Where Does Pioglitazone Fit Today?

A Practical Review

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LOUISIANA DEPARTMENT OF HEALTH

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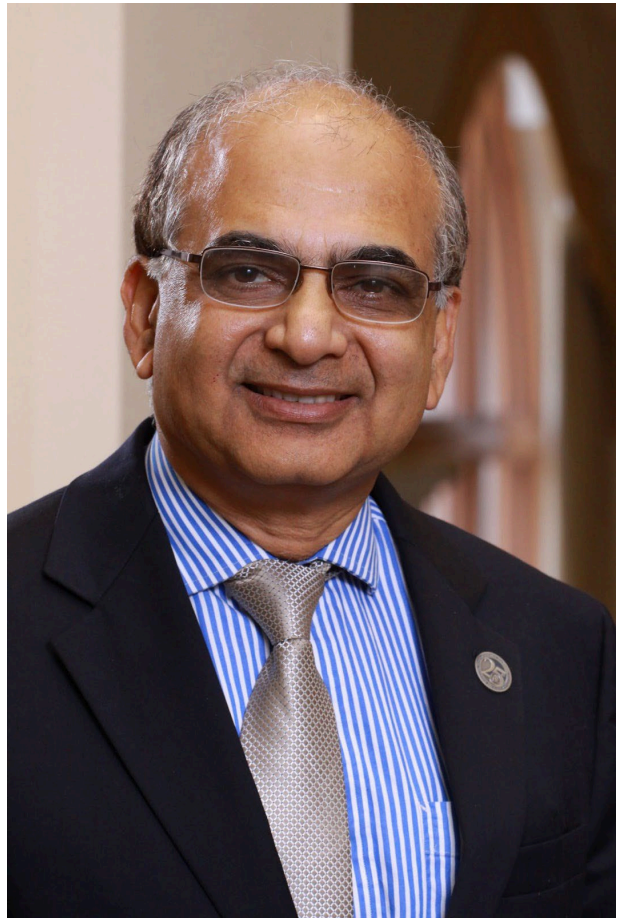
Objectives

- Review unmet needs in diabetes
- Discuss the importance of insulin resistance
- Discuss the place of Pioglitazone in treatment today

Speaker

- Vivian Fonseca
- Professor of Endocrinology and Assistant Dean
- Tulane University School of Medicine
  New Orleans, USA



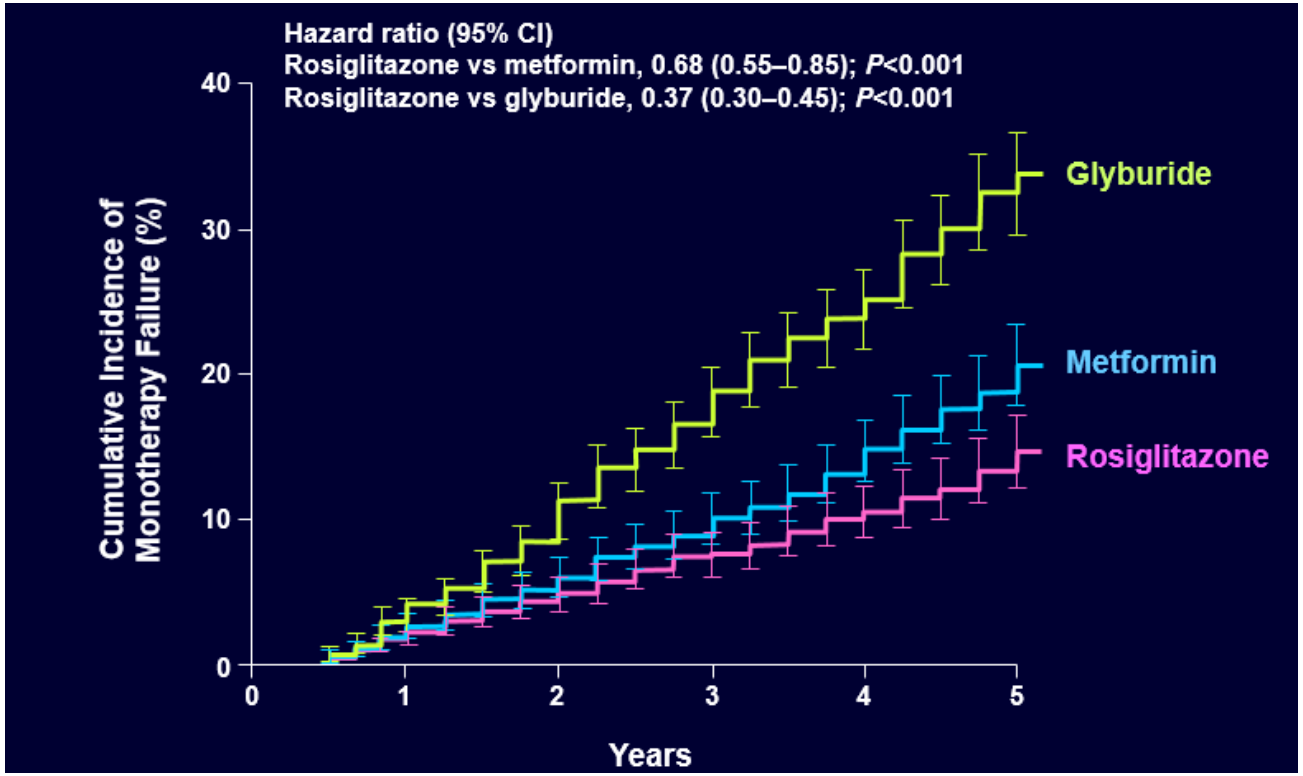
Current treatment paradigm

Diet & insulin exercise → **Monotherapy** → **Combinations of oral agents** →

- Problems
- Glycemic targets often not met
- Monotherapy not effective long-term
- Treatment fails to address dual impairments
- Step-wise approach tends to perpetuate “failure”
- Glucose toxicity interferes with treatment response

Harris MI et al. Diabetes Care 1999;22:403-8.
Harris MI et al. Diabetes Care 1998;21:518-24.

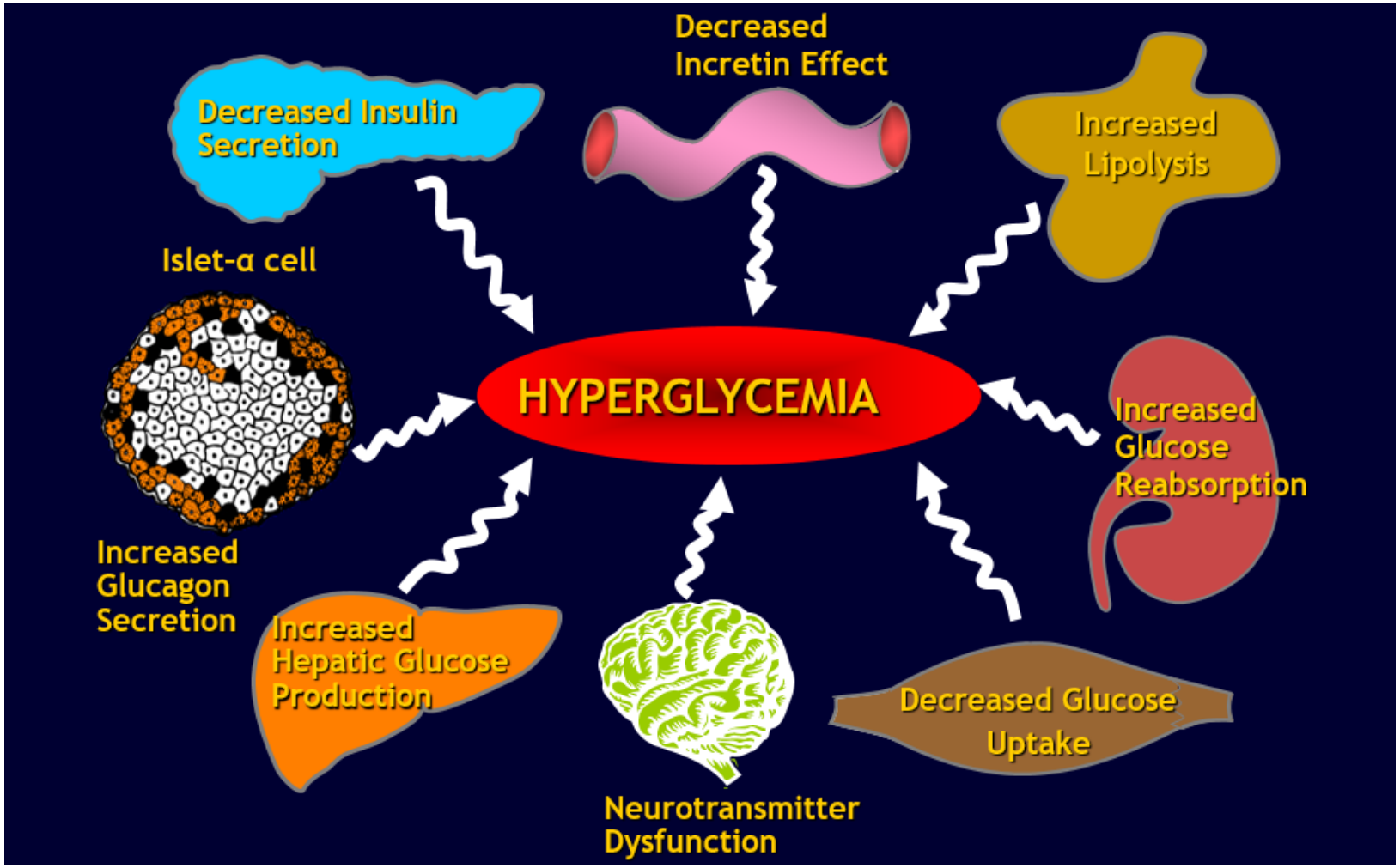
Primary endpoint: Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure



No. at risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

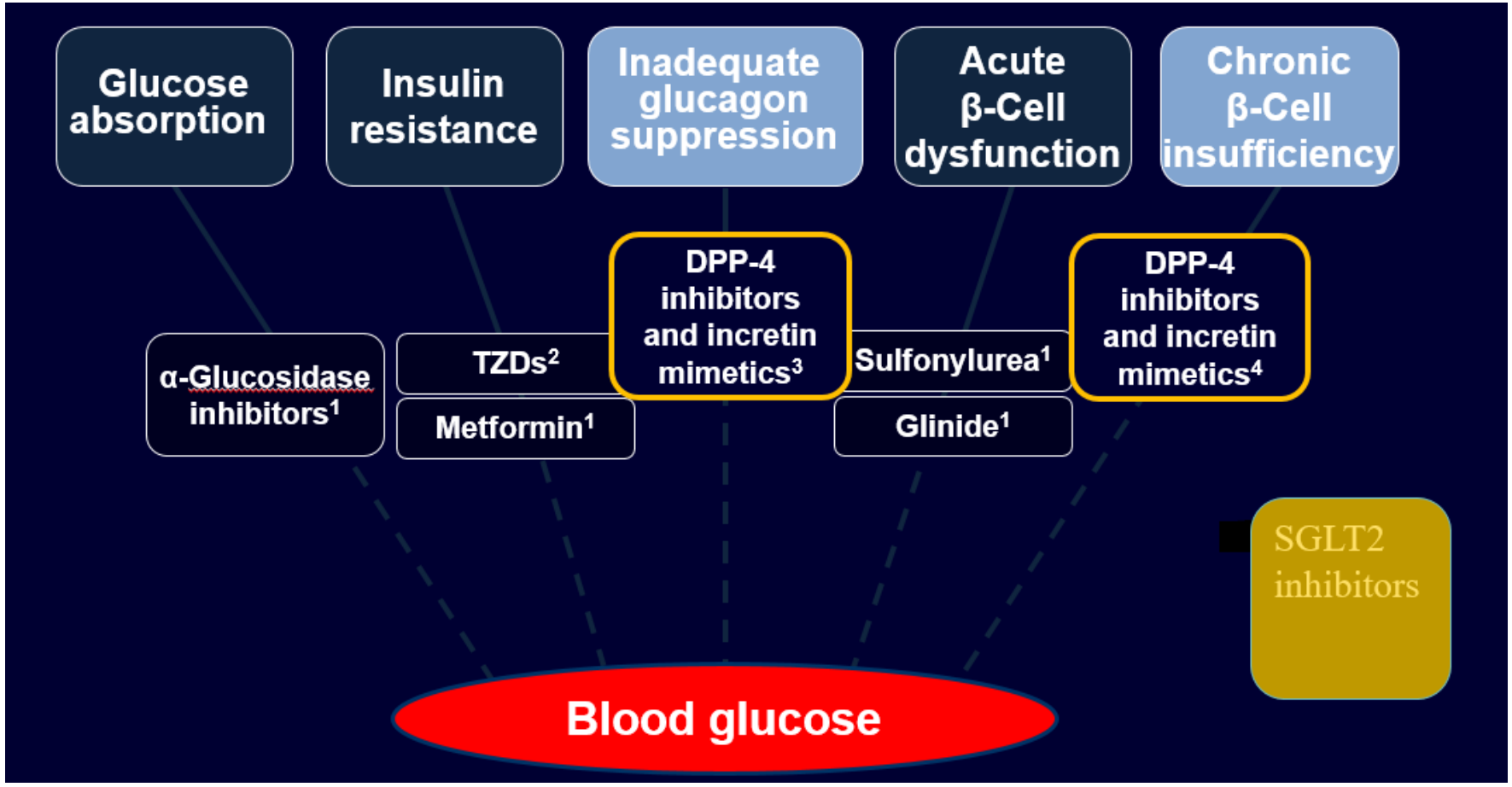
Kahn SE, et al. *N Engl J Med* 2006;355:2427–2443.

