The promise of the thiazolidinediones in the management of type 2 diabetes-associated cardiovascular disease

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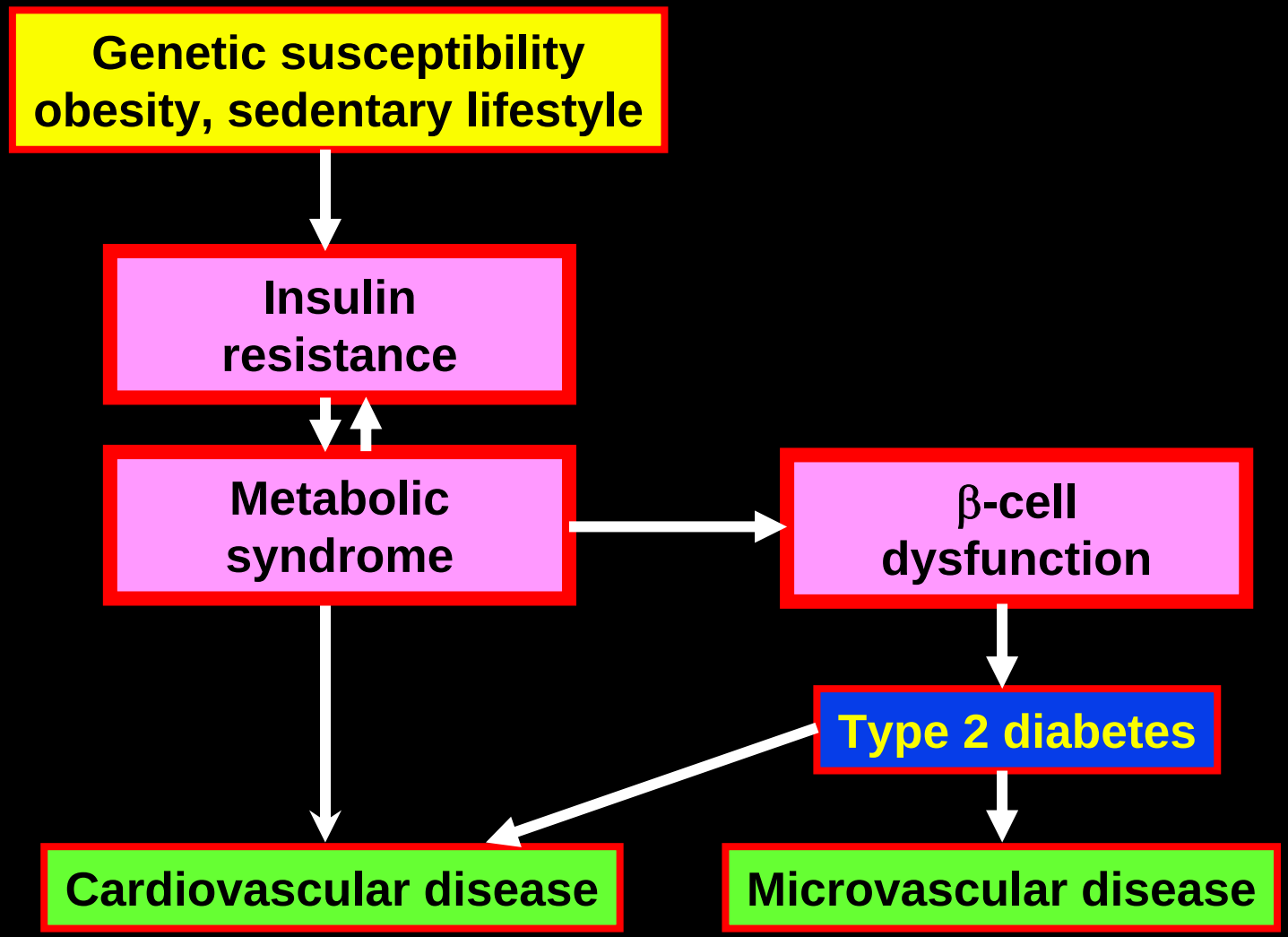
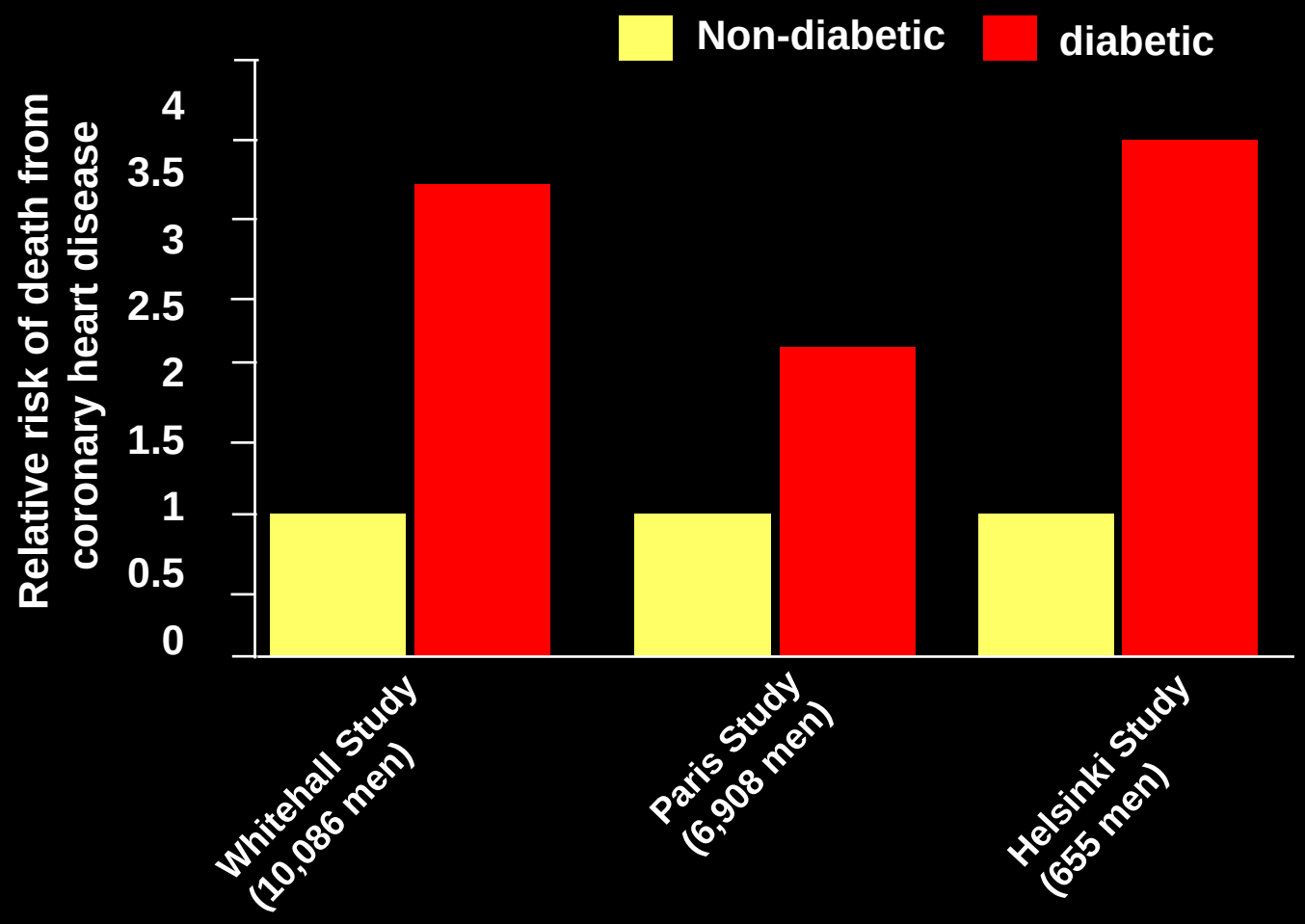
Type 2 diabetes - a cardiovascular disease associated with hyperglycemia

