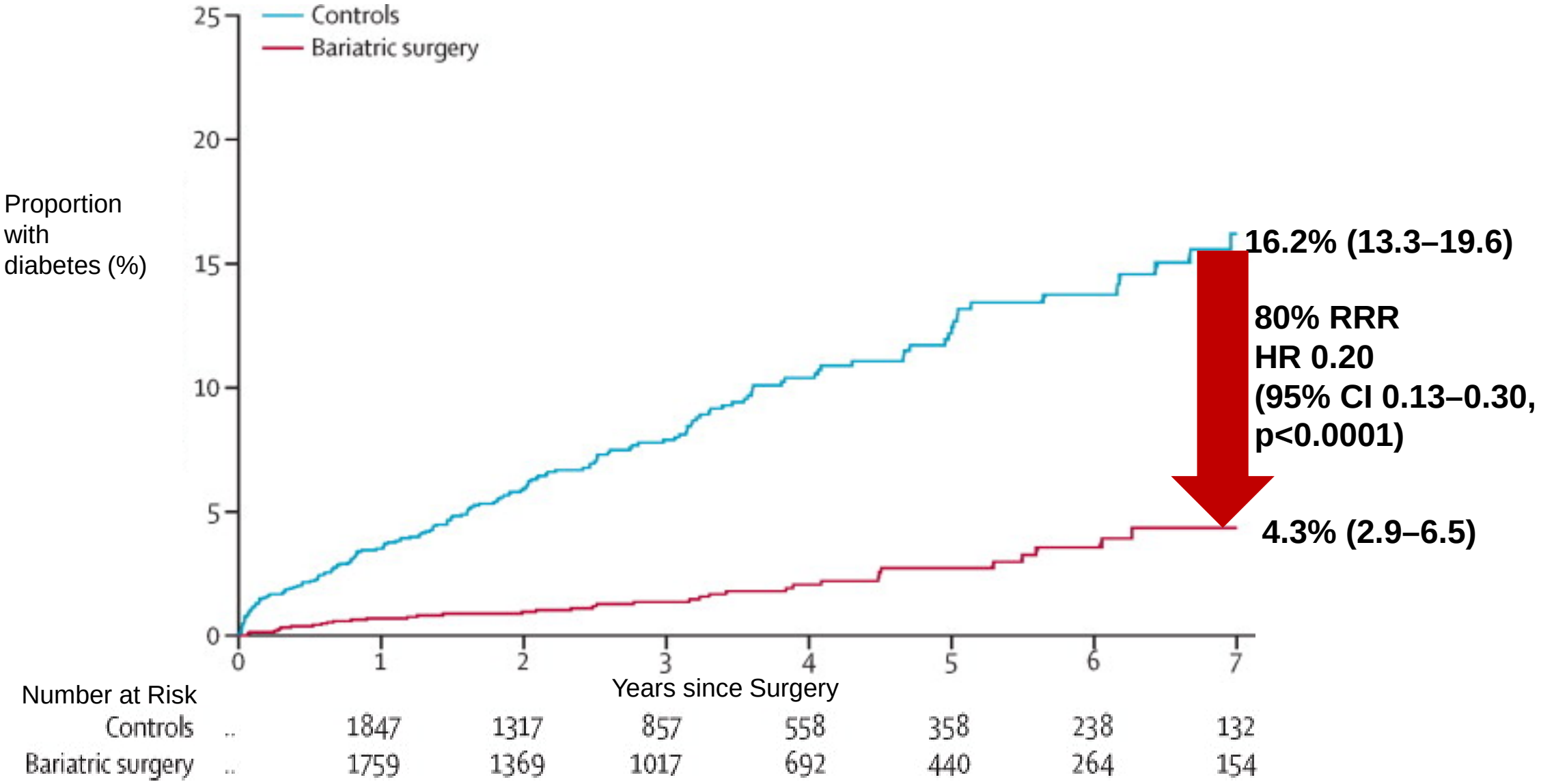
2009 Food and Health Survey: Consumer Attitudes toward Food. Nutrition & Health: International Food Information Council Foundation May 20, 2009.
Sarlio-Lähteenkorva S, Rissanen A, Kaprio J. A descriptive study of weight loss maintenance: 6 and 15 year follow-up of initially overweight adults. *International Journal of Obesity*. 2000;24(1):116–125.
Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. *Obesity Research*. 2004;12, supplement:151S–62S.

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



Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, Grunberger G, Handelsman Y, Hennekens CH, Hurley DL, McGill J, Palumbo P, Umpierrez G; on behalf of the AACE Obesity Scientific Committee (*2014*) American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the 2014 Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease. Endocrine Practice: September 2014, Vol. 20, No. 9, pp. 977-989.