OMINOUS OCTET



DeFronzo R et al. Diabetes 2009;58:773-95.

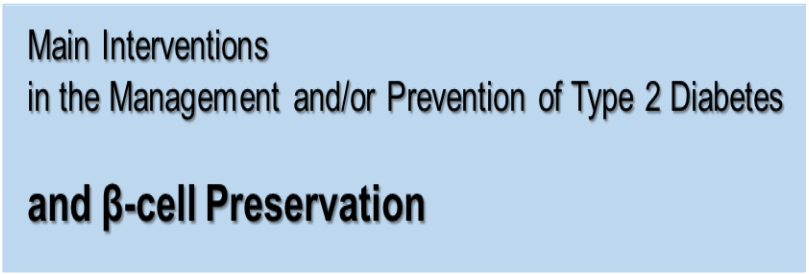
Multiple treatments are needed to address all core defects in T2DM



1. Inzucchi SE. JAMA 2002;287:360–72. 2. DeFronzo RA. Br J Diabetes Vasc Dis 2003;3(suppl 1):S24–S40.
3. Nauck MA. Am J Med 2011;124(1 Suppl):S3-18. 4. Garber AJ. Diabetes Care 2011; 34(Suppl 2):S258-S263.

Main Interventions in the Management and/or Prevention of Type 2 Diabetes and β-cell Preservation

- Intensive lifestyle modification
- Early short-term intensive insulin therapy
- Incretin-based agents
- SGLT2-inhibitors
- Sulfonylureas
- Metformin
- Thiazolidinediones (TZDs)
- Early intensive treatment with multiple agents

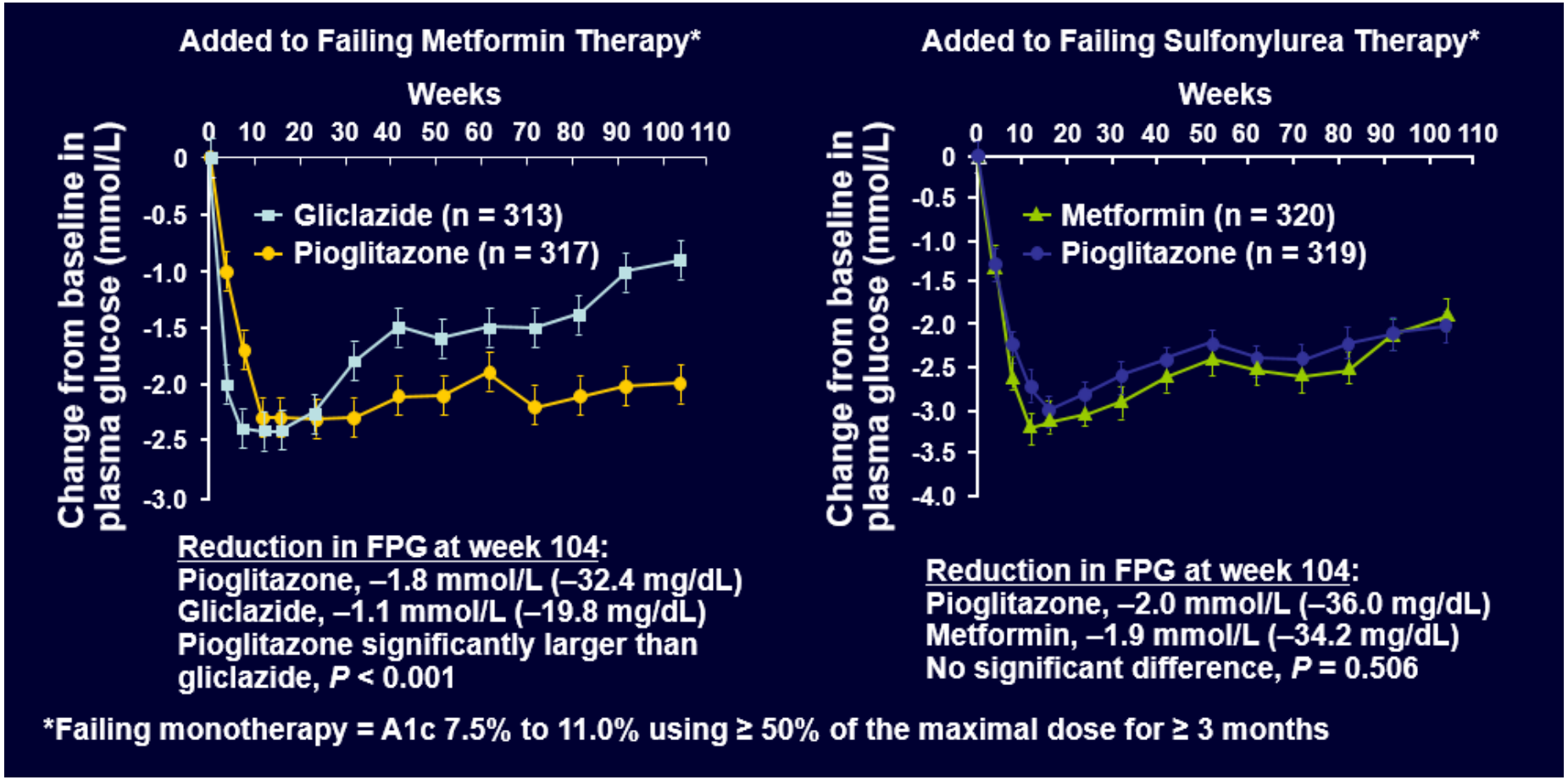


TZDs are the best agents for β-cell Preservation How does it work

- Reversal of gluco-toxicity
- Reduction in plasma FFA (reversal of lipo-toxicity)
- Mobilization of toxic lipid metabolites (FACoA, DAG, ceramides) out of the β-cell (reversal of lipo-toxicity)
- Direct effect on the β-cell (which express PPARg)?
- **Reduction of insulin-resistance results in a reduction in insulin secretory demands and consequently of β-cell stress**

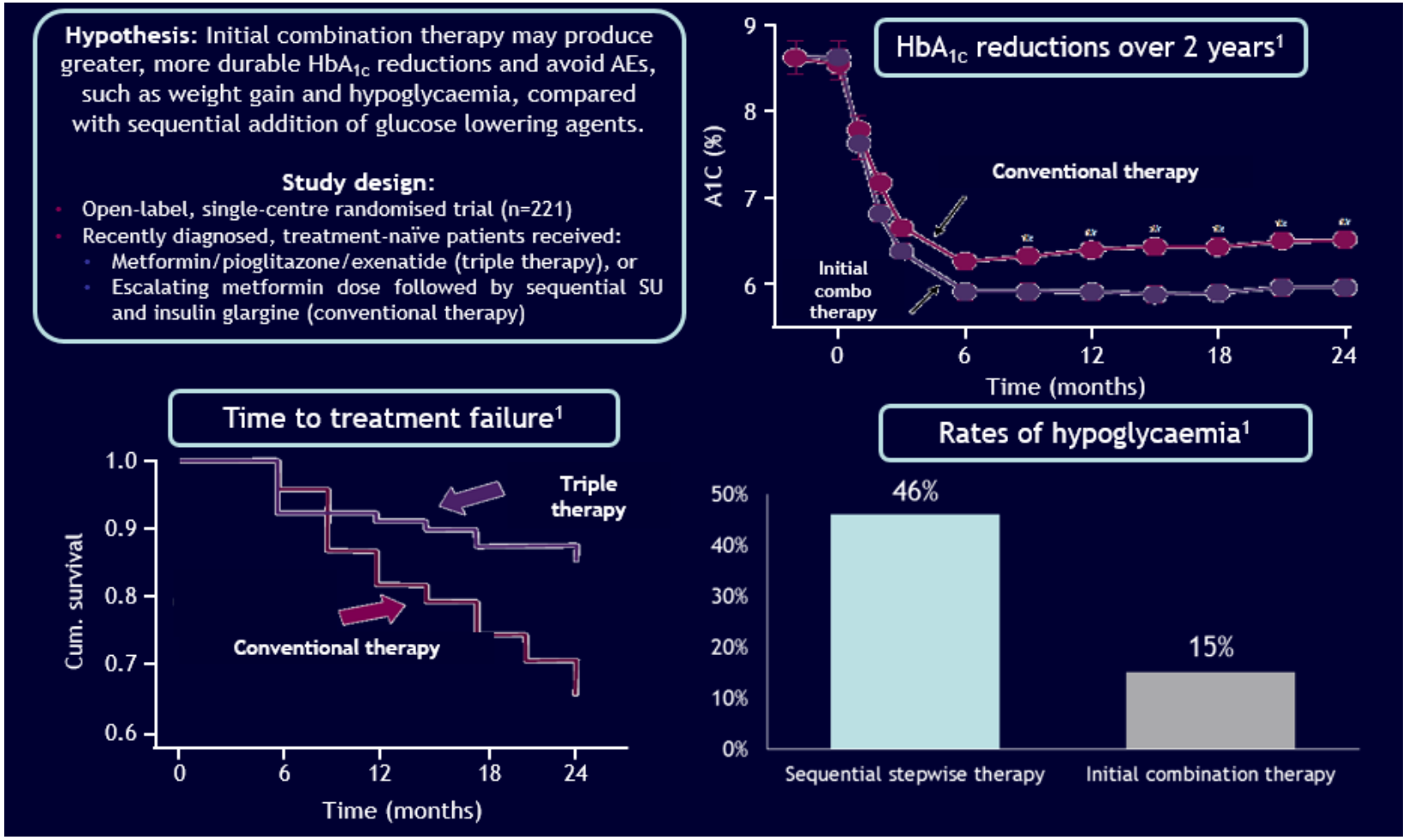
Curr Diab Rep. 2013 April ; 13(2): 252–260.

Quartet: Durability of combined glycemic therapies



Charbonnel B et al. Diabetologia 2005;48(6):1093-104.

Clinical Trial data support early, combination therapy to improve glycaemic control



AE, adverse event.

1. Abdul-Ghani MA, et al. Diabetes Obes Metab 2015;17:268–75.

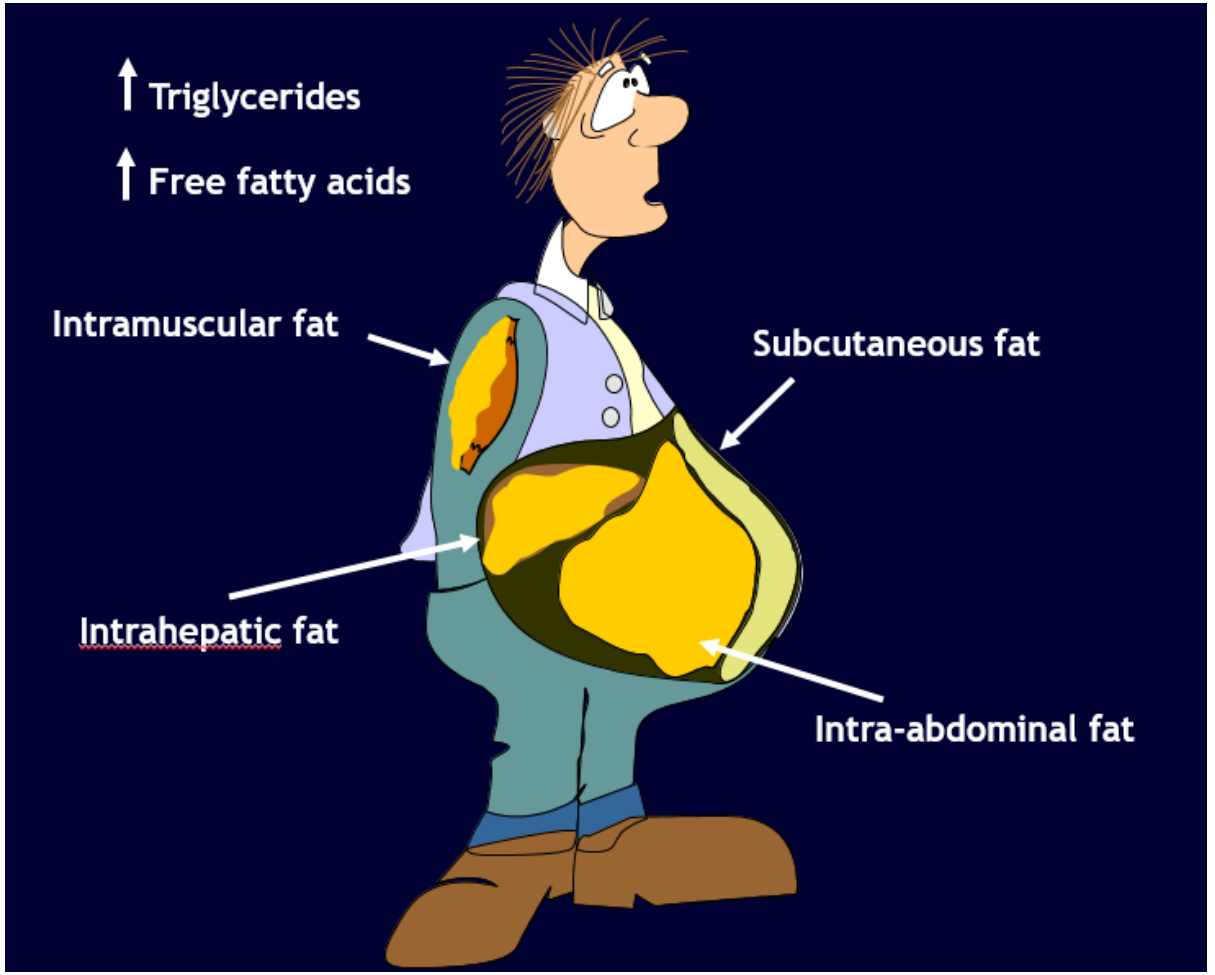
Obesity → Insulin Resistance

- Established links:
  - Visceral adiposity
  - Increased free fatty acids
  - Cellular defects in insulin signaling
  - Hypertrophic fat cells

All are improved by pioglitazone treatment.