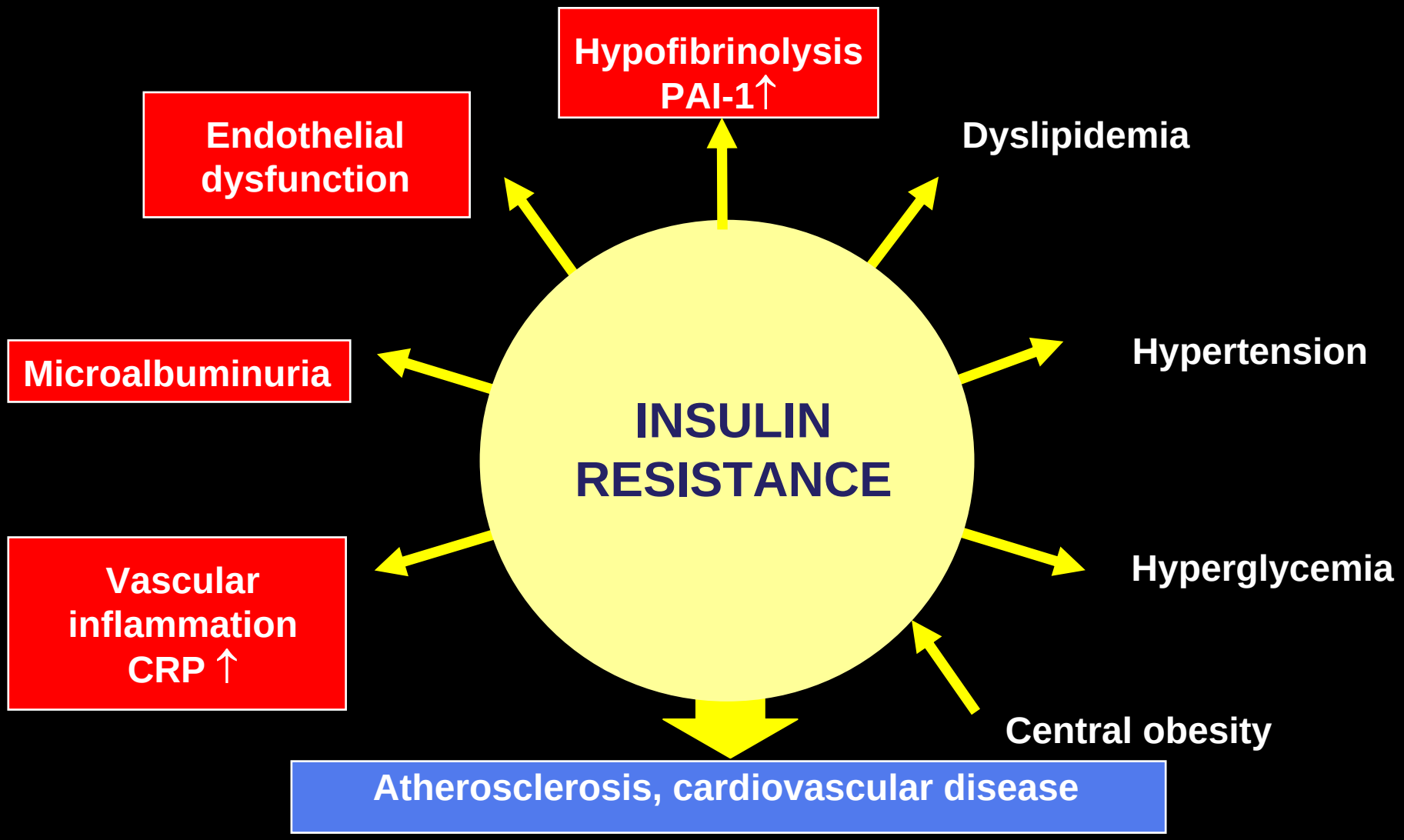


Risk of death due to heart disease is increased 2- to 3-fold in men with type 2 diabetes



