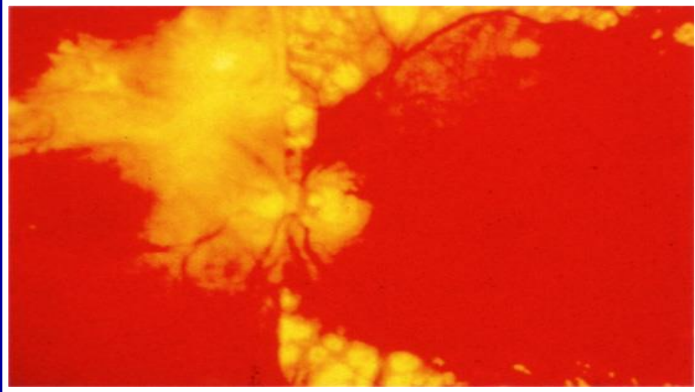


# **INSULIN RESISTANCE, T2DM, AND ASCVD: THE MISSING LINKS**

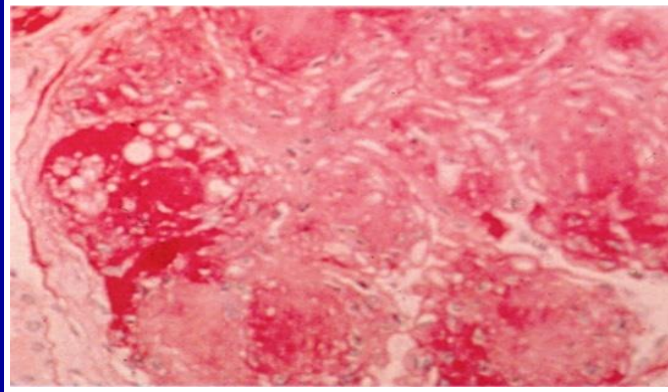
**Ralph A. DeFronzo, M.D.  
Professor of Medicine  
University of Texas Health  
Science Center  
San Antonio, Texas**