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



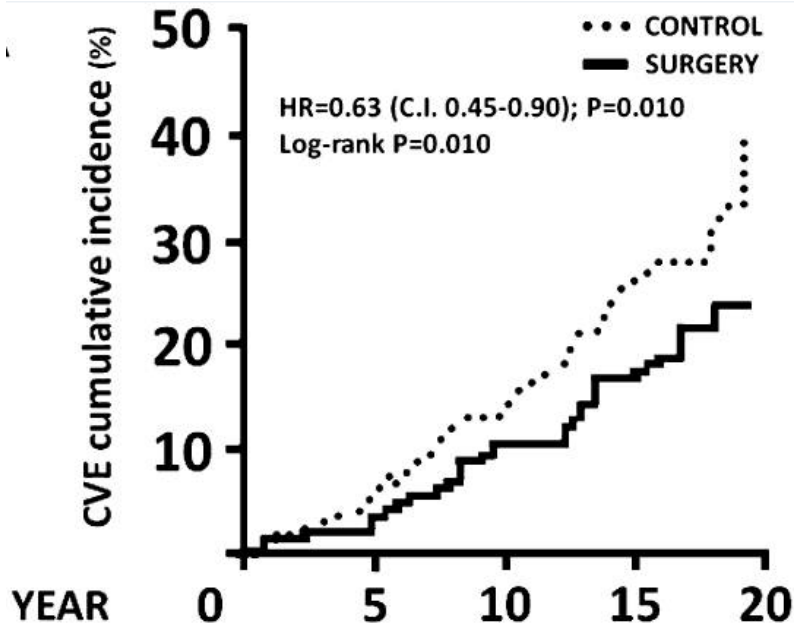
Booth H, Khan O, Prevost T et al. Lancet Diabetes Endocrinol. 2014 Dec;2(12):963-968.

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

Cumulative incidence of CV Events (MI + Stroke)

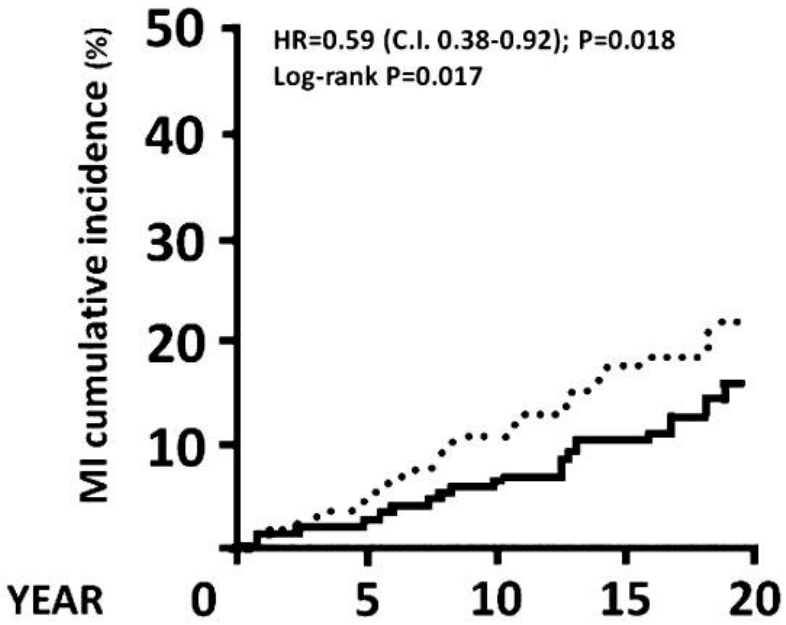
-37% RRR



Surgery N=	345	325	268	144	36
Control N=	262	242	195	85	9

Cumulative incidence of CV Events (MI only)

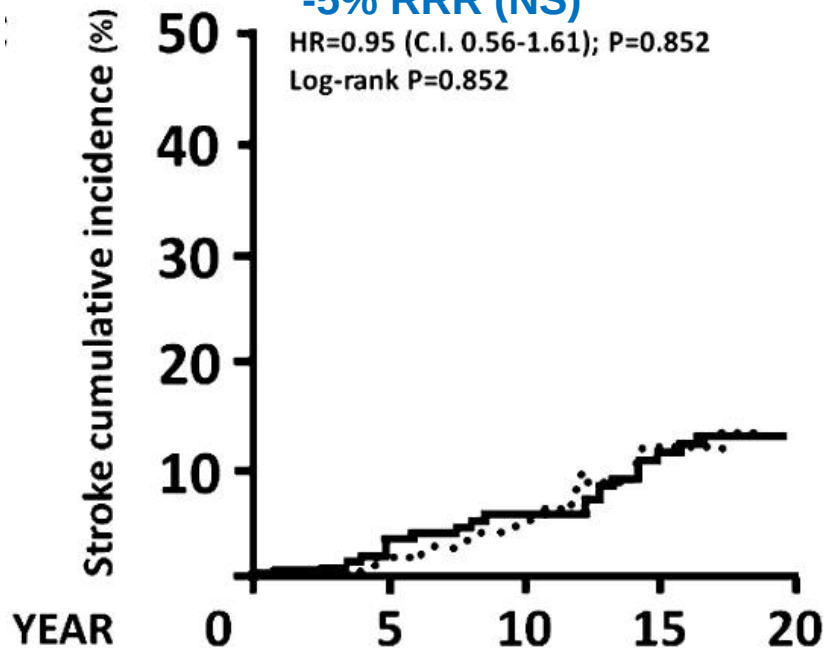
-41% RRR



Surgery N=	345	328	278	153	39
Control N=	262	243	202	96	11

Cumulative incidence of CV Events (Stroke only)

-5% RRR (NS)



Surgery N=	345	332	278	153	37
Control N=	262	250	281	93	14

Romeo S, Maglio C, Burza MD, et al. Diabetes Care. 2012 Dec; 35(12): 2613–2617.