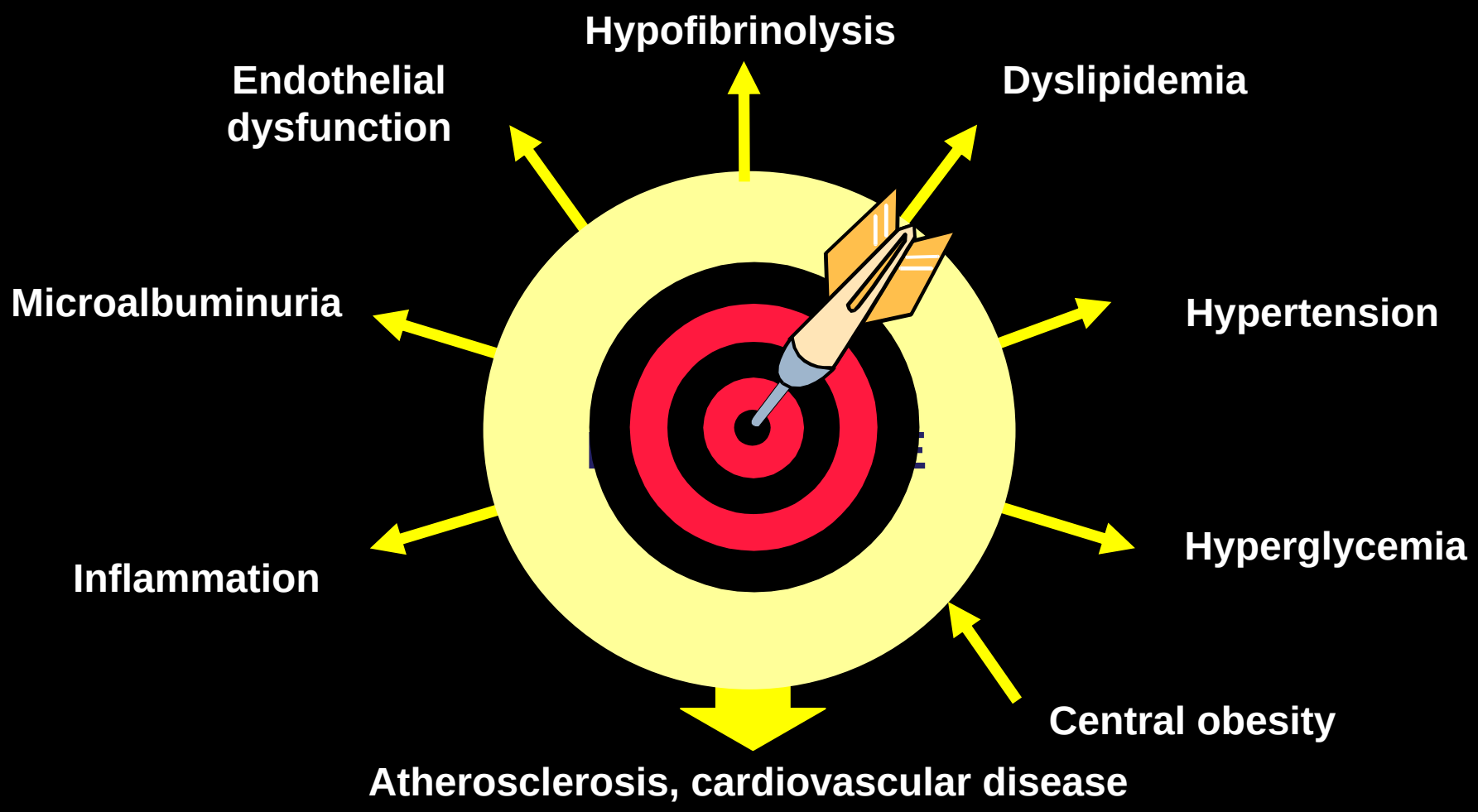
Balkau B & Eschwëge E. *Diabetes, Obesity and Metabolism* 1999;1 :S23–S31.

Insulin Resistance Syndrome



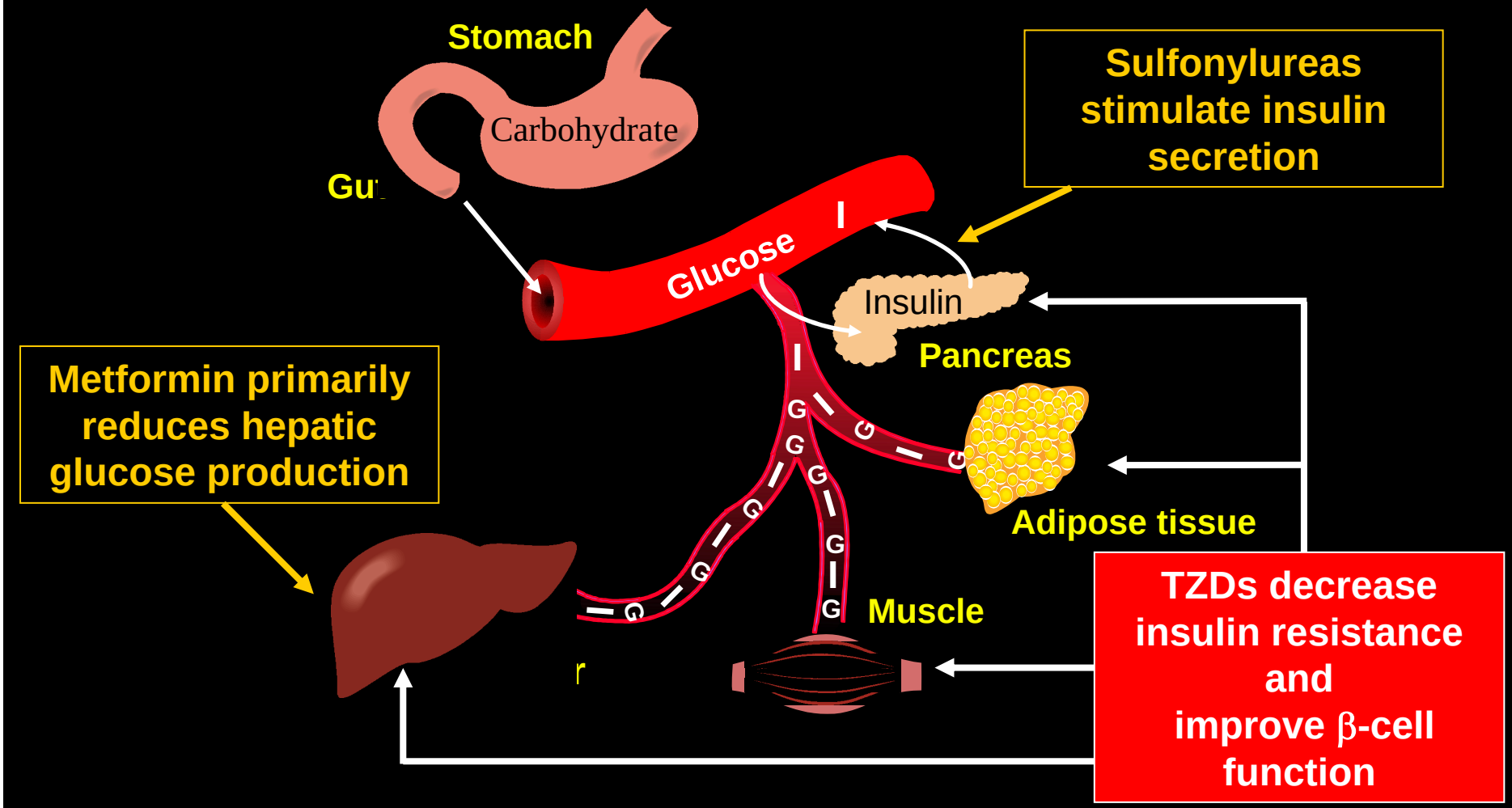
Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Insulin Resistance Syndrome