# UKPDS: EPIDEMIOLOGIC ANALYSIS

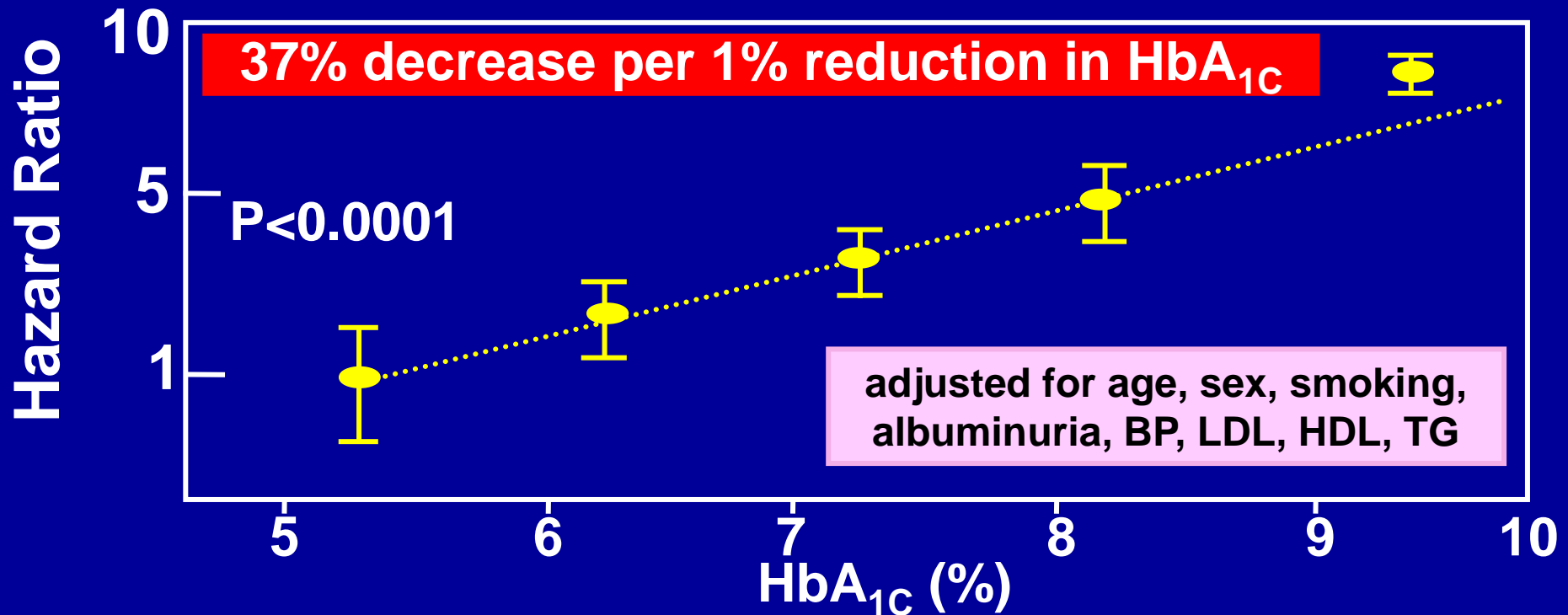
## Retinopathy



## Nephropathy



## Neuropathy



# MACROVASCULAR DISEASE\*

**Heart attack**

**Stroke**

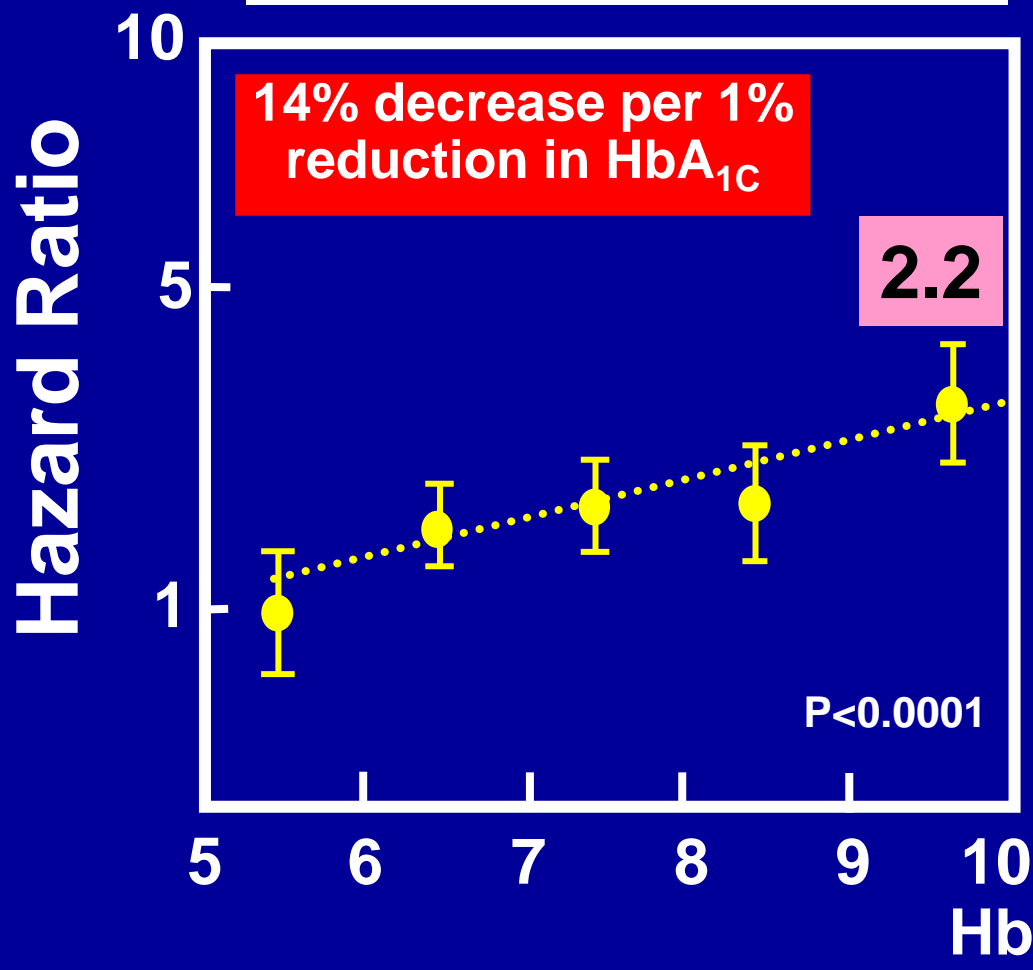
**PVD (Amputation)**

**\*accounts for ~80% of all mortality in T2DM**

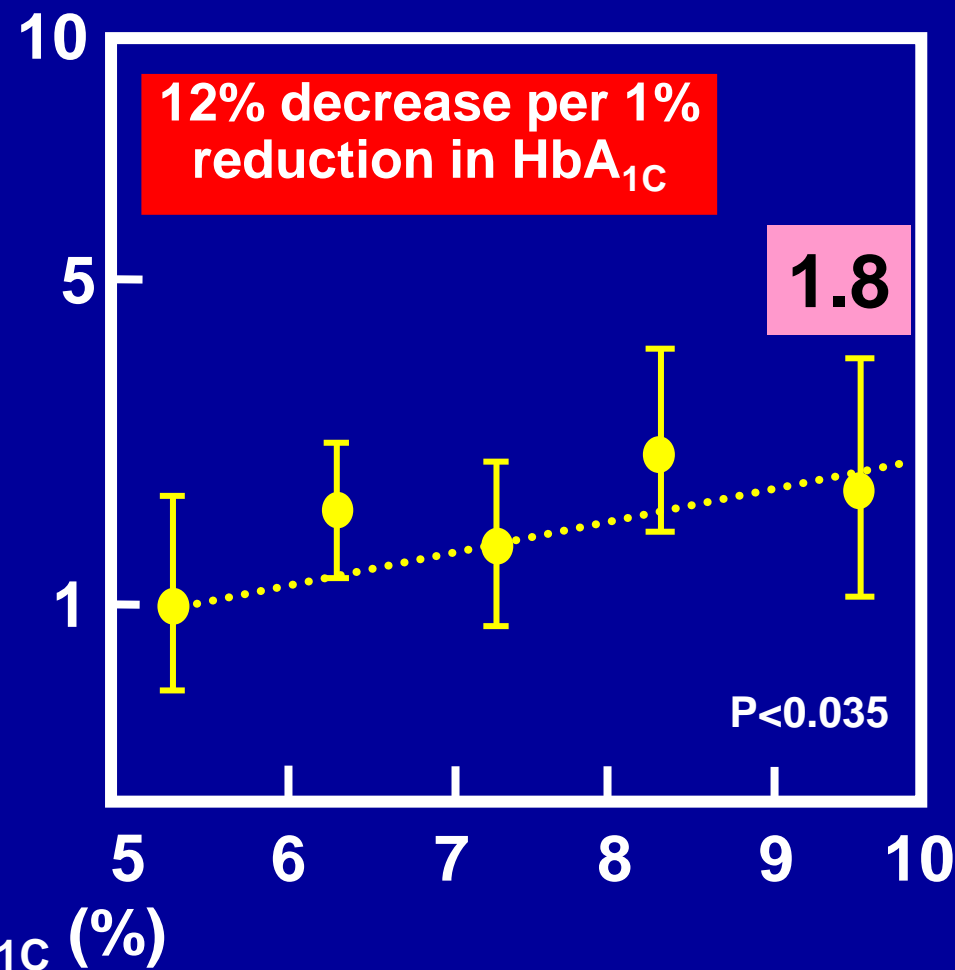
# UKPDS: EPIDEMIOLOGIC ANALYSIS – CARDIOVASCULAR ENDPOINTS

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

## MYOCARDIAL INFARCTION



## STROKE



# INSULIN RESISTANCE

**IS THE UNIFYING  
PATHOGENIC DISTURBANCE  
THAT LINKS ALL  