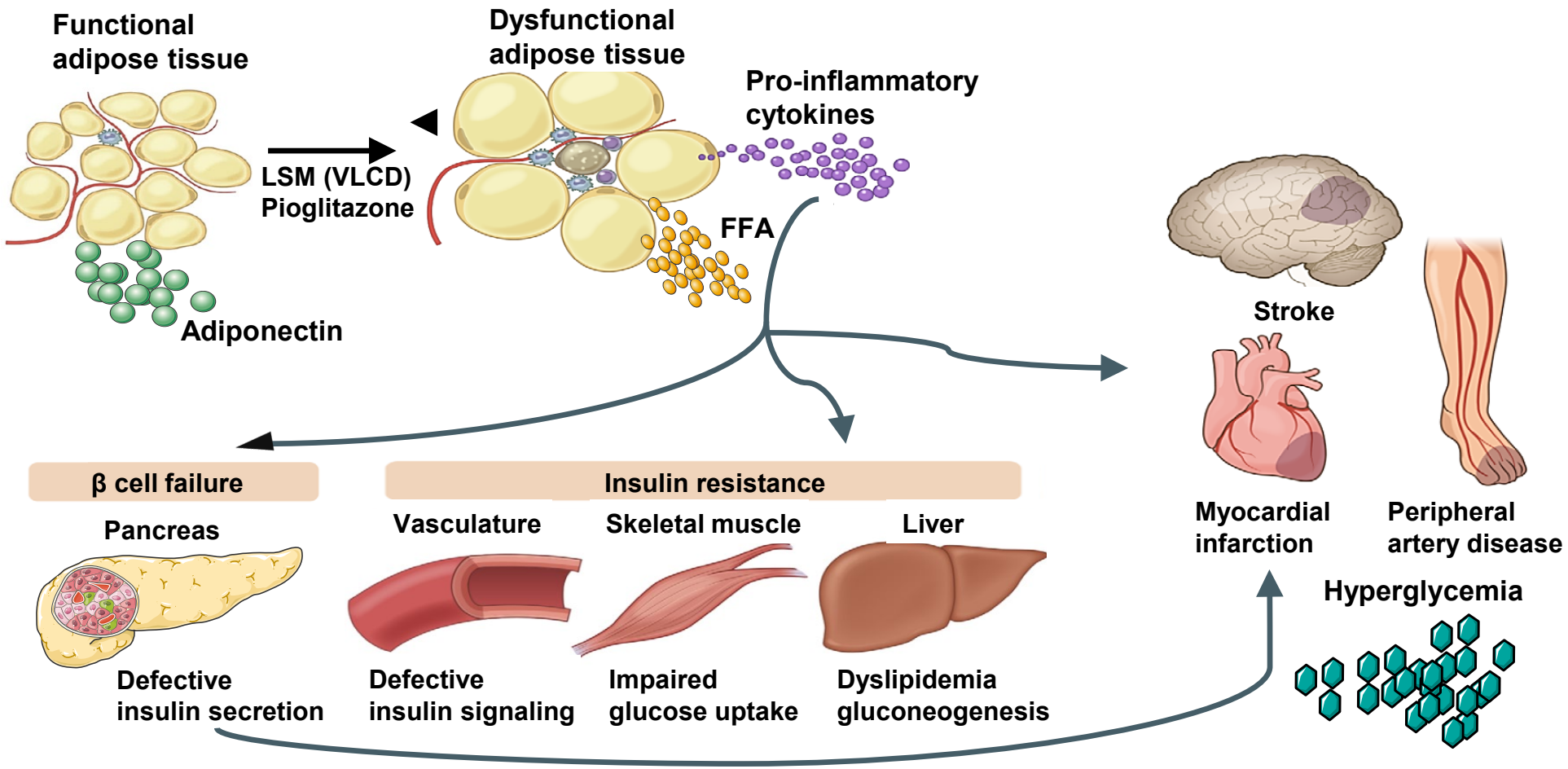
Smith SR, Ravussin E. *Curr Diab Rep.* 2002;2(3):223-230.

Central Adiposity



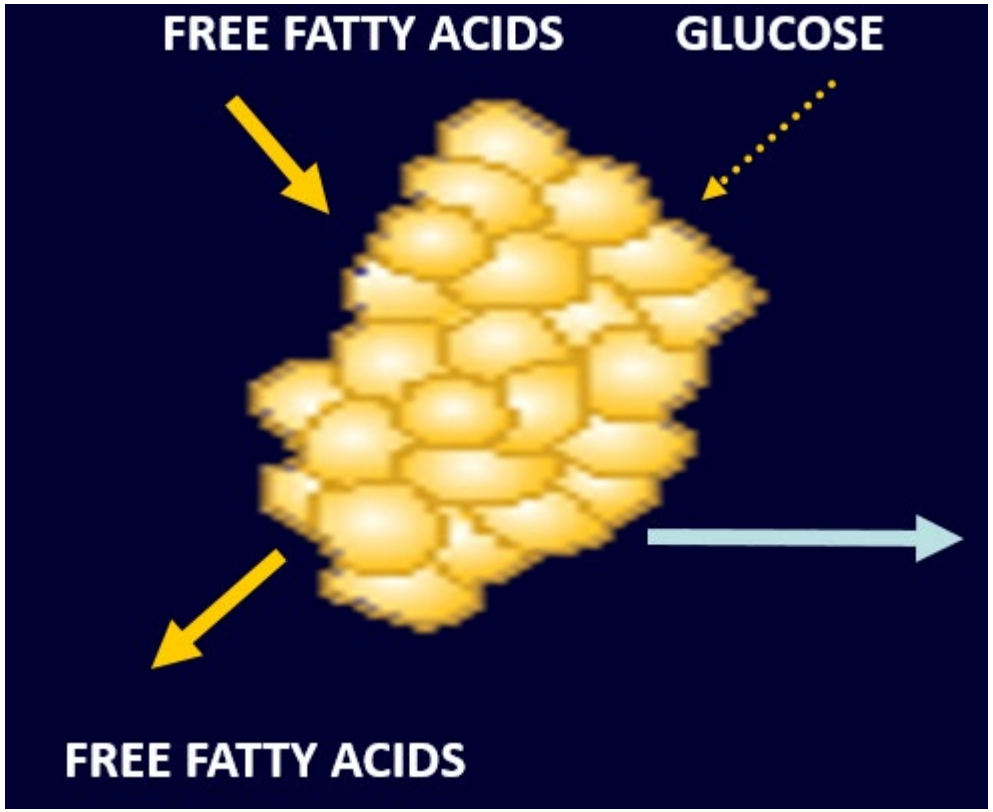
Adapted from: De Fronzo RA. Br J Diabetes Vasc Dis 2003;3 (suppl 1):S24-40.

Adipose tissue dysfunction induced IR, β cell failure and CVD



1. Tsatsoulis A, *et al.* Insulin resistance: an adaptive mechanism becomes maladaptive in the current environment - an evolutionary perspective. *Metabolism.* 2013 May;62(5):622-33. 2. Fuster JJ, *et al.* Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease. *Circ Res.* 2016 May 27;118(11):1786-807.

Adipose tissue: Secretory organ



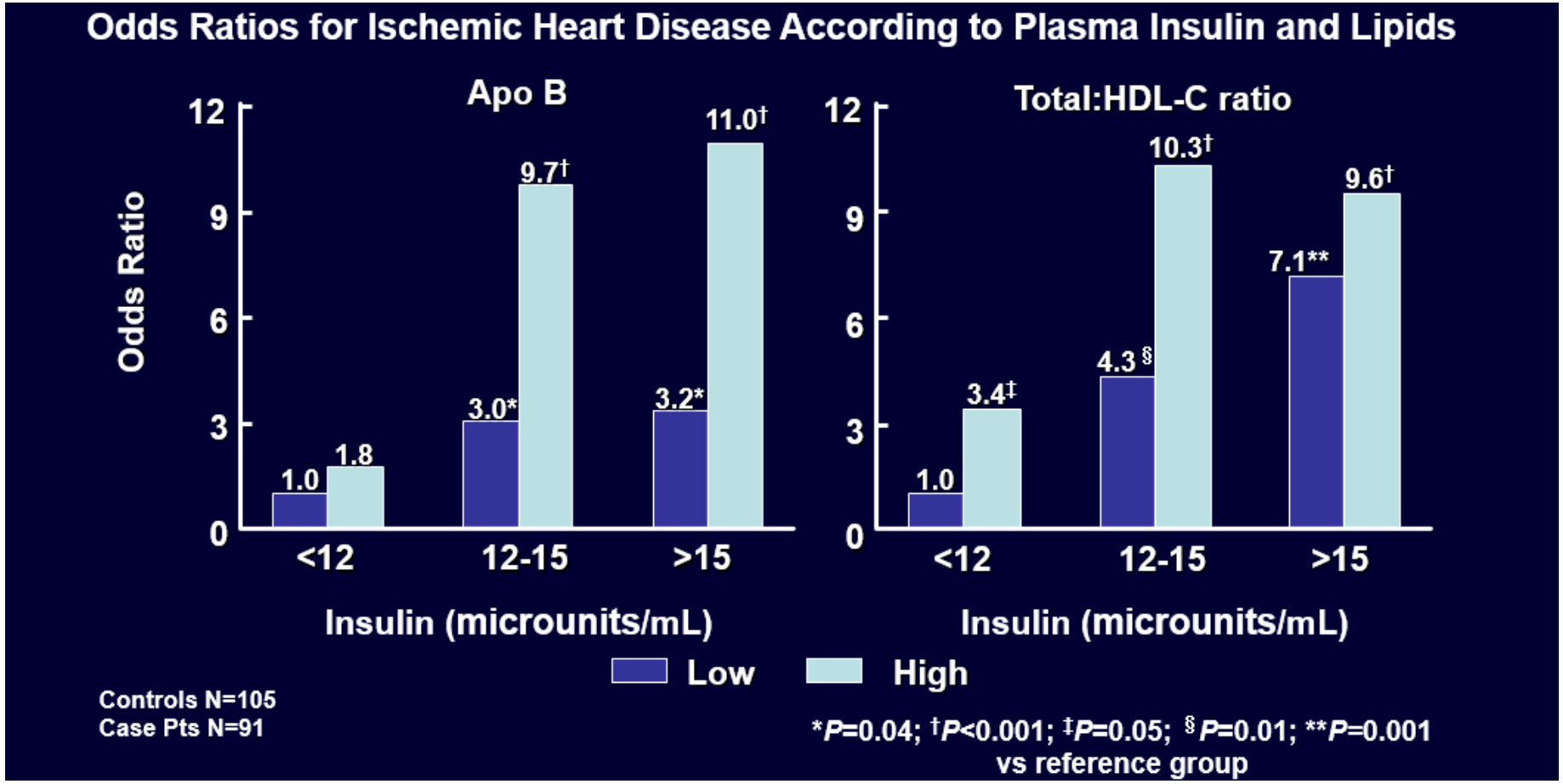
- Leptin
- Angiotensinogen
- Resistin
- Adiponectin (ACRP-30)
- CRP

- TNF–α
- PAI -1
- Serum Amyloid-A
- IL-6

- Estrogens
- Cortisol

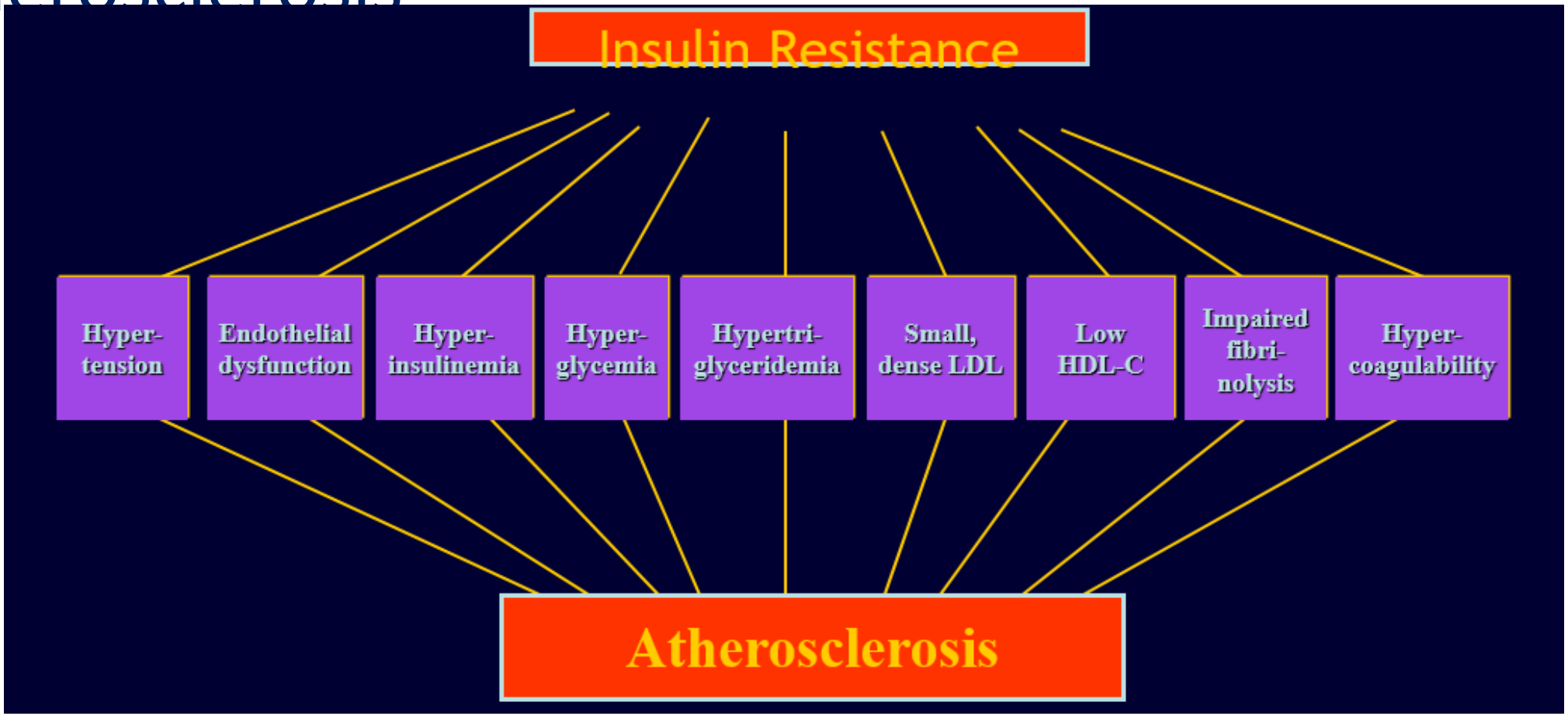
Modified from: Kahn B & Flier J. J Clin Invest 2000;106:473-81.