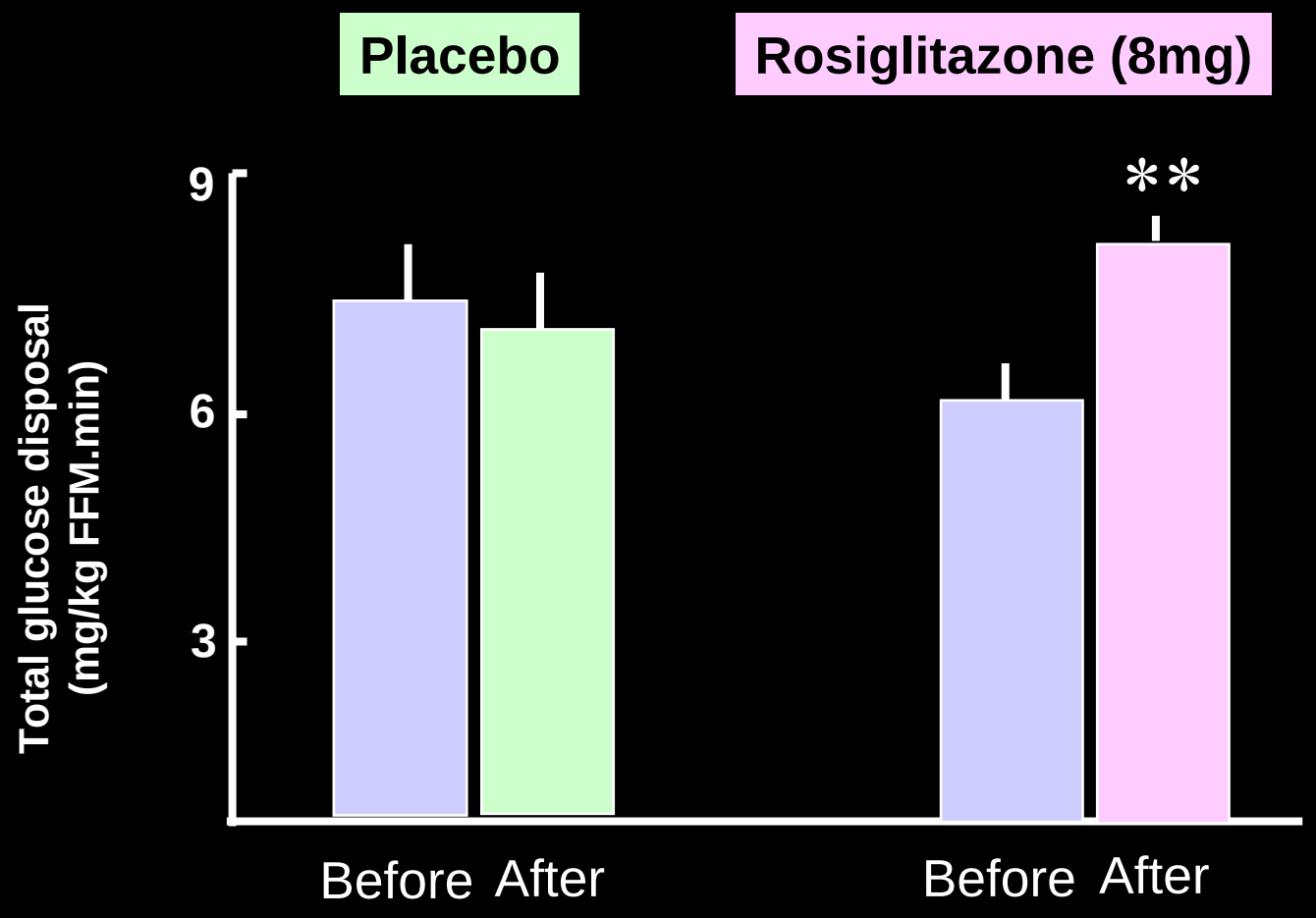
Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Thiazolidinediones have a complementary mode of action to metformin and sulfonylureas



Adapted from Kobayashi M. *Diabetes Obes Metab* 1999; 1 (Suppl. 1):S32–S40.
Nattrass M & Bailey CJ. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999; 13:309–329.

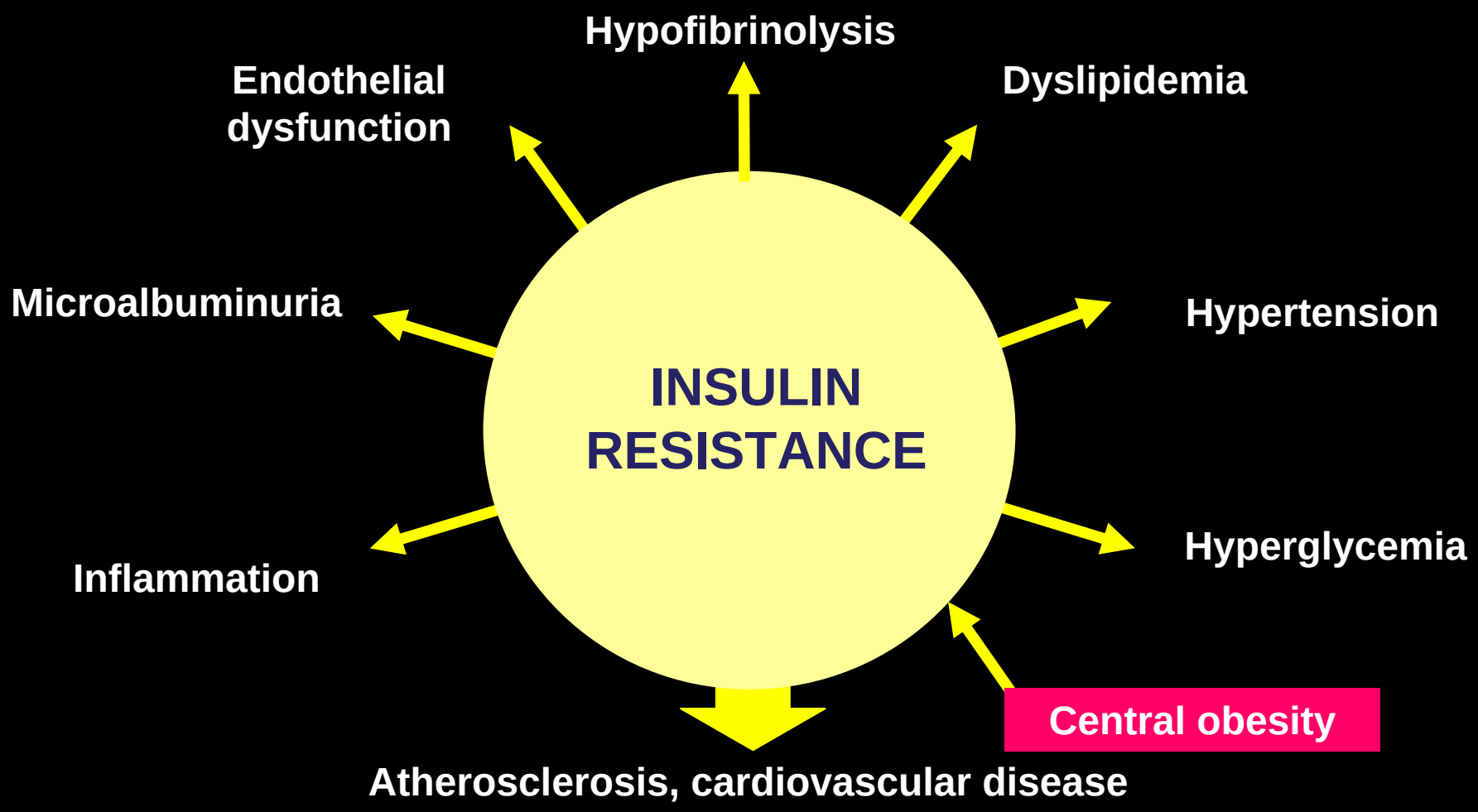
Rosiglitazone increases insulin-mediated glucose disposal in type 2 diabetes