COMPONENTS OF THE**

**INSULIN RESISTANCE  
(METABOLIC) SYNDROME**

# **INSULIN RESISTANCE (METABOLIC) SYNDROME**

**Obesity (visceral)**

**Diabetes/IGT**

**Hypertension**

**Dyslipidemia**

**Increased PAI-1**

**Endothelial Dysfunction**

**Lipotoxicity**

**NAFLD/NASH**

**Inflammation**

**ASCVD**

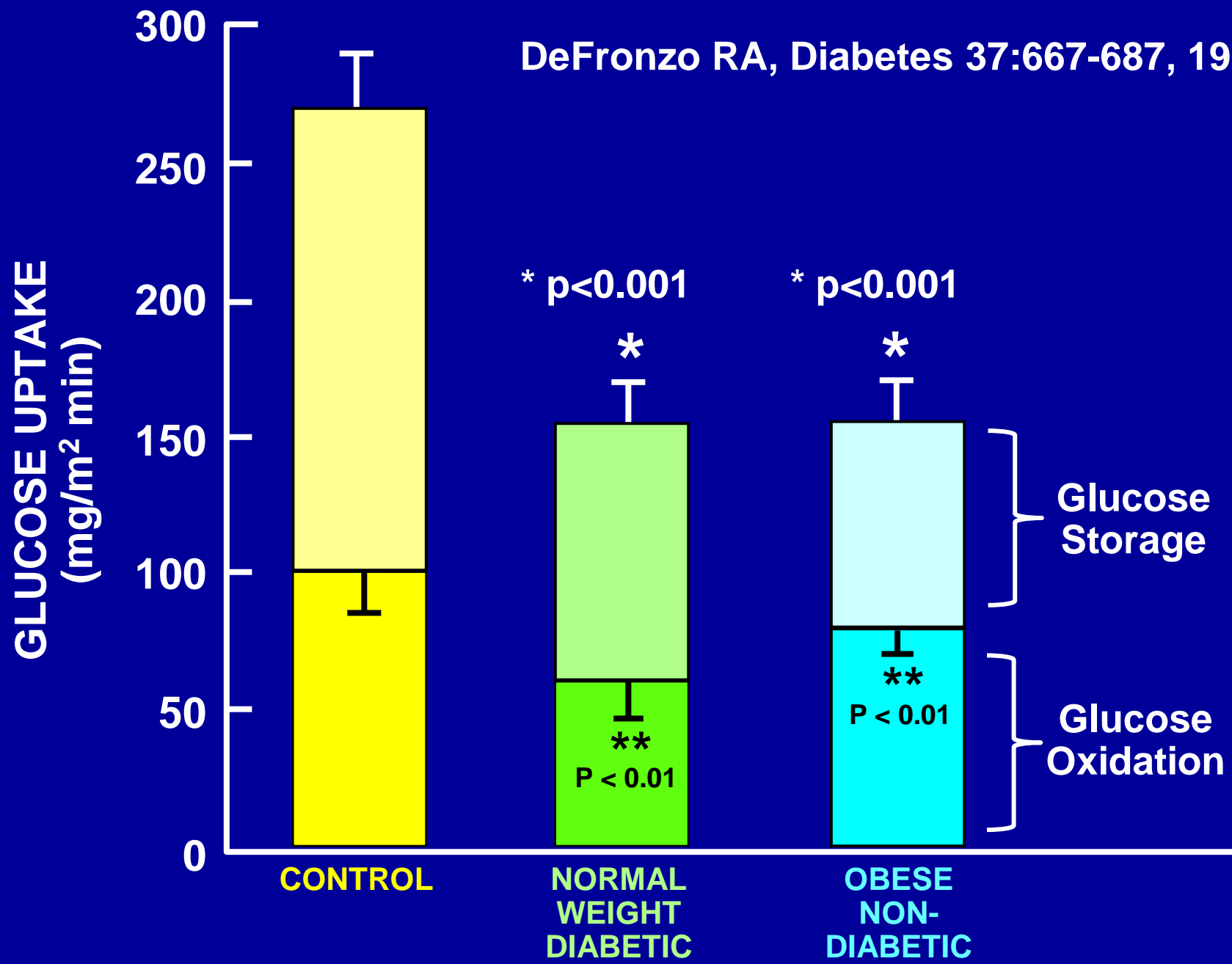
**Hyperinsulinemia**

**INSULIN RESISTANCE**

**WHAT DOES  
T2DM HAVE IN  
COMMON WITH  
OBESITY**

# INSULIN-STIMULATED GLUCOSE UPTAKE IN T2DM AND OBESITY

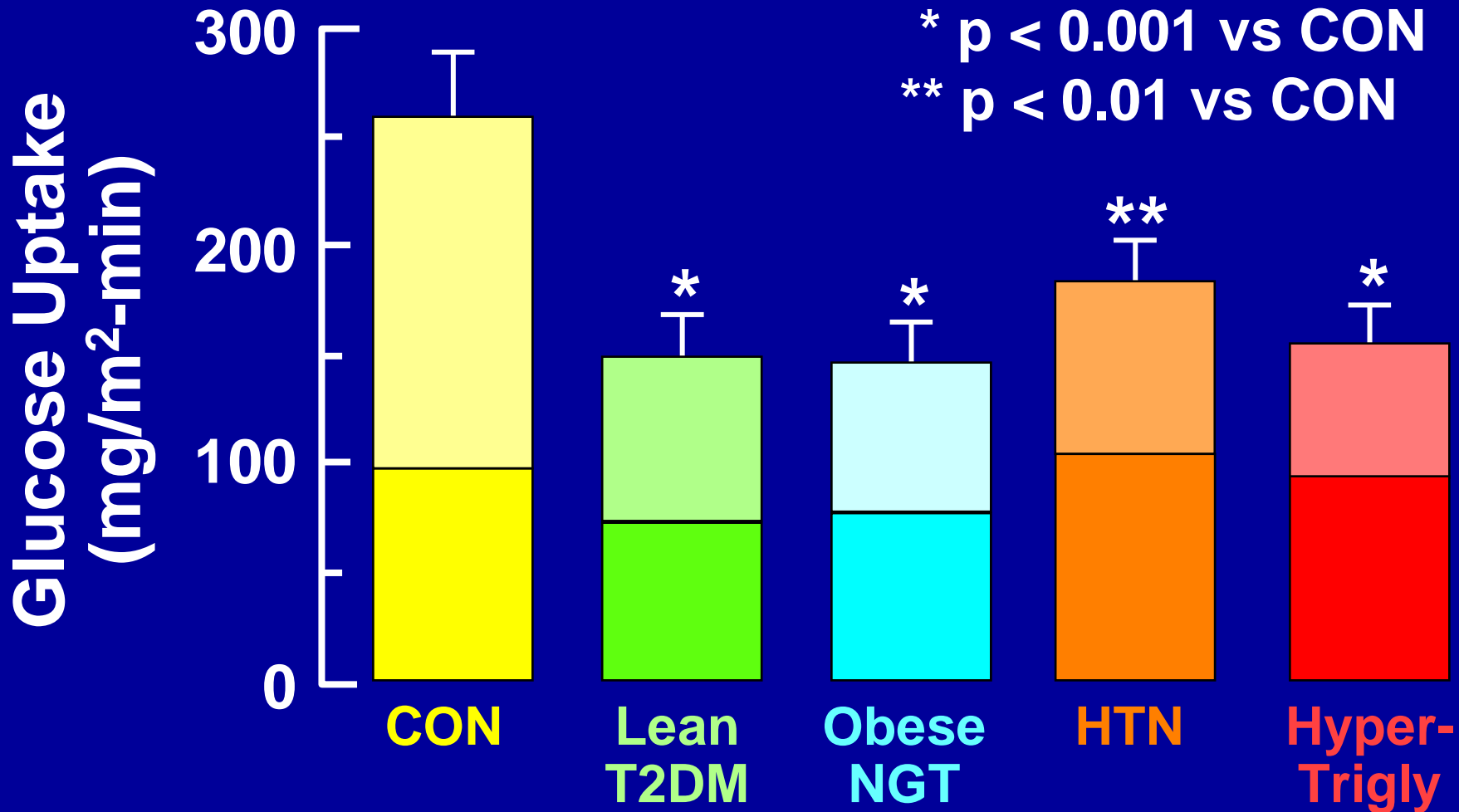
DeFronzo RA, Diabetes 37:667-687, 1988