Hyperinsulinemia/insulin resistance: Increased risk of ischemic heart disease

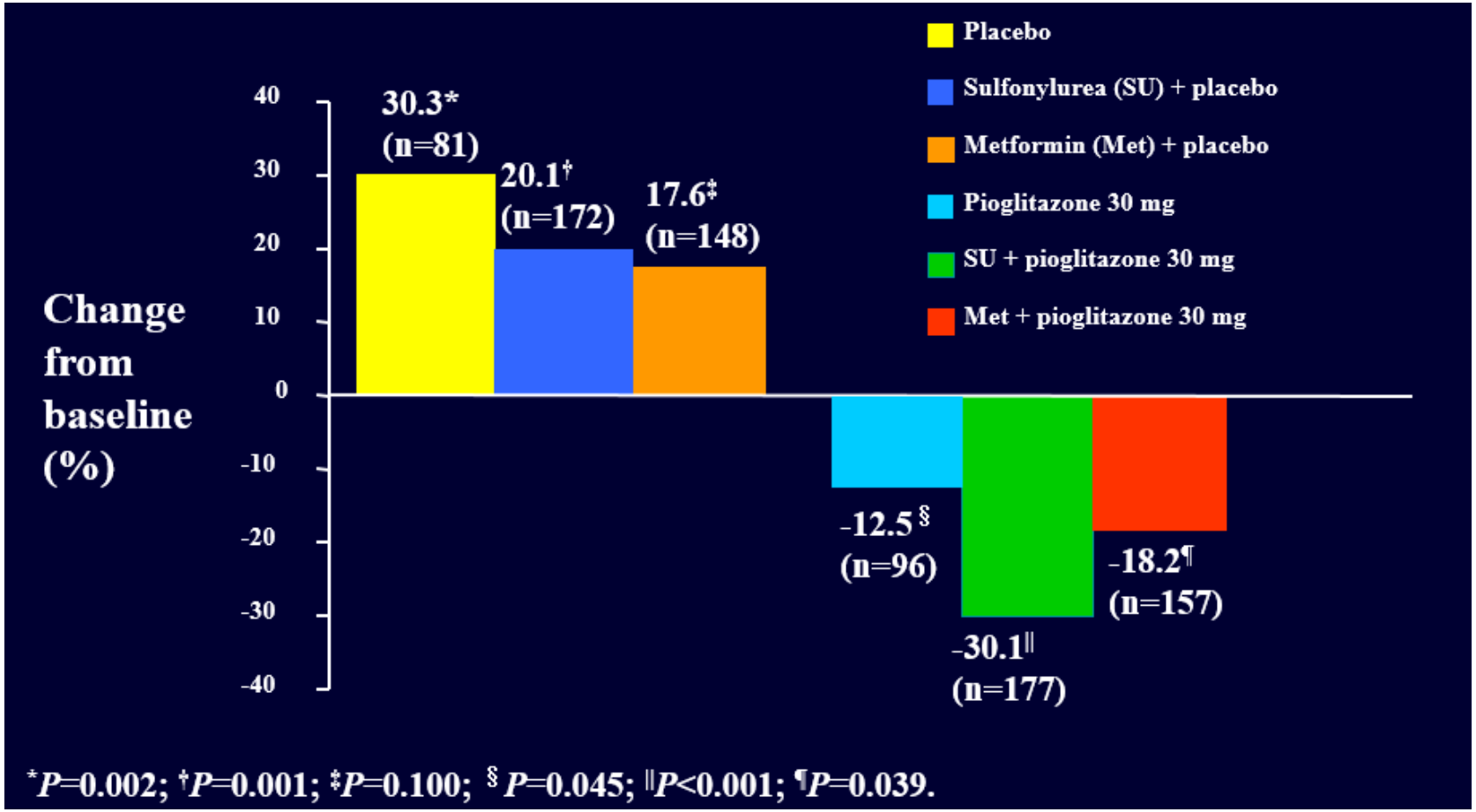


Despres JP et al. N Engl J Med 1996;334(15):952-7.

Interrelationship Between Insulin Resistance and Atherosclerosis

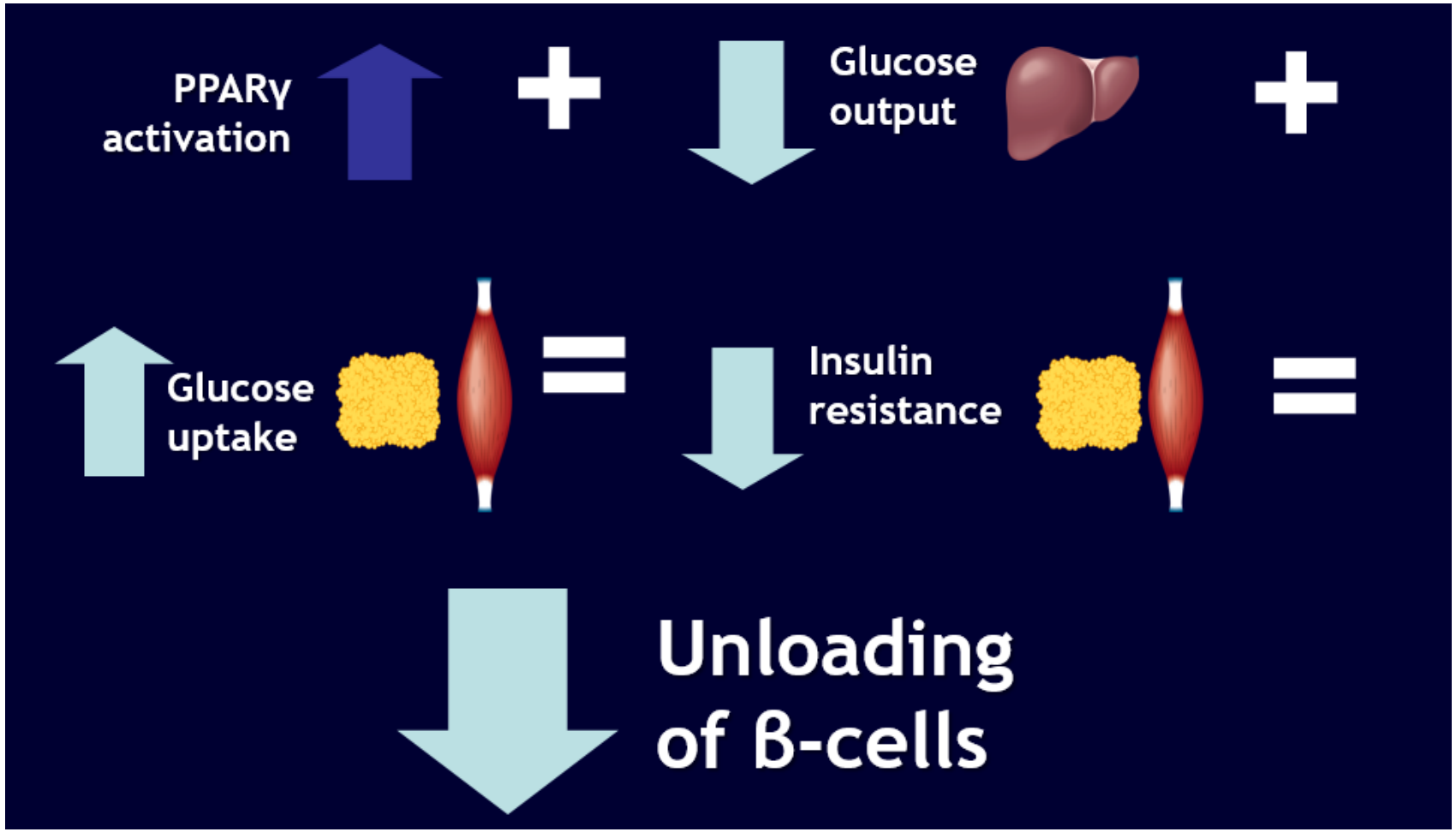


Effect of Pioglitazone on Insulin Resistance: HOMA-IR

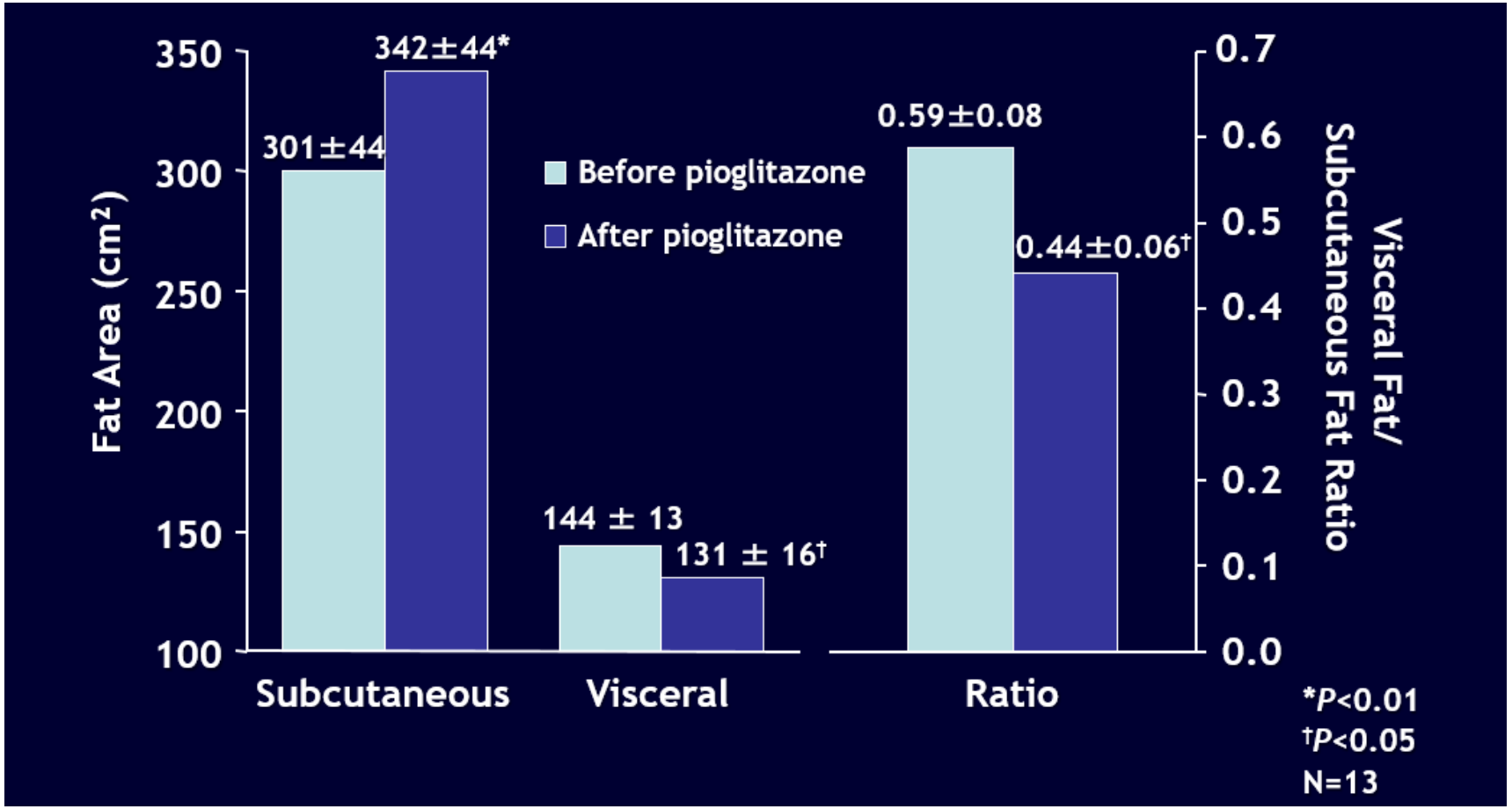


Rosenstock J for the Pioglitazone HCl Study Group. *Diabetologia.* 2000;43(suppl 1):A192.