12 weeks therapy, n = 14-15

Miyazaki et al (2001) Diabetologia 44: 2210

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

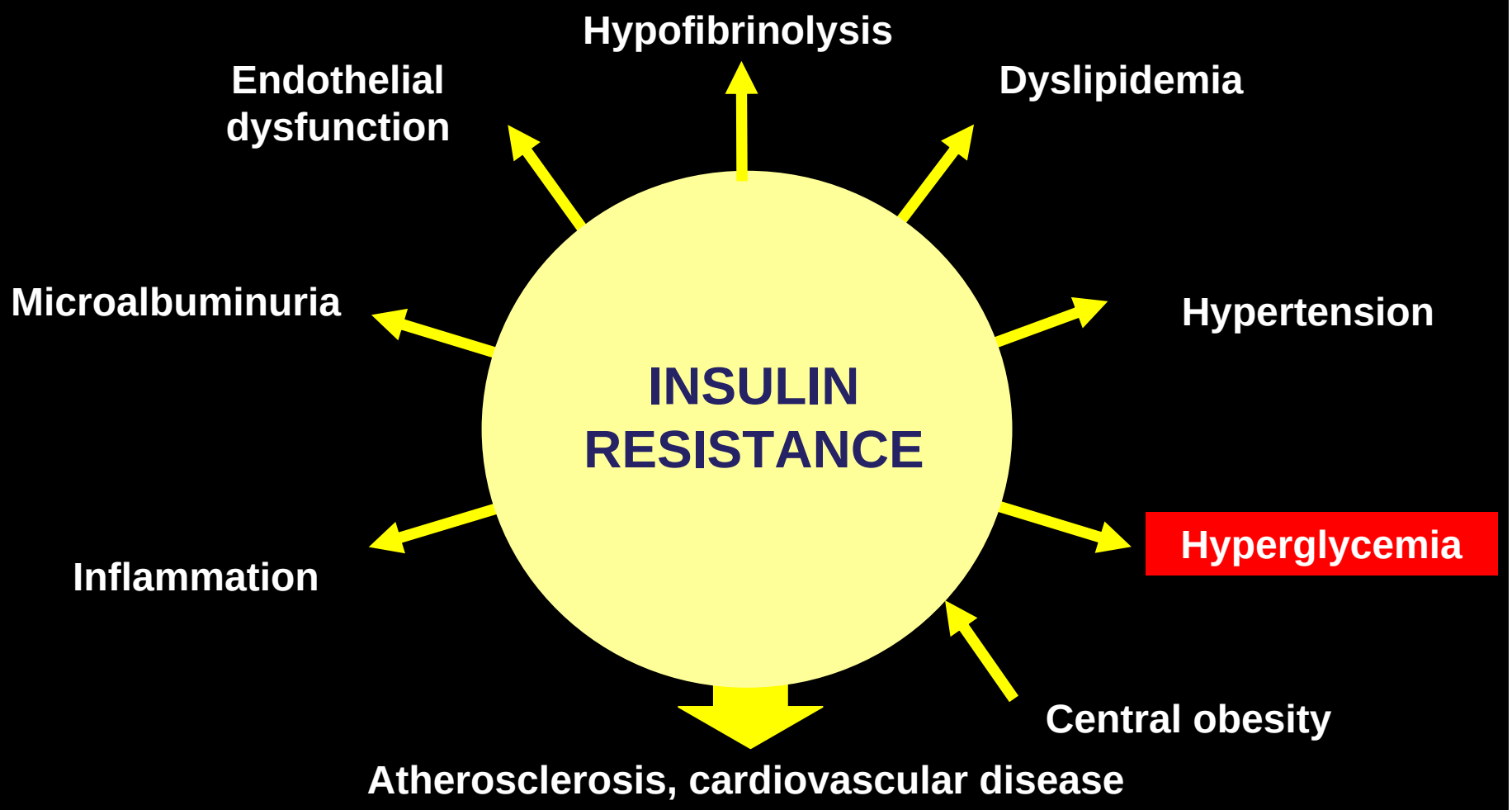
Rosiglitazone does not increase visceral fat mass in type 2 diabetics

Adiposity (Δ from b/l)	Kelley DE, *et al.*[1]	Carey DG, *et al.*[2]	Banerji M, *et al.*[3]	Virtanen KA, *et al.*[4]
RSG (8 mg/day) duration (n)	4 months (n = 11)	16 weeks (n = 10)	6 months (n = 16)	26 weeks (n = 14)
VISCERAL	↓ –27 cm^2 (b/l 207 cm^2)	–	–	↓ –0.3 kg (b/l 2.3 kg)*
SUB-CUTANEOUS	**NA**	↑ 25 cm^2* (b/l 304.8 cm^2)	↑ 0.68 liters†	–
VISCERAL:SUB-CUTANEOUS RATIO	**NA**	↓ –0.039* (b/l 0.72)	**NA**	**NA**

*$P \leq 0.05$ vs baseline
†$P < 0.04$ vs baseline
NA = not applicable (not measured)