**WHAT DO  
HYPERTENSION AND  
DYSLIPIDEMIA HAVE  
IN COMMON WITH  
TYPE 2 DIABETES  
AND OBESITY?**

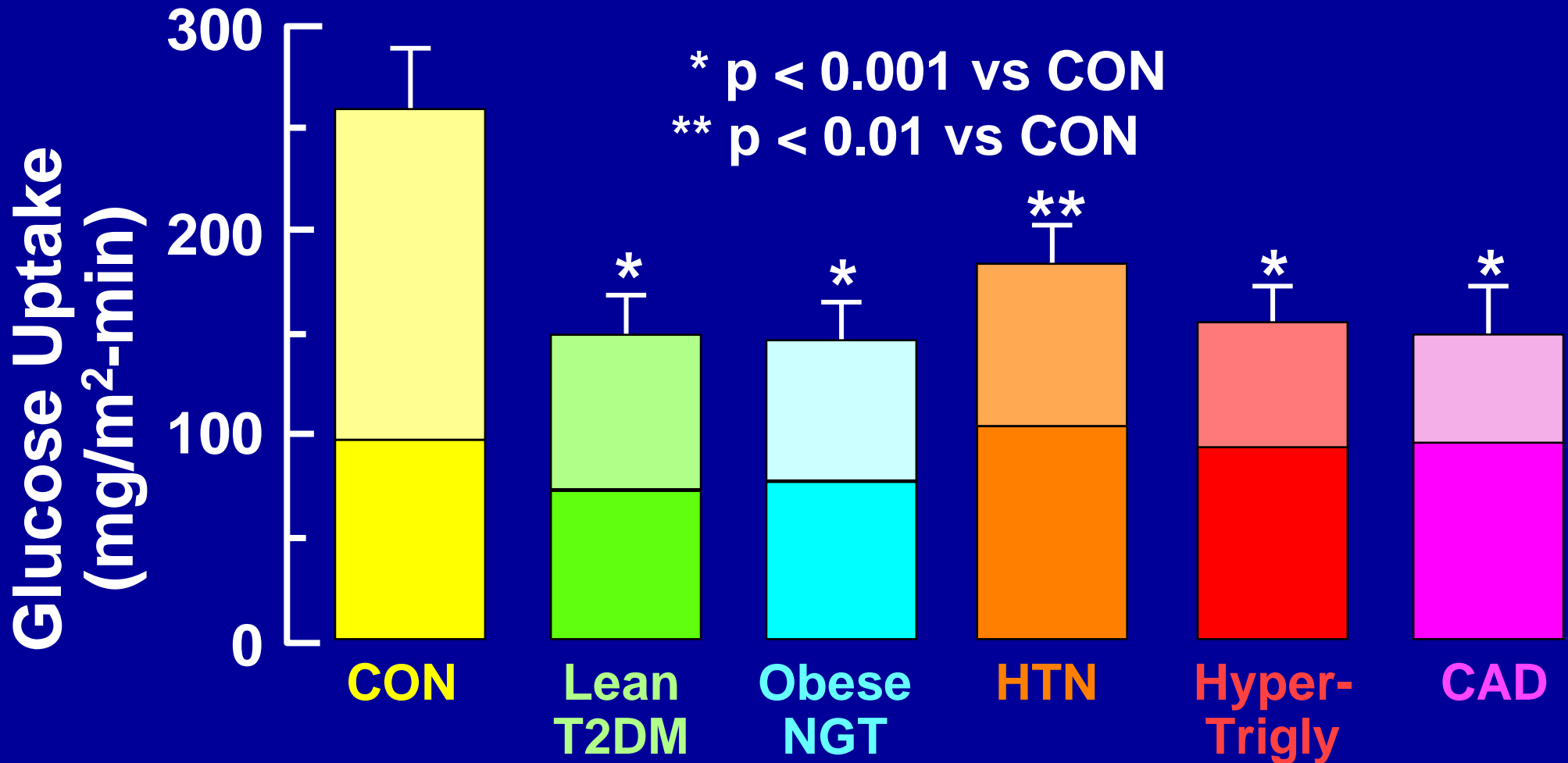
# INSULIN SENSITIVITY IN THE IRS



**WHAT DOES  
CORONARY ARTERY  
DISEASE HAVE IN  
COMMON WITH T2DM,  
OBESITY,  
DYSLIPIDEMIA, AND  
HYPERTENSION?**

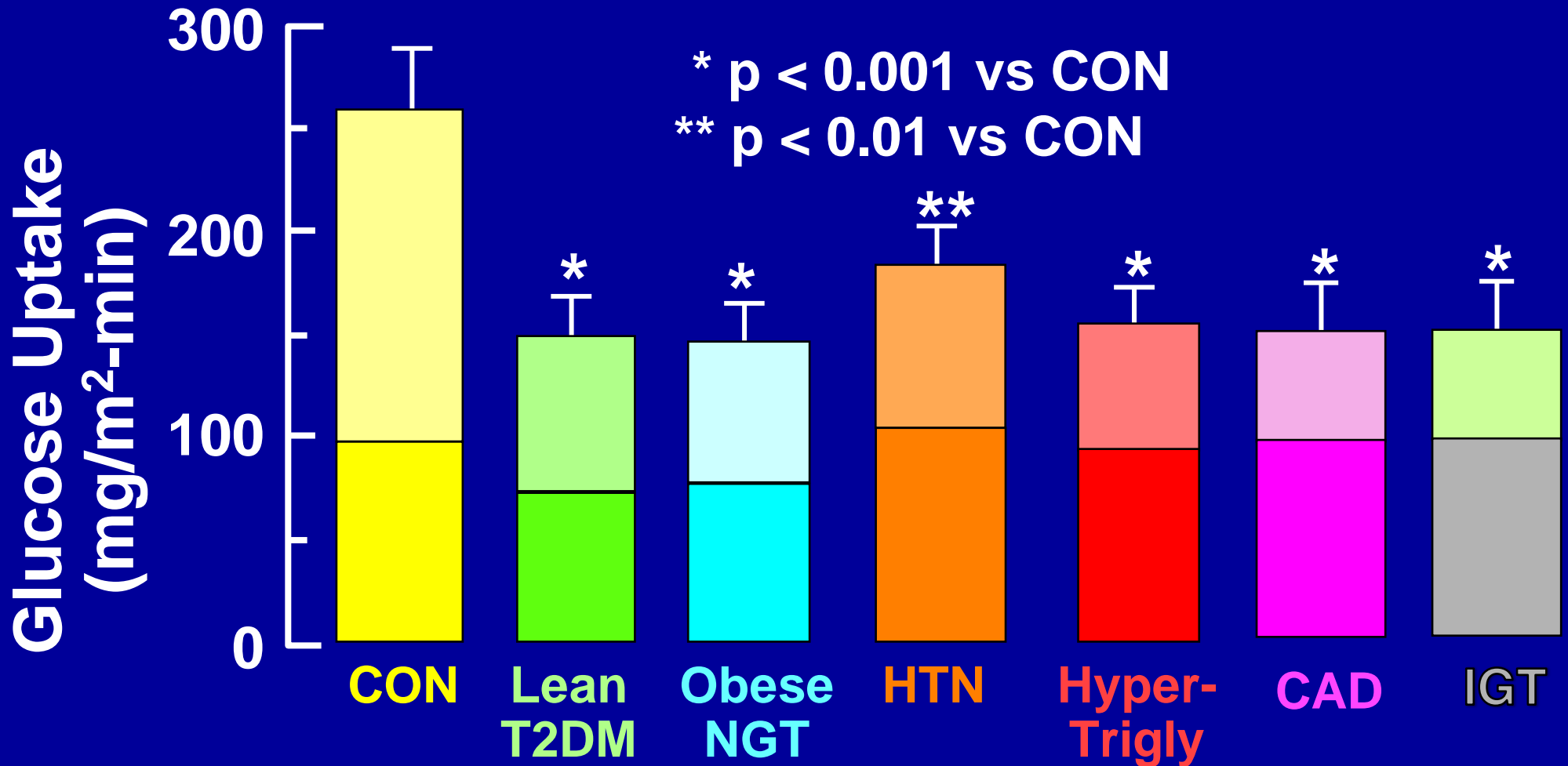
# INSULIN SENSITIVITY IN THE IRS

Bressler & DeFronzo, Diabetologia 39:1345-50, 1996



# INSULIN SENSITIVITY IN THE IRS

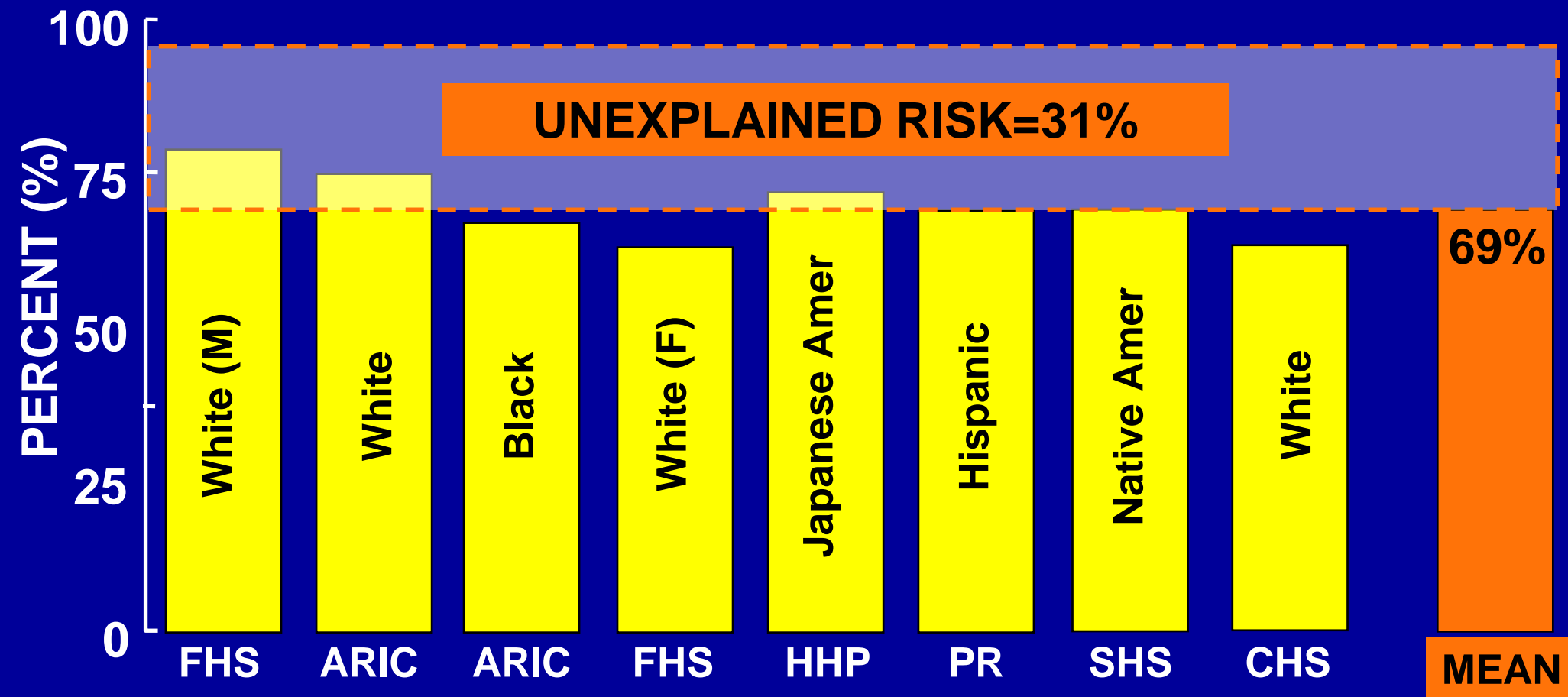
Bressler & DeFronzo, Diabetologia 39:1345-50, 1996