PPARγ activation and the pancreas

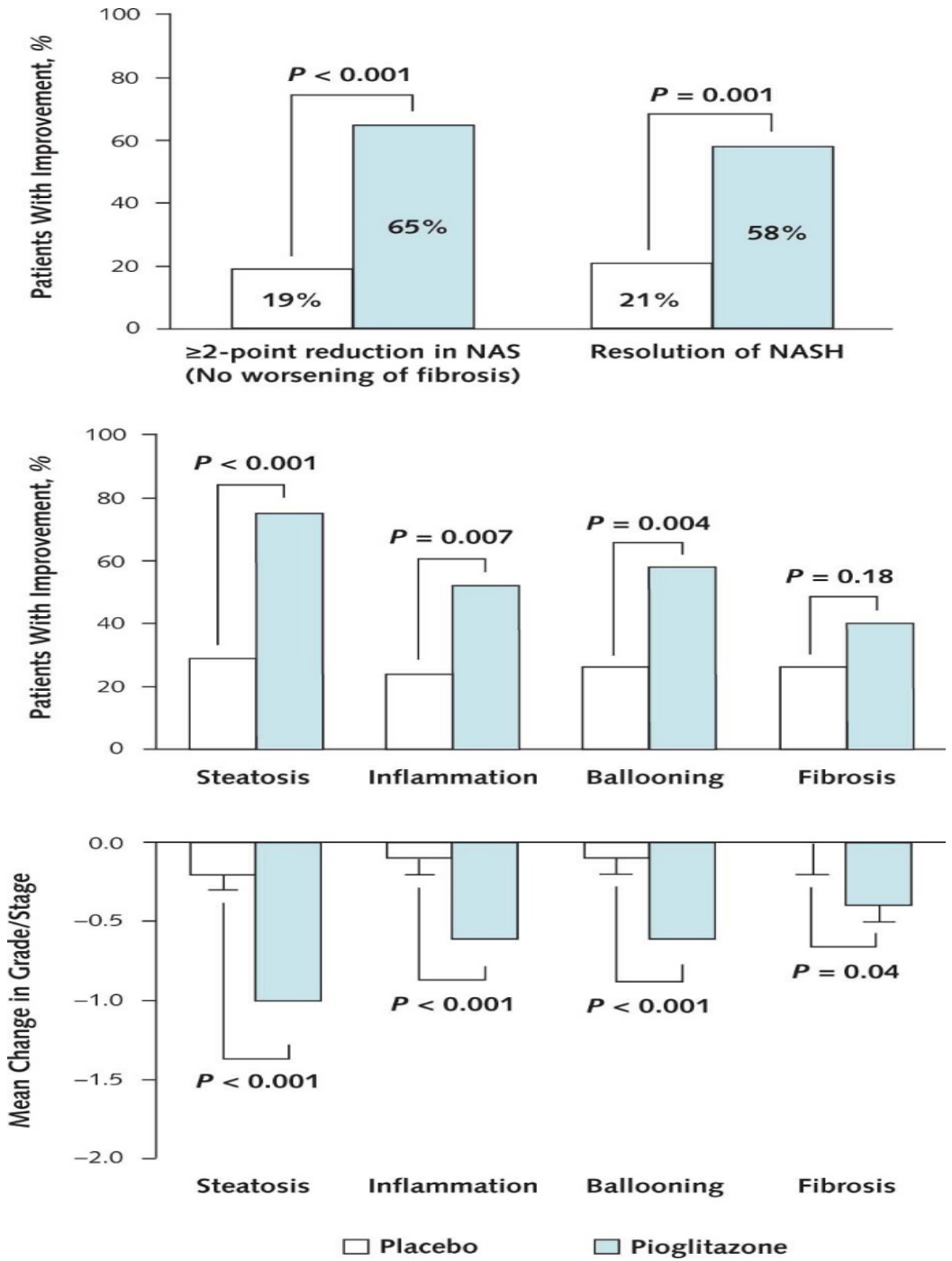


Effect of pioglitazone on abdominal fat distribution



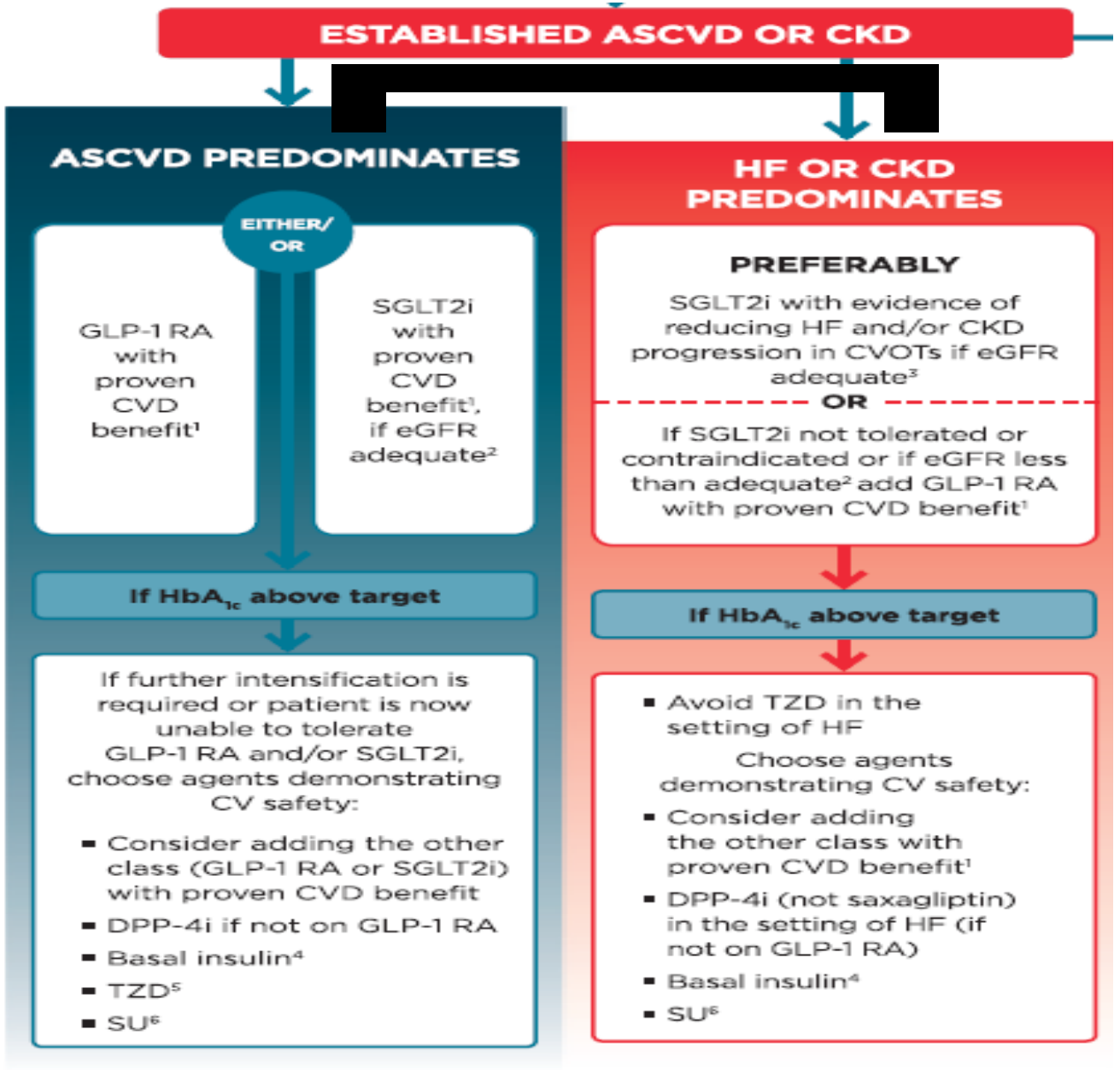
Miyazaki Y et al. J Clin Endocrinol Metab 2002;87(6):2784-91.

NASH: Histologic changes after 18 mo of pioglitazone



Cusi K et al *Ann Intern Med.* 2016;165(5):305-315

Glucose-lowering Medications in T2DM: ADA Recommendations for Overall Approach



ADA Standards of Medical Care in Diabetes - 2019. Davies et al. *Diabetes Care* 2018;42(S1):S1–S194.

Comparing recent CVOTs

	SGLT-2is		GLP-1 RA				TZD	DPP-4is		
Trial	**EMPA-REG**	**CANVAS**	**ELIXA**	**LEADER**	**SUSTAIN**	**EXSCEL**	**PROactive**	**SAVOR**	**EXAMINE**	**TECOS**
	empagliflozin(Jardiance)	Canagliflozin(Invokana)	Lixisenatide (Lyxumia)	Liraglutide (Victoza)	Semaglutide	Weekly Exenatide (Bydureon)	Pioglitazone (Actos)	Saxagliptin (Onglyza)	Alogliptin (Nesina)	Sitagliptin (Januvia)
MACE	**0.86*** 0.74, 0.99	**0.86*** 0.75, 0.97	**1.02** 0.89, 1.17	**0.87*** 0.78, 0.97	**0.74*** 0.58, 0.95	**0.91** 0.83, 1.00	**0.84*** 0.72, 0.98	**1.0** 0.89, 1.08	**0.96** Upper=<1.16	**0.98(4P)** 0.89 1.08
CV death	**0.62*** 0.49, 0.77	**0.87** 0.72, 1.06	**0.98** 0.78, 1.22	**0.78*** 0.66, 0.93	**0.98** 0.65, 1.48	**0.88** 0.76. 1.02	**0.94** 0.74, 1.20	**1.03** 0.87, 1.22	**0.79** 0.60, 1.04	**1.03** 0.89, 1.19
Non-fatal MI	**0.67** 0.70, 1.09	**0.85** 0.69, 1.05	**1.03** 0.87, 1.22	**0.88** 0.75, 1.03	**0.74** 0.51, 1.08	**0.97** 0.85, 1,19	**0.83** 0.65, 1.06	**1.95** 0.80, 1.12	**1.08** 0.88, 1.33	**0.95** 0.81, 1.11
Non-fatal stroke	**1.24** 0.92, 1.67	**0.90** 0.71, 1.15	**1.12** 0.79, 1.58	**0.89** 0.72, 1.11	**0.61*** 0.38, 0.99	**0.85** 0.70, 1.03	**0.81** 0.61, 1.07	**1.11** 0.88, 1.39	**0.91** 0.55, 1.50	**0.97** 0.89, 1.08
Hospitalized HF	**0.65*** 0.50, 0.85	**0.67*** 0.52, 0.87	**0.96** 0.75, 1.23	**0.87** 0.73, 1.05	**1.11** 0.77, 1.61	**0.94** 0.78, 1.13	**1.15** 0.65, 2.03	**1.27*** 1.07, 1.51	**1.07** 0.78, 1.15	**1.00** 0.83, 1.20
All-cause death	**0.68*** 0.57, 0.82	**0.87** 0.74, 1.01	**0.94** 0.78, 1.13	**0.85*** 0.74, 0.97	**1.05** 0.74, 1.50	**0.86** 0.77, 0.97	**0.96** 0.78, 1.18	**1.11** 0.96, 1.27	**0.88** 0.71, 1.09	**1.01** 0.90, 1.14

Big Changes in Guidelines: But What is the Reality in Practice?

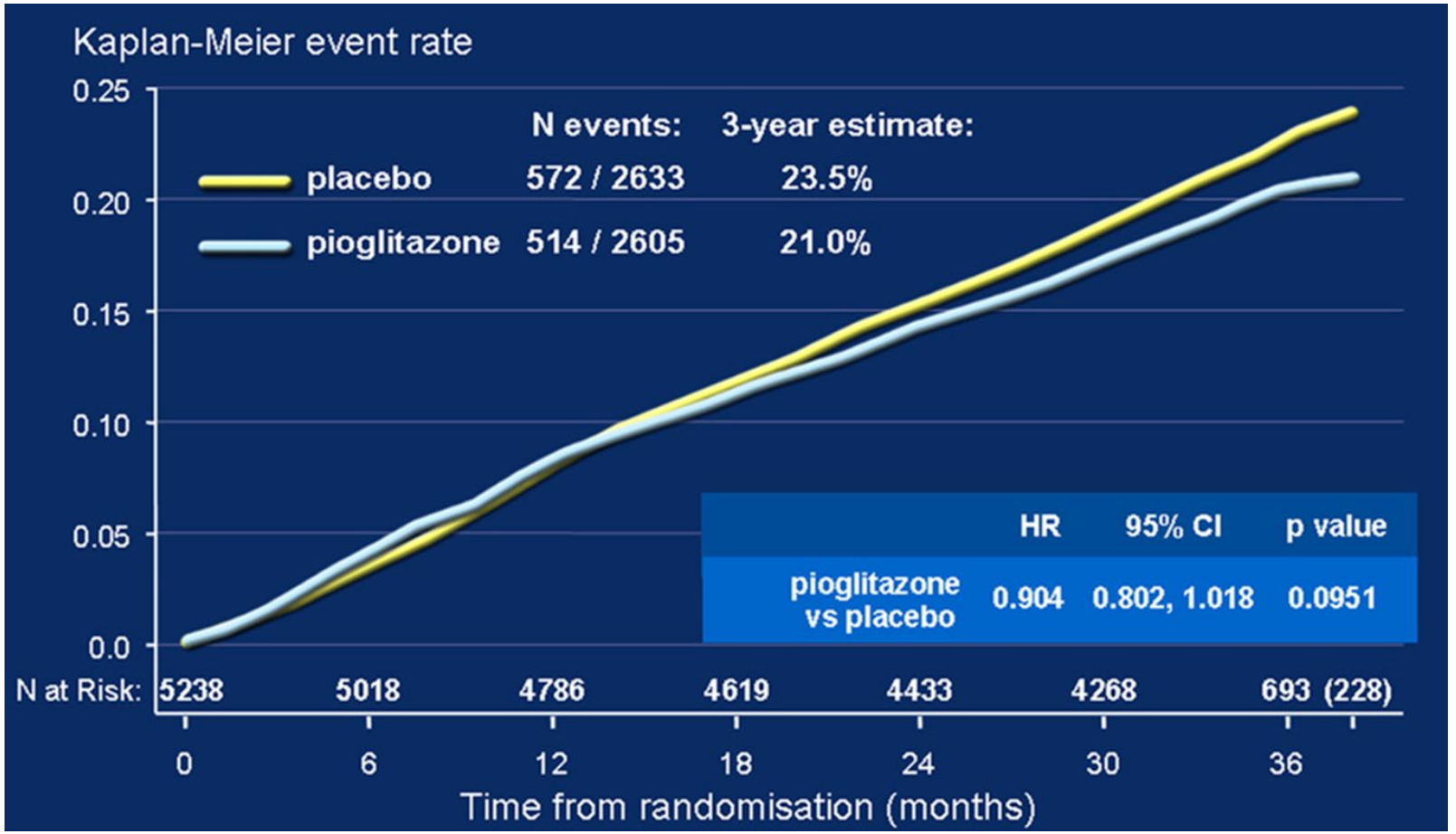
- MI rates have fallen– prediction of future events is challenging
- Statins and RAAS blockade remain the first line choice for prevention of CVD and CKD
- Microvascular Disease remains a challenge and glucose control is important
- Adherence to GLP-1 RA therapy is poor
- Efficacy of SGLT2i is modest – durability is also poor
- Hospitalization for CHF – RR reduced but absolute rates are very low in diabetes
- Stroke and PVD remain neglected problems
- Insulin Resistance not adequately managed
- DPP-4 inhibitors – modest effects but very safe and well tolerated