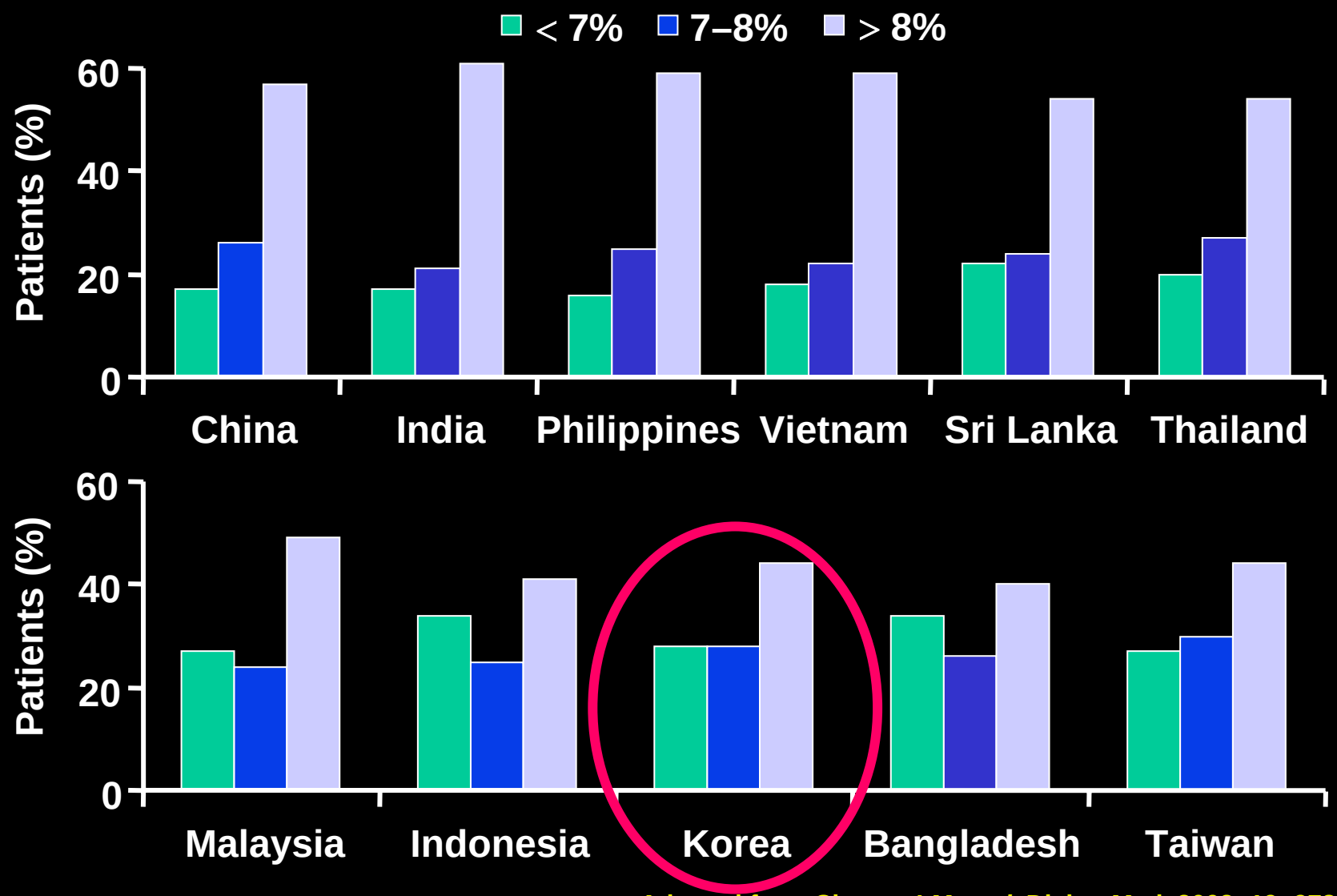
[1]Kelley DE, *et al*. *Diabetes* 2002; 51 (Suppl. 2):A35.
[2]Carey DG, *et al*. *Obes Res* 2002; 10:1008–1015; [3]Banerji M, *et al*. *Diabetes* 2001; 50:A356.
[4]Virtanen KA, *et al*. Diabetes 2003; 52:283–290.

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Diabcare-Asia 1998: HbA_{1c} of diabetes clinic patients



Adapted from Chuang LM *et al*. Diabet Med. 2002; 19: 978–85.

RECORD - Cardiovascular Outcomes Trial

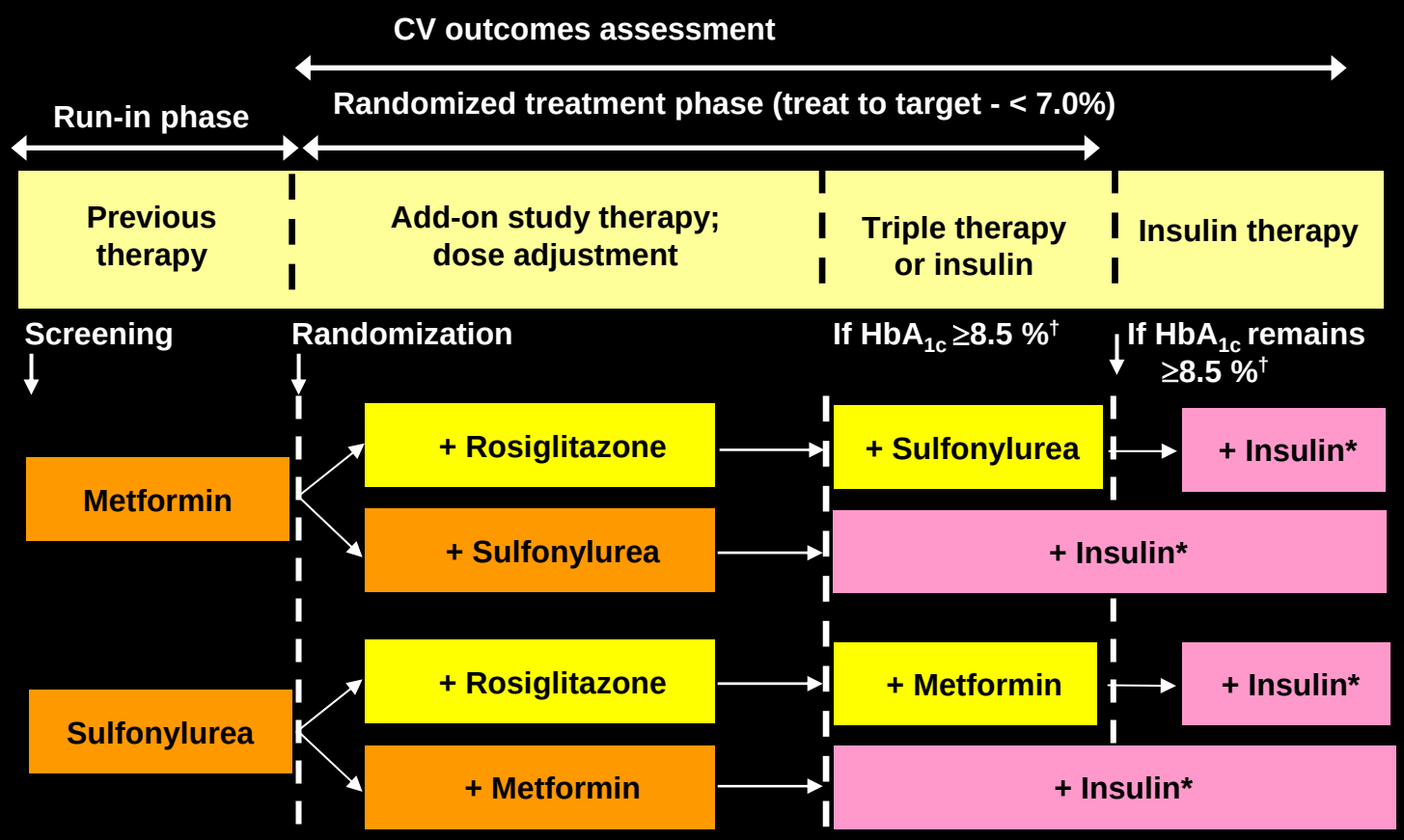
18 months interim analysis

Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD)