**MULTIPLE PROSPECTIVE  
EPIDEMIOLOGIC STUDIES HAVE  
DEMONSTRATED THAT BOTH IR  
AND IRS PREDICT CVD, AS WELL  
AS FUTURE DIABETES (Botnia,  
Verona, Framingham, SAHS,  
Bruneck, Malmo, IRAS, ARIC,  
Reaven, Gast meta-analysis of 17  
studies [HOMA-IR])**

# PREDICTIVE (%) VALUE OF FRAMINGHAM CARDIOVASCULAR RISK ENGINE IN MEN

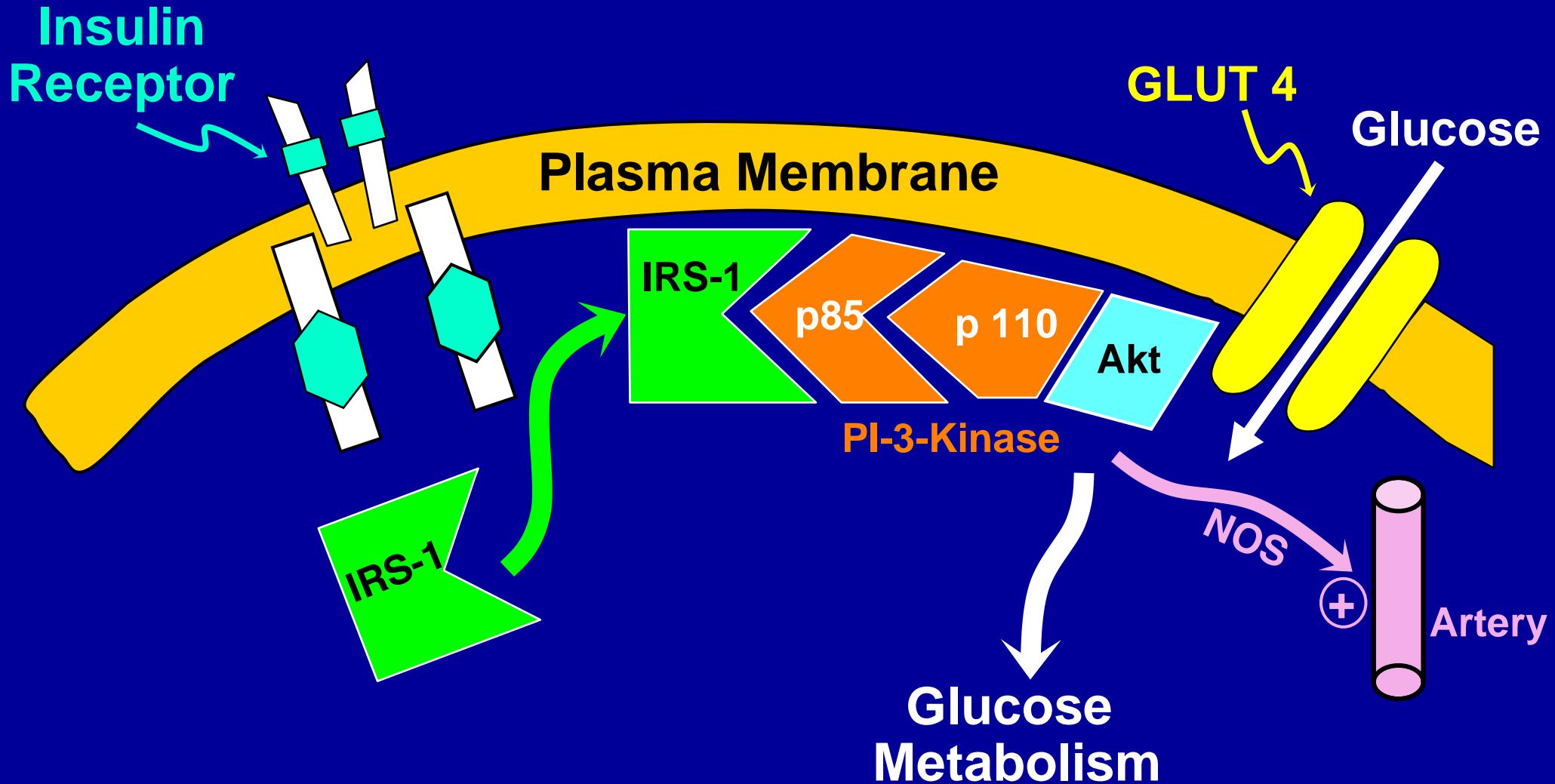
D'Agostino RB et al, JAMA 286:180-87, 2001