Effects of PPARγ and PPARα ligands on lipids

	Pioglitazone	Rosiglitazone	Fenofibrate	Gemfibrozil
Triglycerides	↓↓	↓	↓↓↓	↓↓↓
HDL-C	↑	↑	↑↑	↑
LDL-C	↓/No Change	↑	↓	↓/No Change
Small, dense LDL	↓	↓	↓	↓

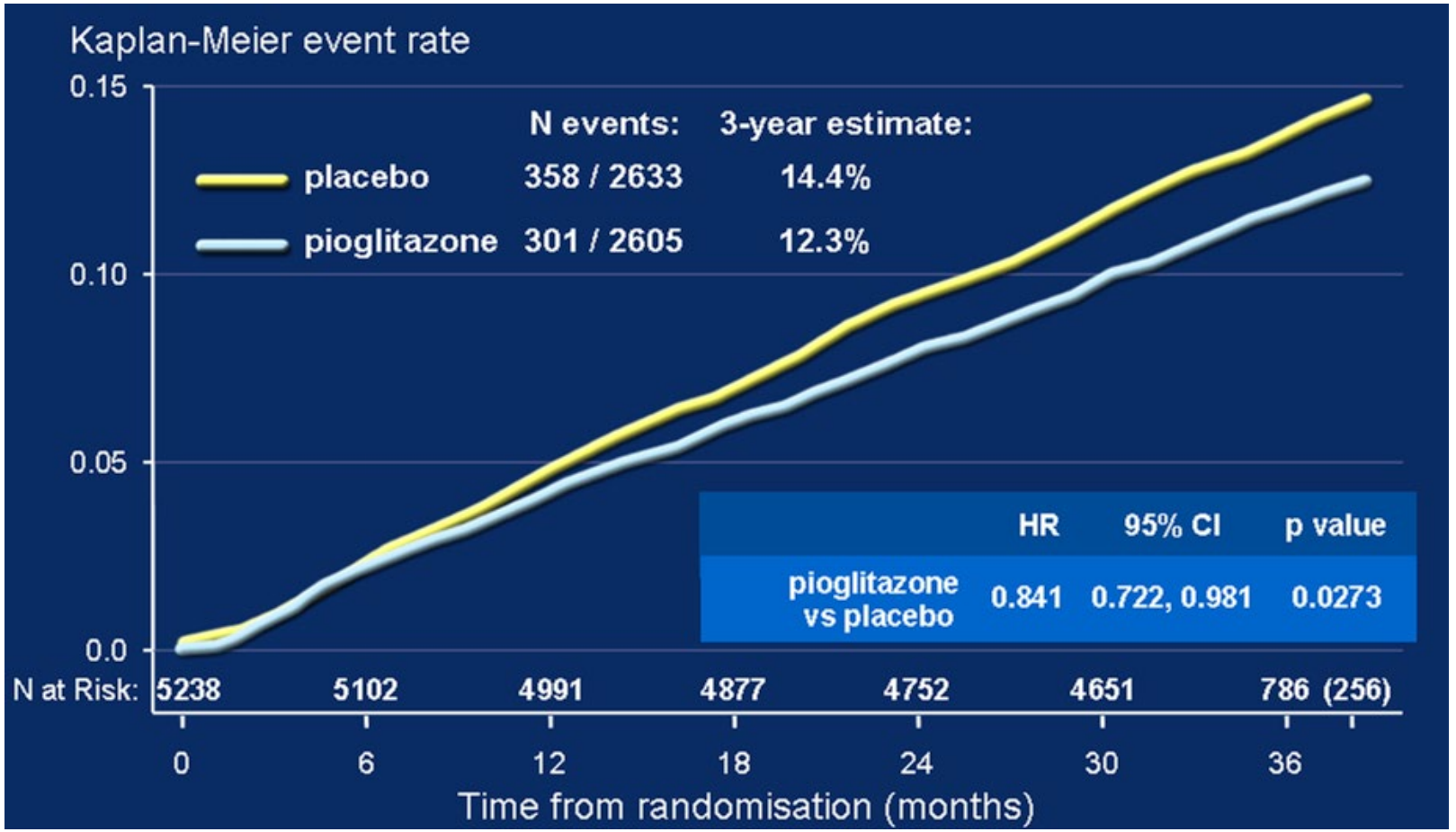
Aguilar-Salinas CA et al. Metabolism 2001;50(6):729-33. Boyle PJ et al. Clin Ther 2002;24(3):378-96.
Fruchart JC et al. Bull Acad Natl Med 2001;185(1):63-74; discussion 74-65. Guay DR. Ann Pharmacother 1999;33(10):1083-103. Insua A et al. Endocr Pract 2002;8(2):96-101. Inzucchi SE. JAMA 2002;287(3):360-72.
Nyman JA et al. Arch Intern Med 2002;162(2):177-82.

PROactive: Time to primary composite endpoint



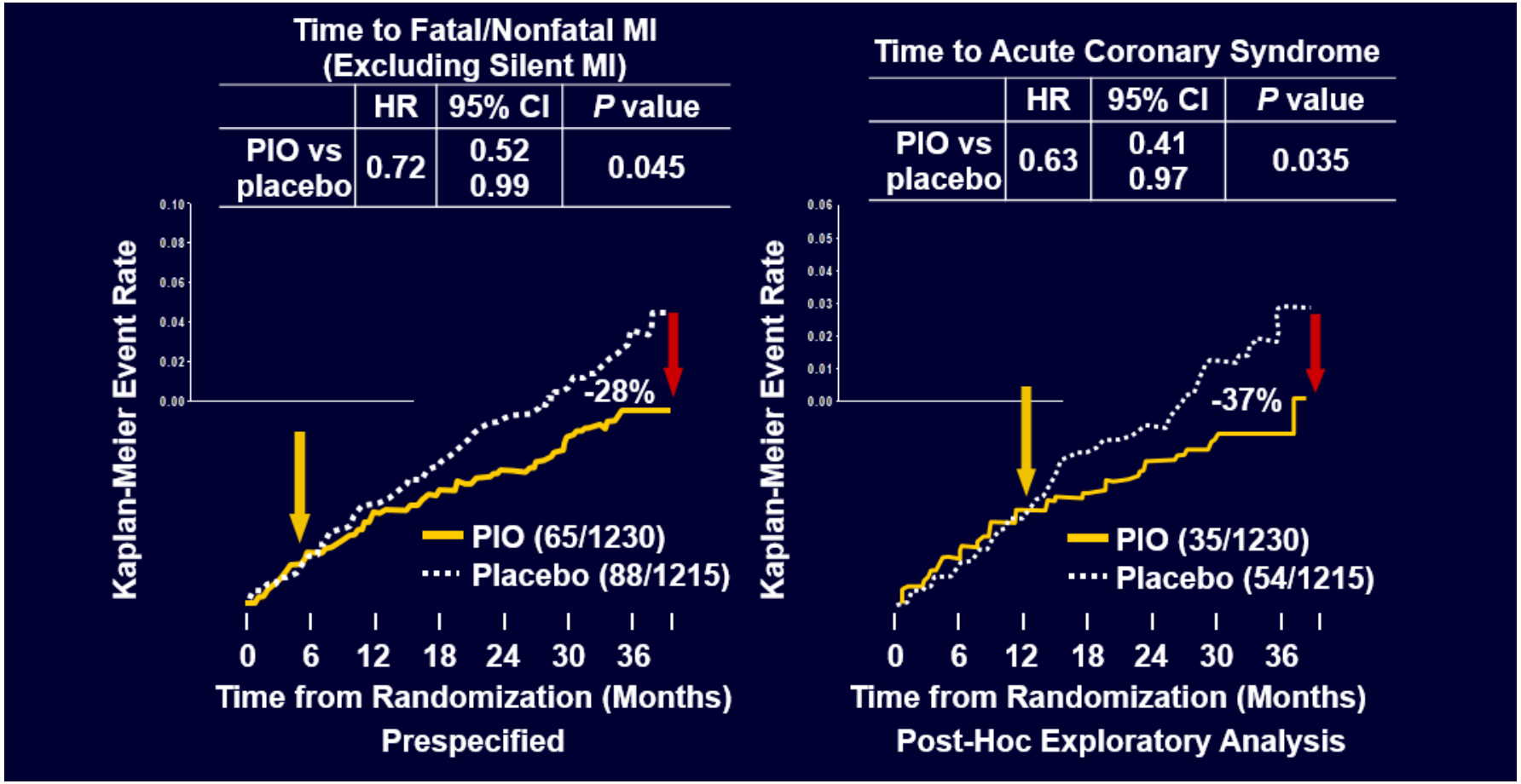
Dormandy JA et al. Lancet 2005;366:1279-89

Time to Death, MI (Excluding Silent), or Stroke



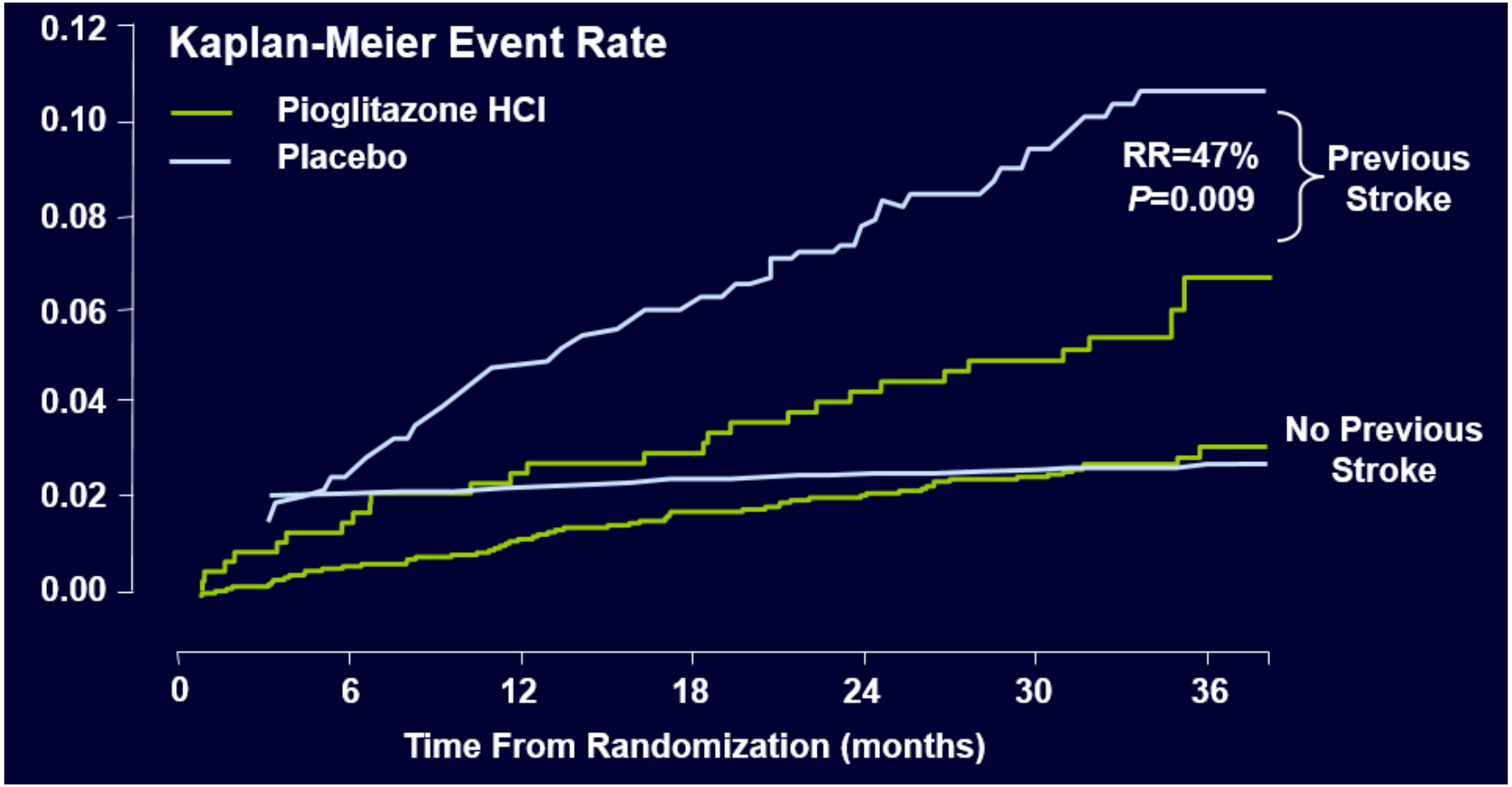
Dormandy JA et al. Lancet 2005;366:1279-89