- **Design**
  - Randomized, open label, parallel group study (Europe/Australia/NZ)
- **Population**
  - T2DM with HbA_{1c} >7% and <9%, who are inadequately controlled on maximum permitted or maximum tolerated doses of background monotherapy (SU or metformin)
- **Endpoints**
  - Primary endpoint—Time to reach the combined CV endpoint
  - Secondary endpoints—Numerous CV and glycemic endpoints
- **Timings**
  - Fully recruited

EASD Munich 2004

RECORD: Study Design

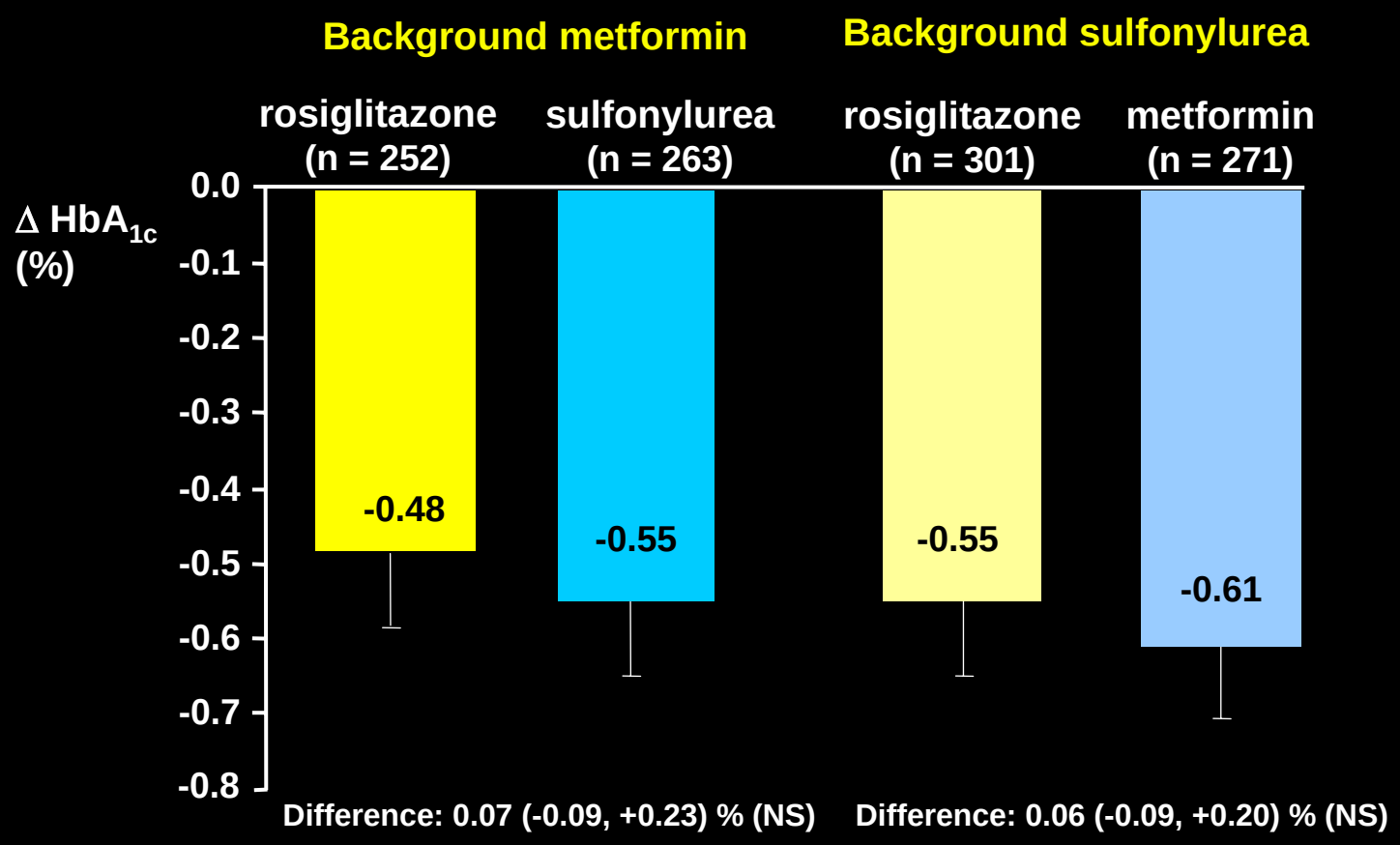


† ≥ 8.5% on two consecutive occasions at least 1 month apart

* +/- MET or SU according to local clinical practice

EASD Munich 2004

RECORD: Change in HbA_{1c} from baseline at 18 months



ITT population. Baseline adjusted. Mean ± SE

PD Home et al EASD 2004 A1580

Which patients respond best to TZDs ? The S Korean Experience

Kim et al 2005 Diabetes Research & Clin Practice 67:43-52