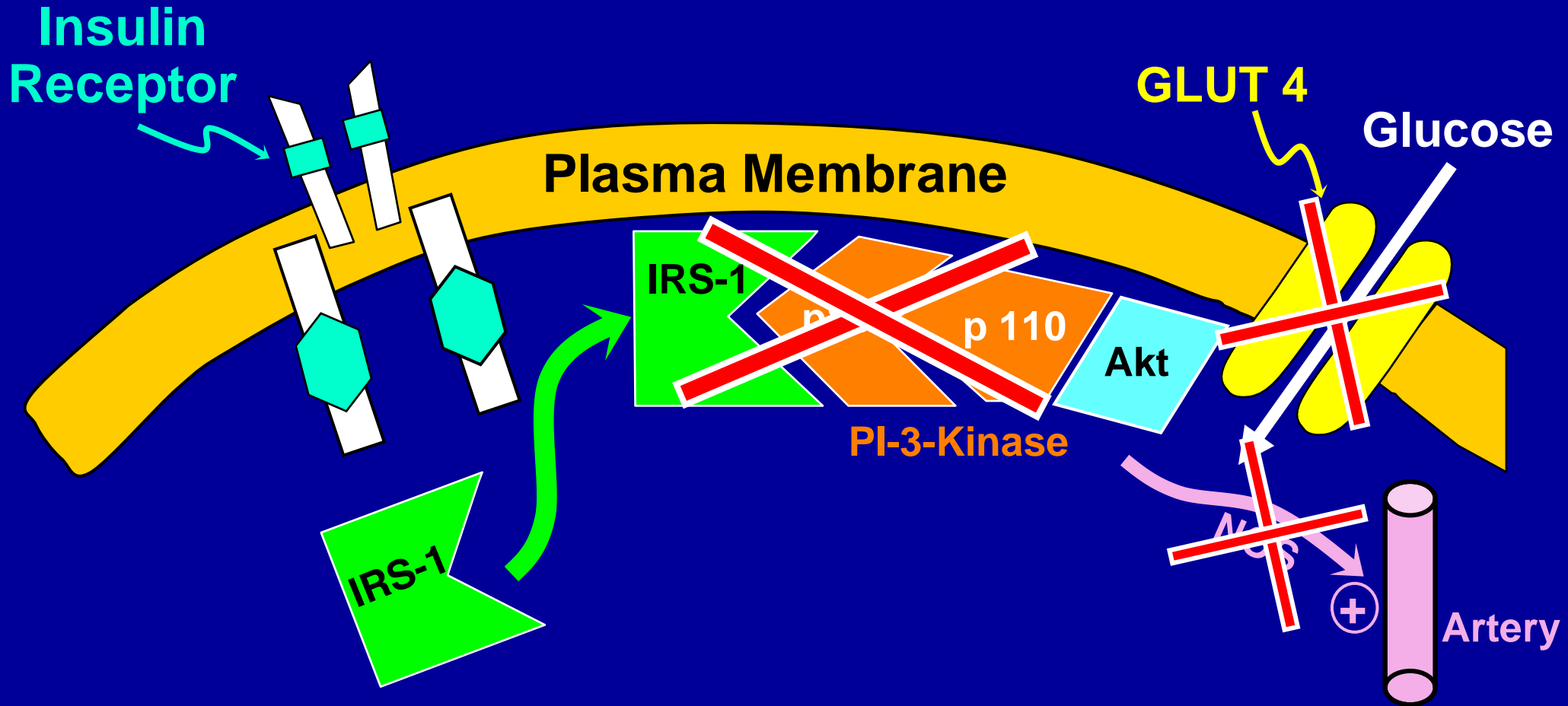
**MOLECULAR  
ETIOLOGY  
OF THE  
INSULIN  
RESISTANCE  
SYNDROME**



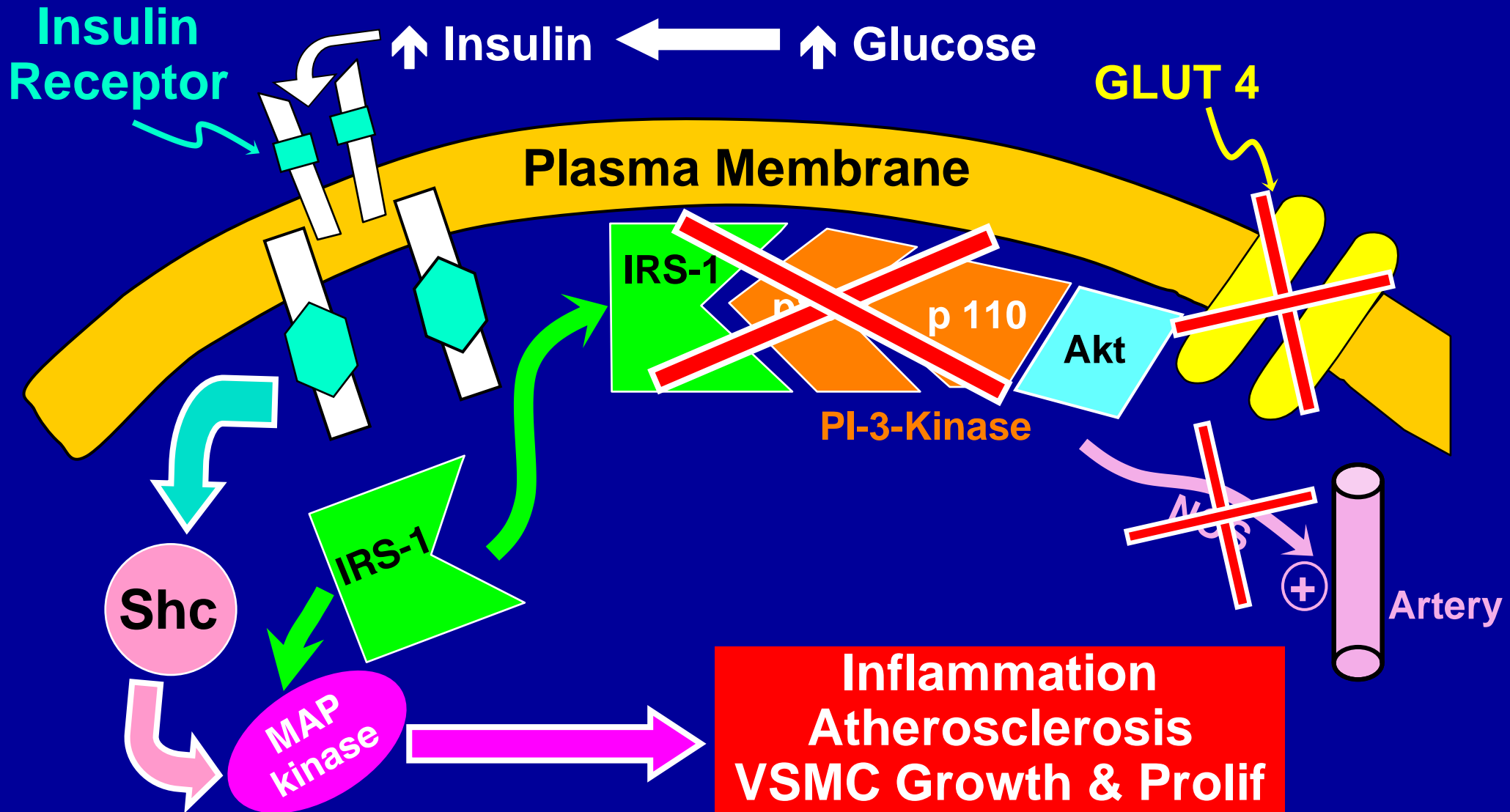
# INSULIN SIGNAL TRANSDUCTION SYSTEM IN HUMANS



# INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS

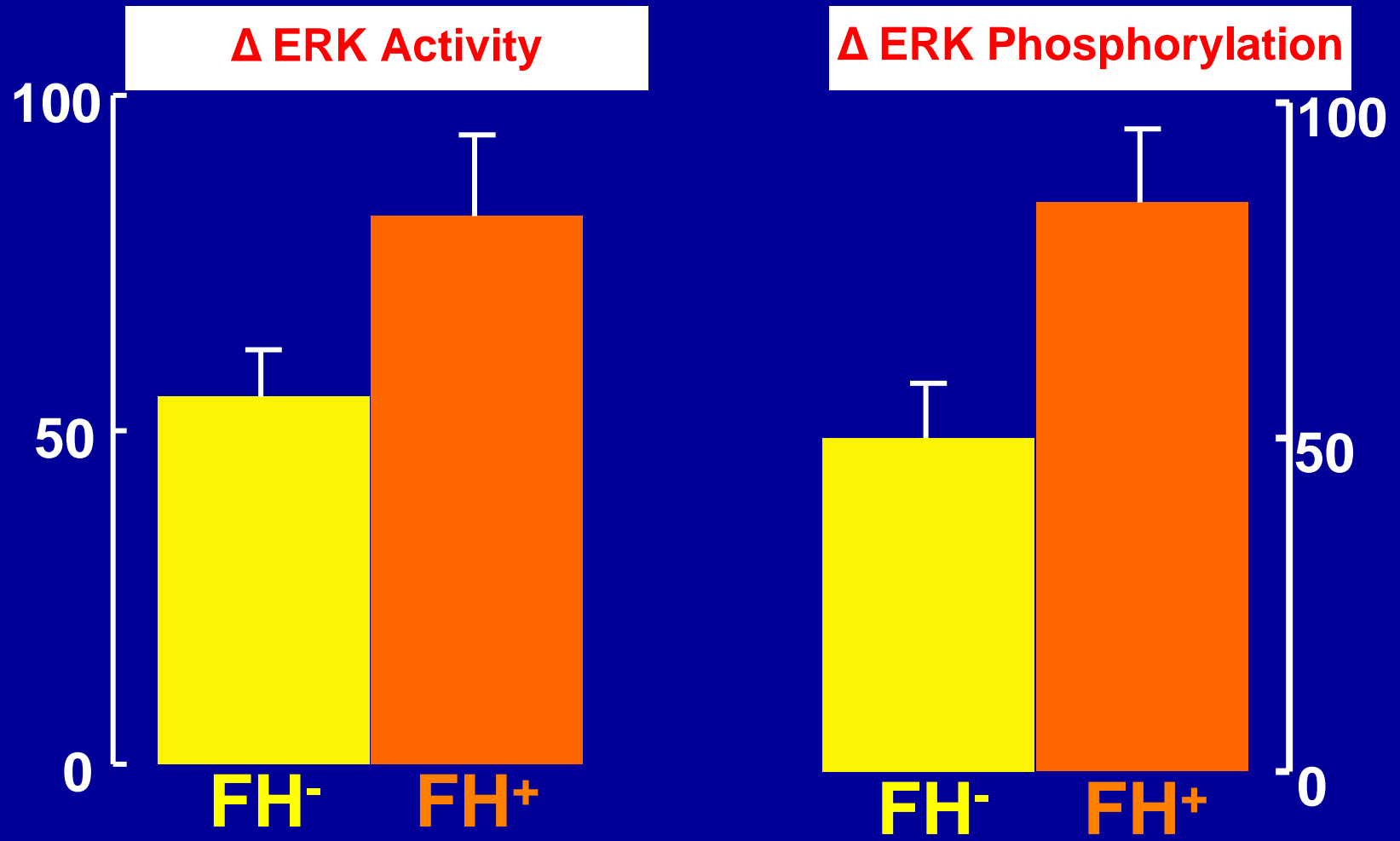


# INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS

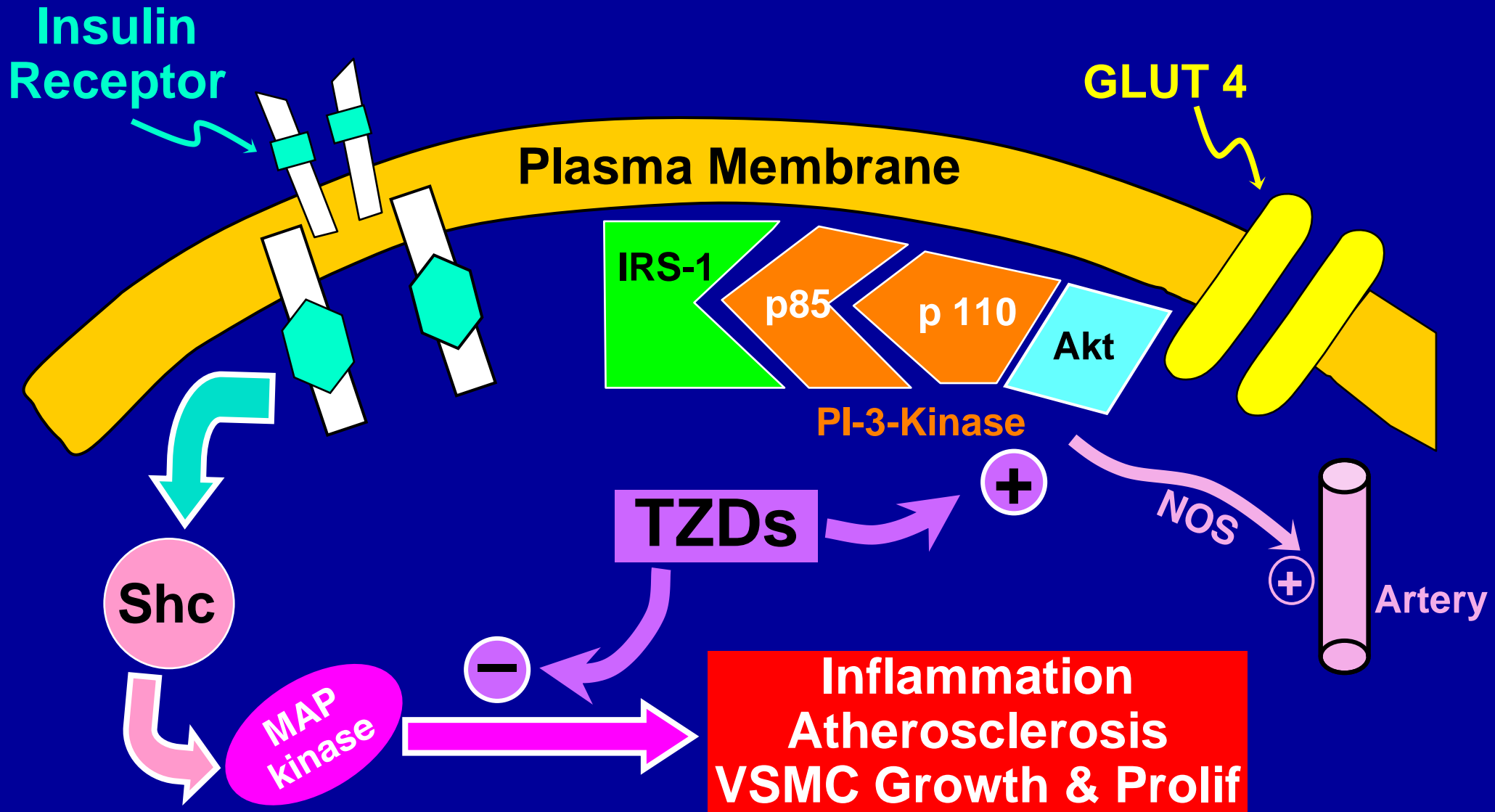


# EFFECT OF INSULIN ON MAP KINASE PATHWAY IN NORMAL-GLUCOSE-TOLERANT, INSULIN-RESISTANT OFFSPRING OF TWO DIABETIC PARENTS

% of insulin-stimulate value in FH-



# INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS: EFFECT OF TZDs



**Does initiation of  
antidiabetic therapy in  
the PREDIABETIC  
and/or PRE-  
PREDIABETIC stage  
prevent cardiovascular  
complications?**

**THE IRIS study (Kernan et al, NEJM, 2016) provides strong evidence that the cardiovascular benefit of PIOGLITAZONE (PROactive) is observed in prediabetic and pre-prediabetic individuals**