PROactive: Pioglitazone (PIO) reduces “hard” coronary heart disease endpoints



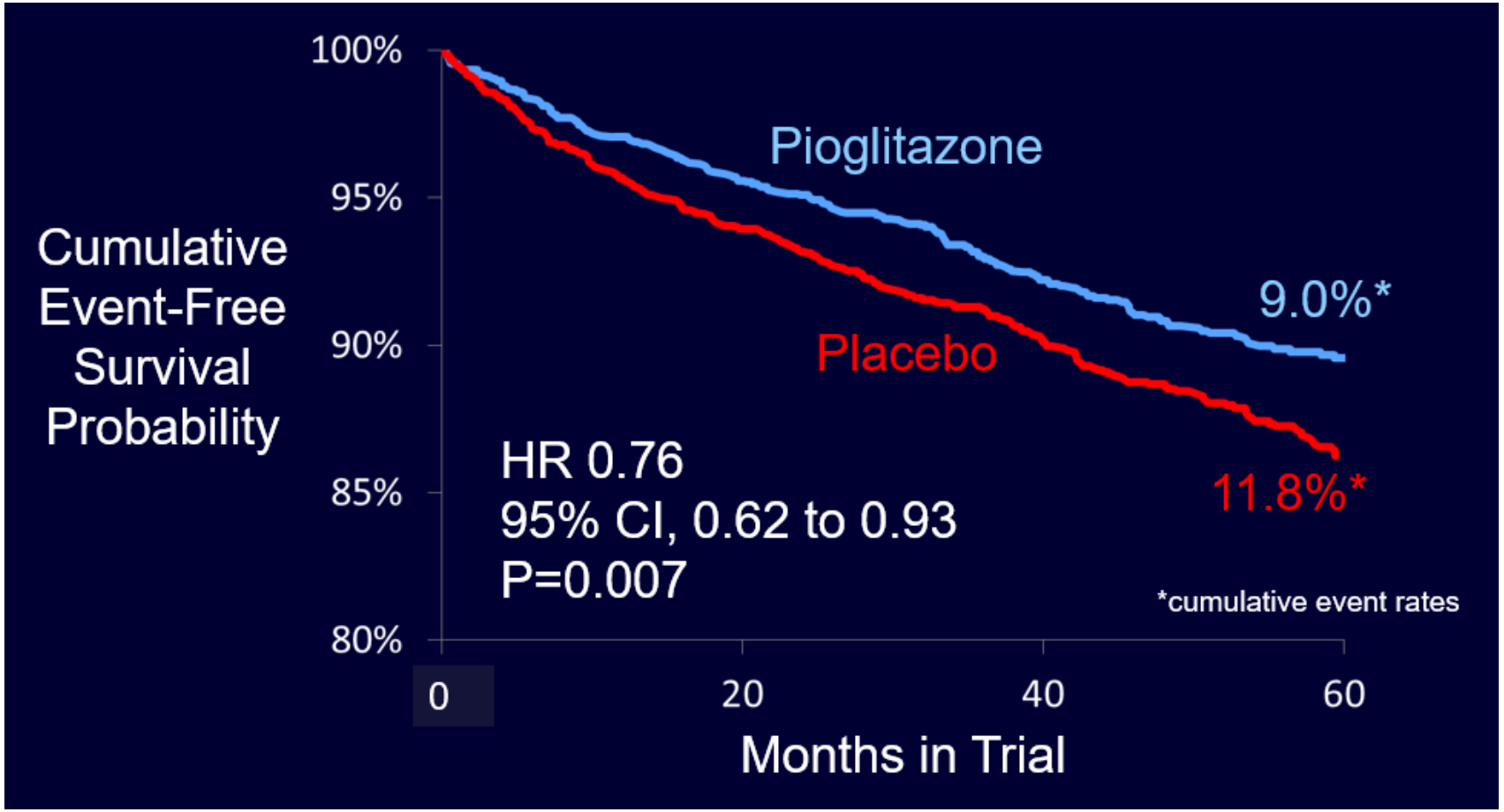
Adapted from Erdmann E et al. J Am Coll Cardiol 2007;49(17):1772-80.

PROactive: Time to fatal/nonfatal stroke in patients with previous stroke



Wilcox R et al. Stroke 2007;38(3):865-73.

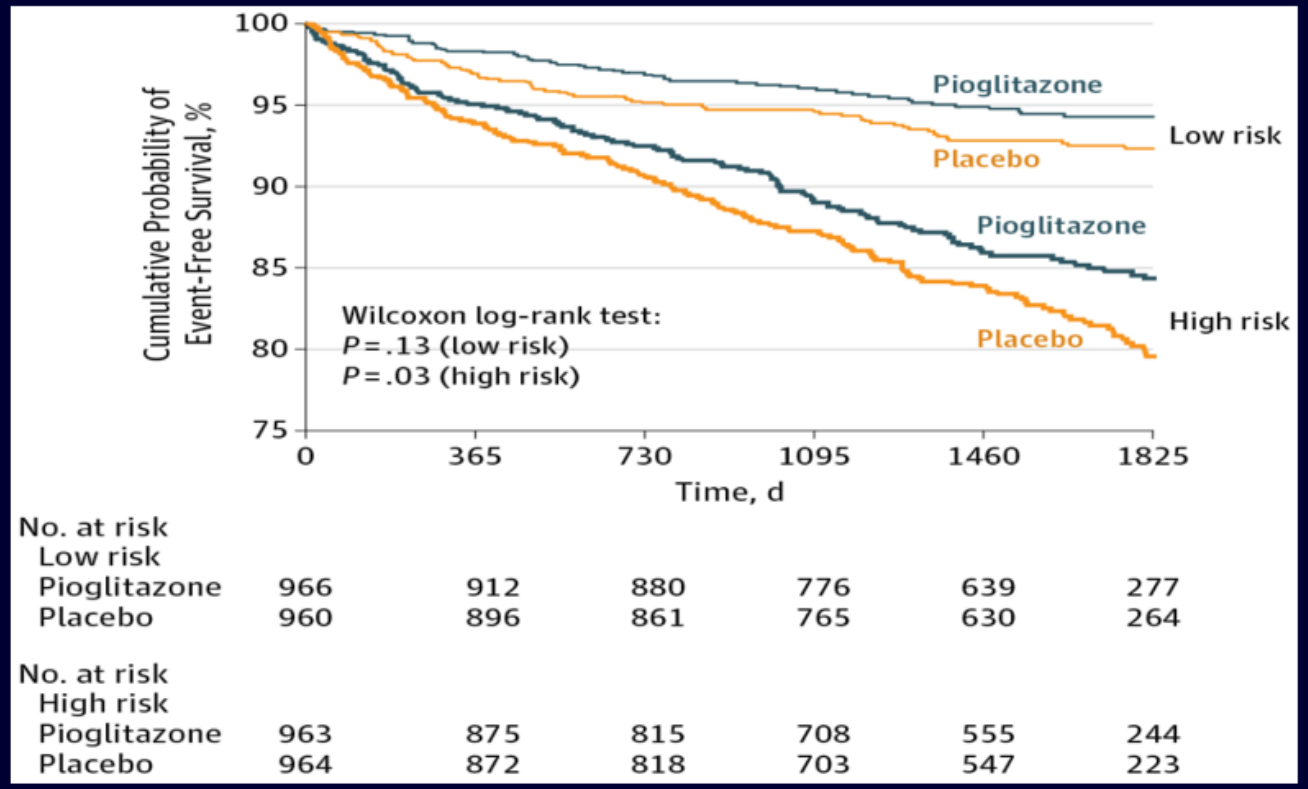
IRIS Primary Outcome



Kernan WN *et al. N Engl J Med*, published on-line Feb 17, 2016 DOI: 10.1056/NEJMoa1506930

JAMA Network

From: Targeting Pioglitazone Hydrochloride Therapy After Stroke or Transient Ischemic Attack According to Pretreatment Risk for Stroke or Myocardial Infarction



No. at risk						
Low risk						
Pioglitazone	966	912	880	776	639	277
Placebo	960	896	861	765	630	264
No. at risk						
High risk						
Pioglitazone	963	875	815	708	555	244
Placebo	964	872	818	703	547	223

JAMA Neurol. 2017;74(11):1319-1327. doi:10.1001/jamaneurol.2017.2136

IRIS: Summary

- Among insulin resistant, non-diabetic patients with ischemic stroke/TIA, pioglitazone over 5 yrs prevented:

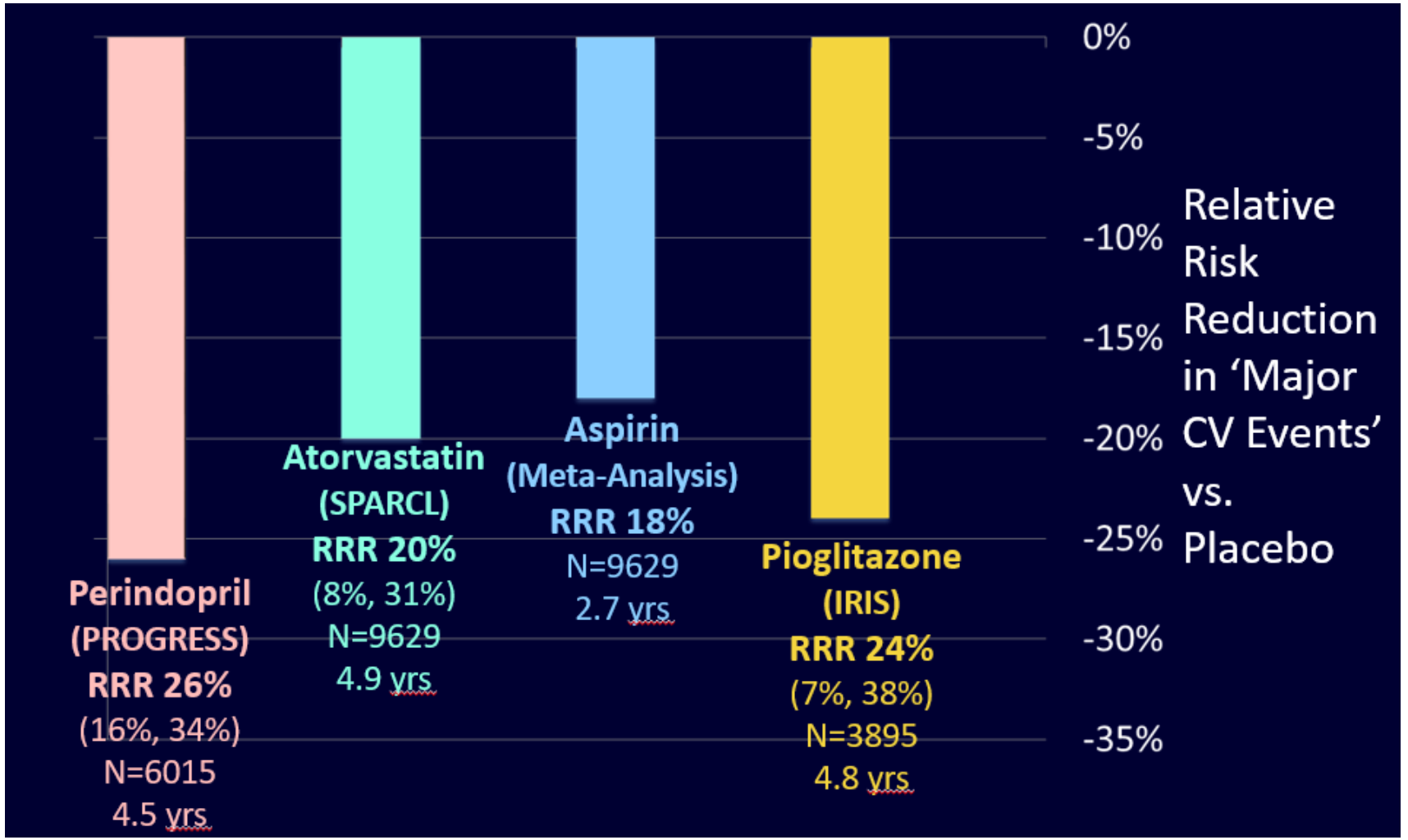
- Stroke or MI
  - Relative Risk Reduction 24%
  - Absolute Risk Reduction 2.9%

- Diabetes
  - Relative Risk Reduction 52%
  - Absolute Risk Reduction 3.9%

- However, serious bone fracture was more common with pioglitazone (5.1% vs. 3.2%)

Kernan WN *et al. N Engl J Med*, published on-line Feb 17, 2016 DOI: 10.1056/NEJMoa1506930

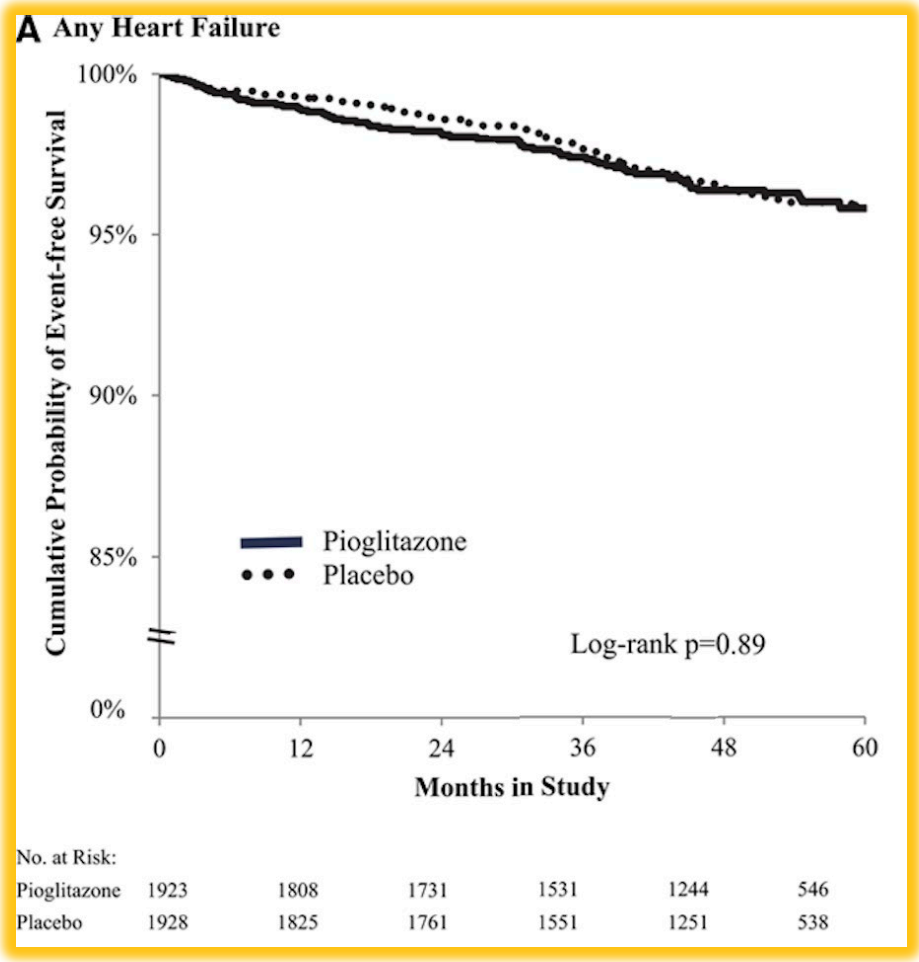
Secondary Prevention in Stroke Patients



PROGRESS Collab Group. Lancet 2001;358:1033; SPARCL Invest. *N Engl J Med* 2006;355:549; Johnson ES *et al Arch Intern Med* 1999; 159:1248; Kernan WN *et al. N Engl J Med* 2016; DOI: 10.1056/NEJMoa1506930

Insulin Resistance Intervention after Stroke (IRIS): HF Safety Endpoint

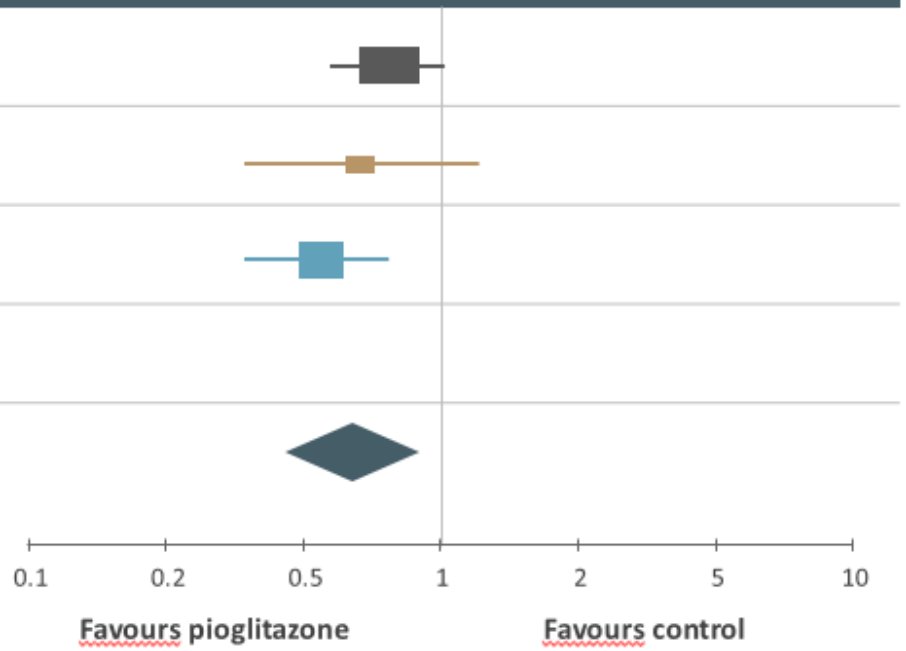
- Pioglitazone did not increase the risk of incident HF, even in those patients with HF risk factors.
- Pio also reduced the incidence of MI, which was a significant post-randomization risk factor for HF.
- Pio also had a beneficial effect on the overall prespecified composite outcome of fatal/nonfatal stroke and MI and hospitalized HF.
- Note: The study drug dose could be reduced for symptoms of edema or excessive weight gain. (mean daily dose on-trial = 29 mg)



3 RCT data with Pioglitazone regarding recurrent stroke and major vascular events in ischemic stroke patients

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95%CI
IRIS	46.8%	0.82 (0.64, 1.05)
J SPIRIT	17.9%	0.66 (0.36, 1.22)
PROactive	35.3%	0.53 (0.37, 0.76)
Total (95% CI)	100%	0.68 (0.50, 0.92)

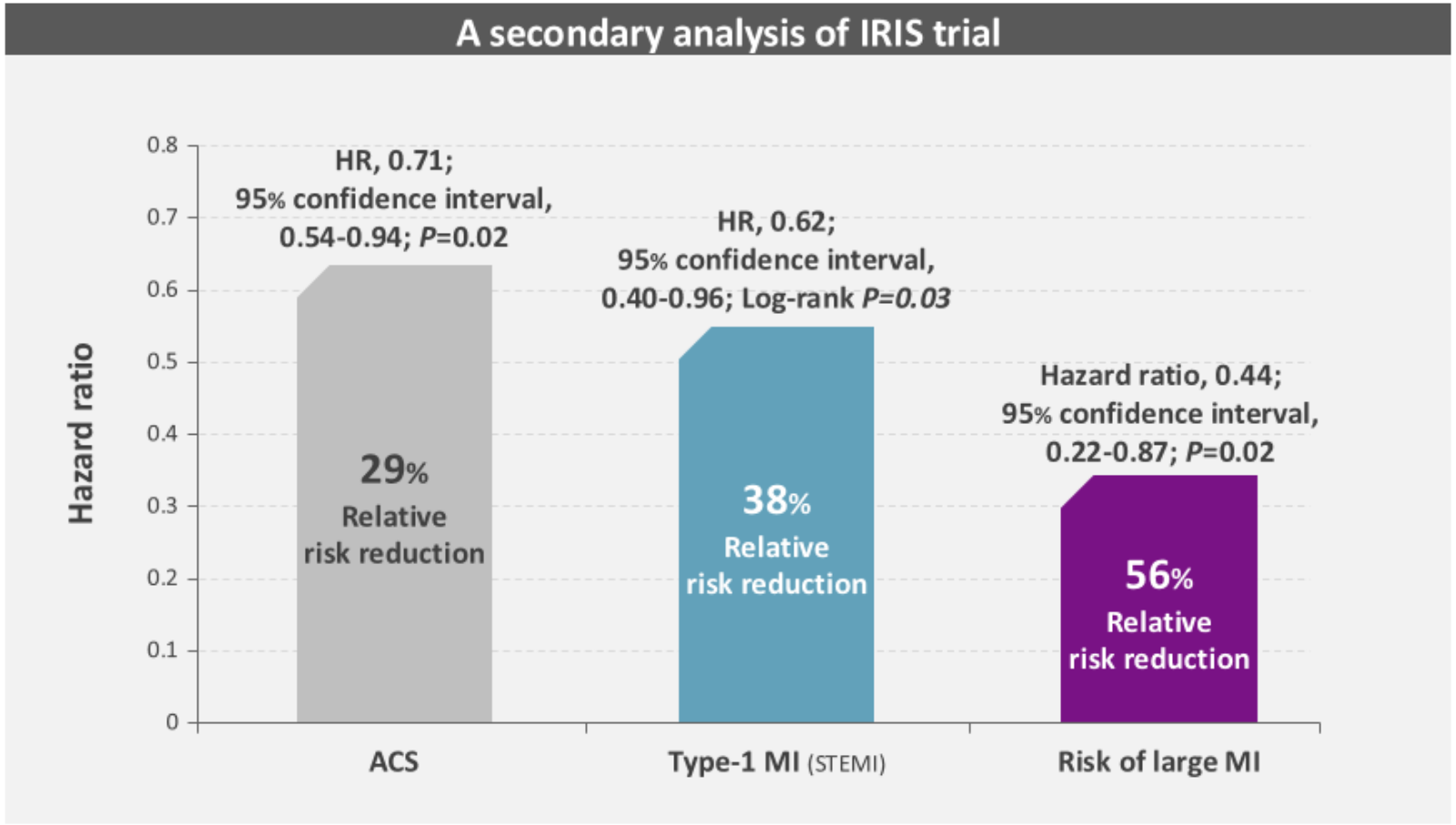
Heterogeneity: Tau^2 =0.03; Chi^2 =3.88, df=2 (p=0.14); I^2=49%
Test for overall effect: Z=2.53 (p=0.01)



Three randomized controlled trials with 4980 participants,
with no evidence of an effect on all-cause mortality and heart failure.

Lee M, *et al.* Pioglitazone for Secondary Stroke Prevention: A Systematic Review and Meta-Analysis. *Stroke*. 2017 Feb;48(2):388-393.

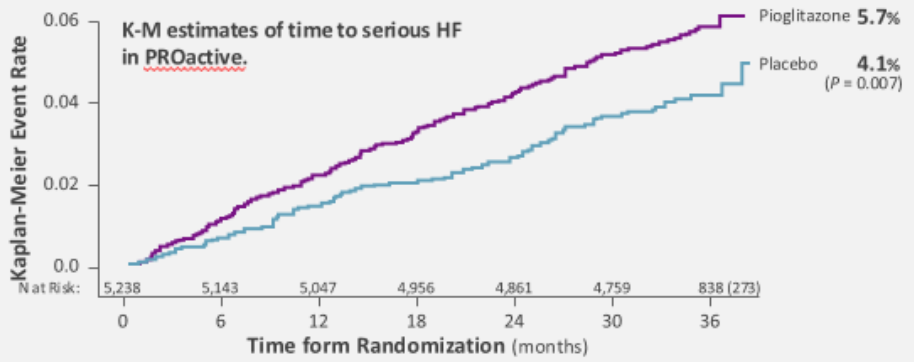
Pioglitazone showed lower risk of ACS, type-1 MI and large MI (>100 troponin) in IRIS trial



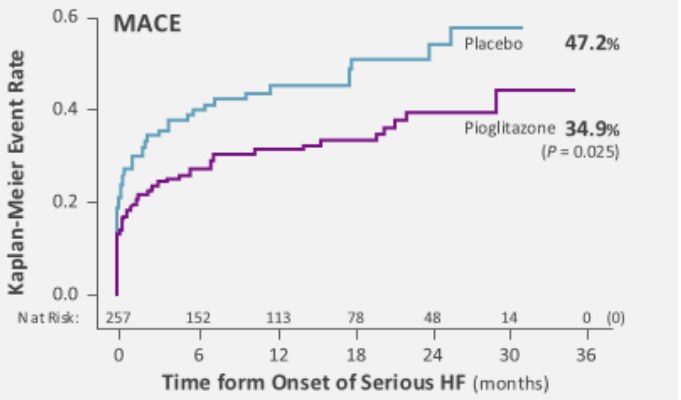
Young LH, *et al.* Cardiac Outcomes After Ischemic Stroke or Transient Ischemic Attack: Effects of Pioglitazone in Patients With Insulin Resistance Without Diabetes Mellitus. *Circulation.* 2017 May 16;135(20):1882-1893.

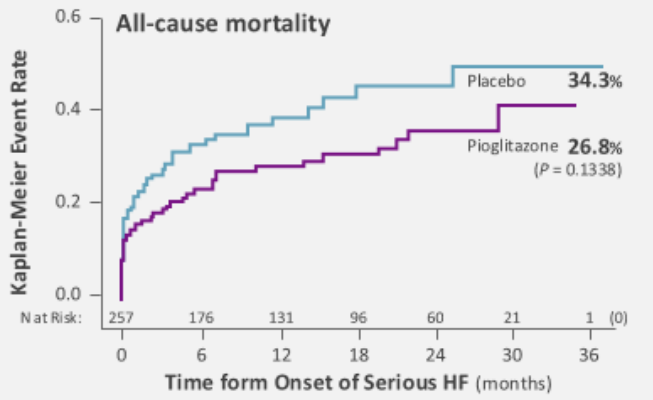
Does Pioglitazone increase heart failure??

Even though there was slight increase in time to serious HF in PROactive study,



Among patients who had heart failure,
Progress after heart failure was less severe in Pioglitazone (MACE and all-cause mortality)





Erdmann E, *et al.* Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care*. 2007 Nov;30(11):2773-8.

Does Pioglitazone Still Have a Place in Therapy? – YES!

- Early – Prevention? – ACT NOW
- Combination with Metformin – Durability
- Insulin Resistance Syndrome
- High insulin doses – with caution
- CVD patients? – PROactive/BARI 2D
- NASH

- Caveats:
  - Use lower doses (15-30 mg)
  - Stop if weight gain and edema
  - Assess osteoporosis risk

Questions?