# PIOGLITAZONE AFTER ISCHEMIC STROKE OR TRANSIENT ISCHEMIC ATTACK: THE IRIS STUDY

## Insulin Resistance after Stroke

Kernan et al, NEJM 374:1321-31, 2016

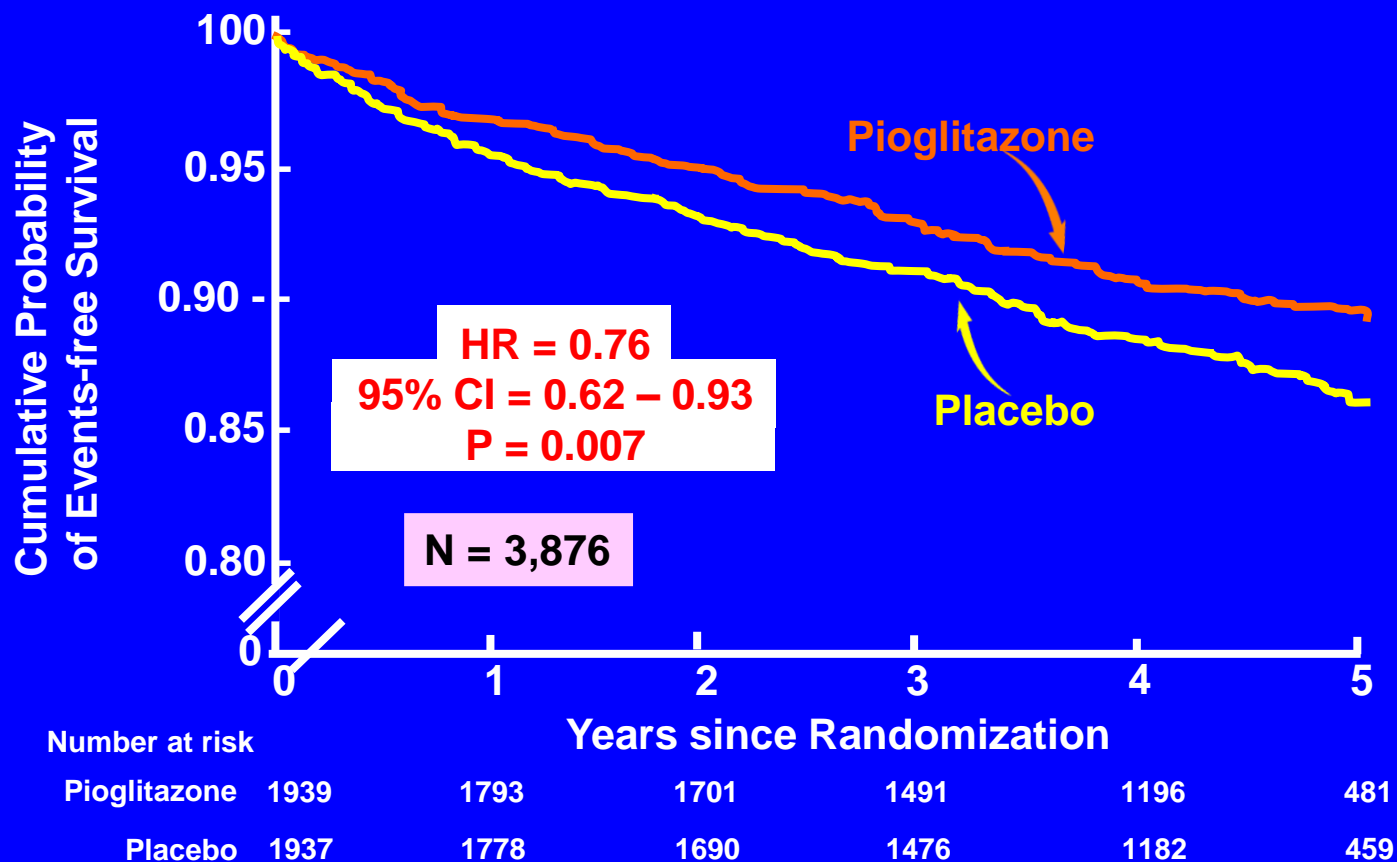
- 3,876 nondiabetic patients with recent ischemic stroke or TIA
- Age = 63.5 y; BMI = 30.0 kg/m<sup>2</sup>
- FPG = 98 mg/dl; FPI = 19 uU/ml
- HOMA-IR = 4.7 (range = 3.7-6.2)\*
- A1c = 5.8±0.4%

**HOMA > 3.0 indicates insulin resistance**



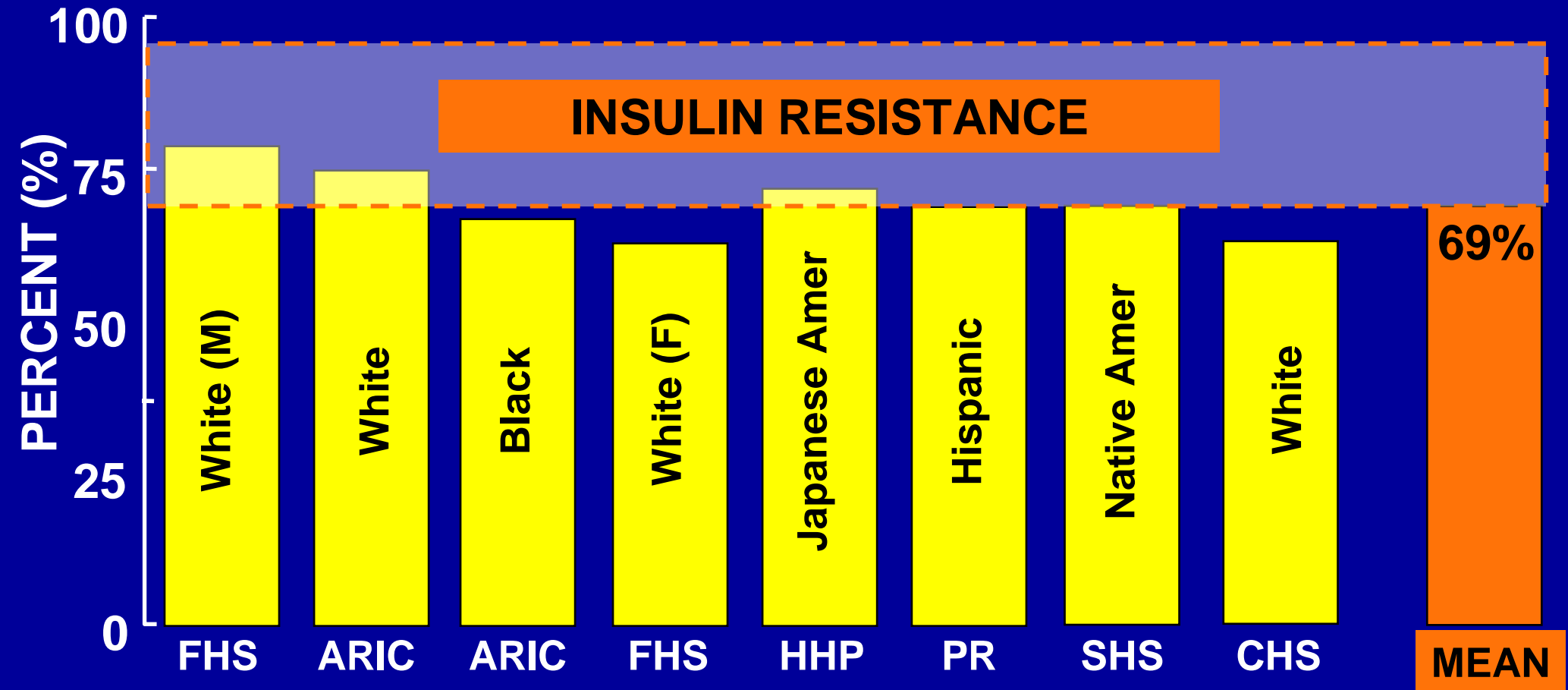
# EFFECT OF PIOGLITAZONE VERSUS PLACEBO ON RECURRENT STROKE / MI IN IRIS STUDY

Kernan et al, NEJM, February 17, 2016



# PREDICTIVE (%) VALUE OF FRAMINGHAM CARDIOVASCULAR RISK ENGINE IN MEN

D'Agostino RB et al, JAMA 286:180-87, 2001



**THANK  
YOU!**