125 type 2 diabetic patients, poorly controlled on met or SU

4mg Rosiglitazone added – 12 weeks therapy

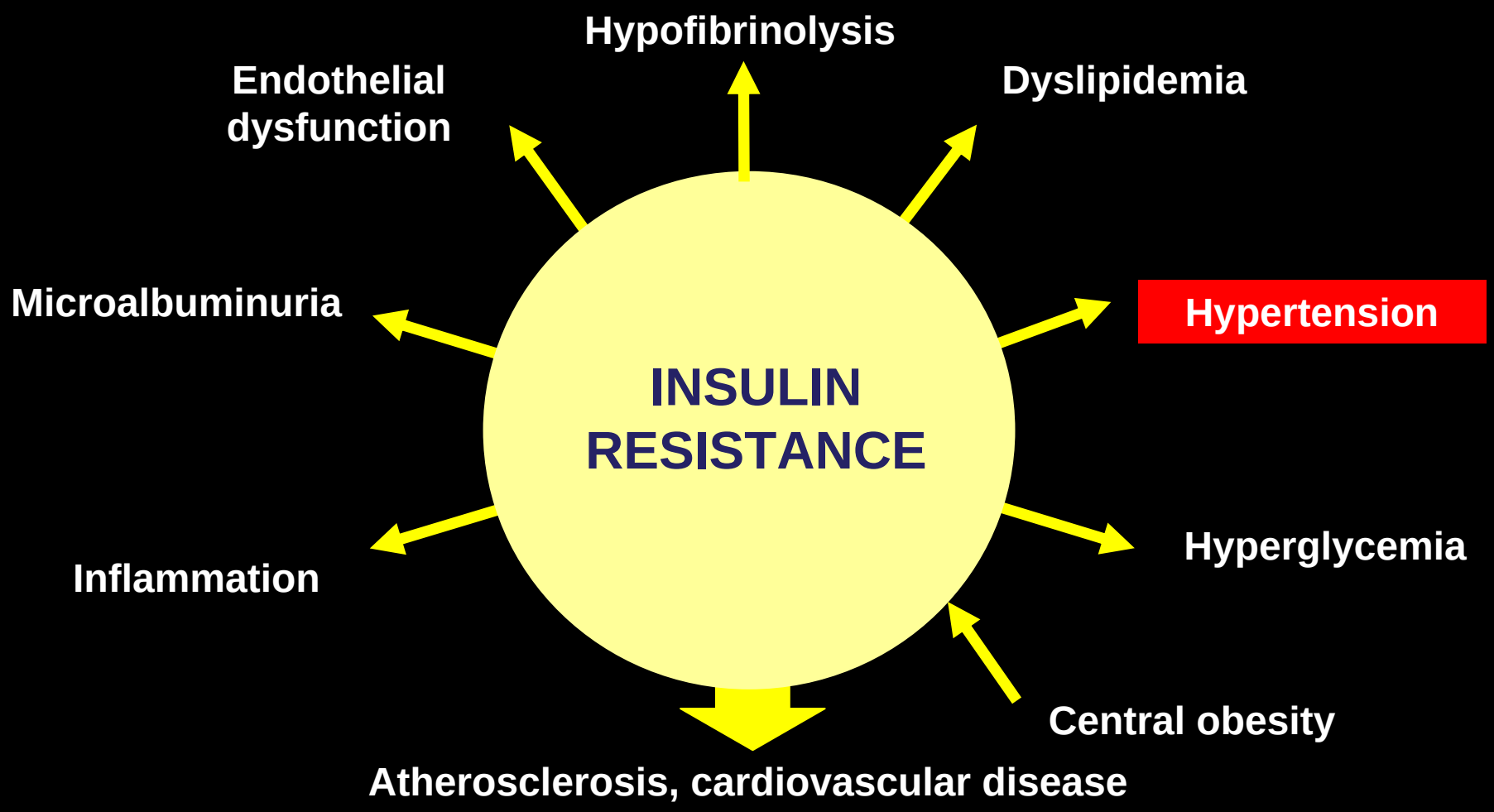
75% of patients responded (HbA1c > 1%)

Predictors of response
- Female
- Insulin resistance
- Higher waist;hip ratio (central obesity)
- Higher C-peptide (β-cell function)

Kang et al 2005 Diabetes Care 28:1139-44

"Polymorphisms in the adiponectin gene define responsiveness to rosiglitazone"

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

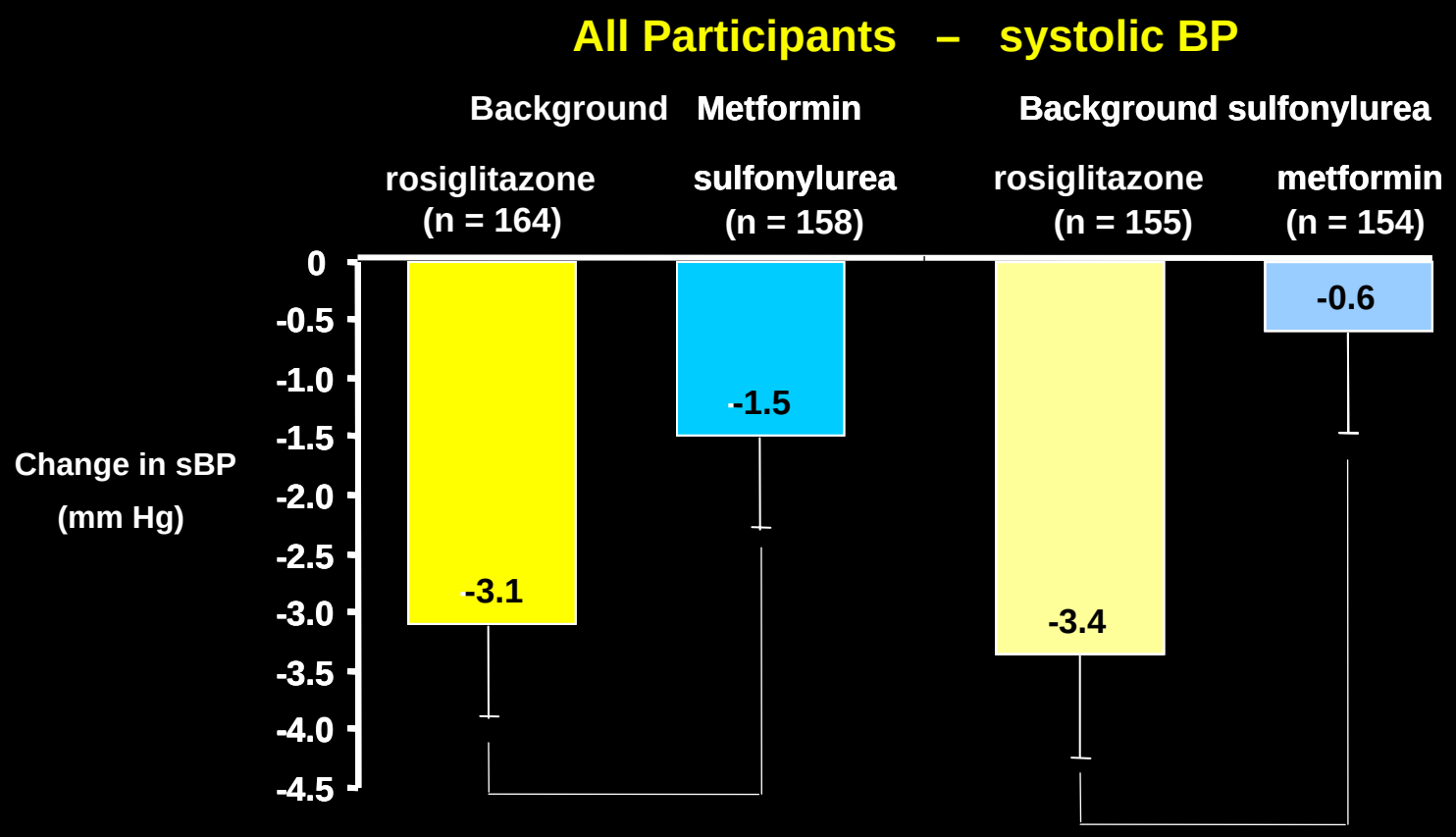
Tight blood pressure control reduces cardiovascular risk in diabetes

Tight blood pressure control (< 144/82 mmHg) compared to less tight control (< 154/87 mmHg) is associated with a reduction in risk of:

- **34% for macrovascular disease**
- **32% for diabetes-related mortality**

UKPDS 38. *BMJ* 1998; 317:703–713.

RECORD - Change in 24hr ambulatory systolic blood pressure after 6 months

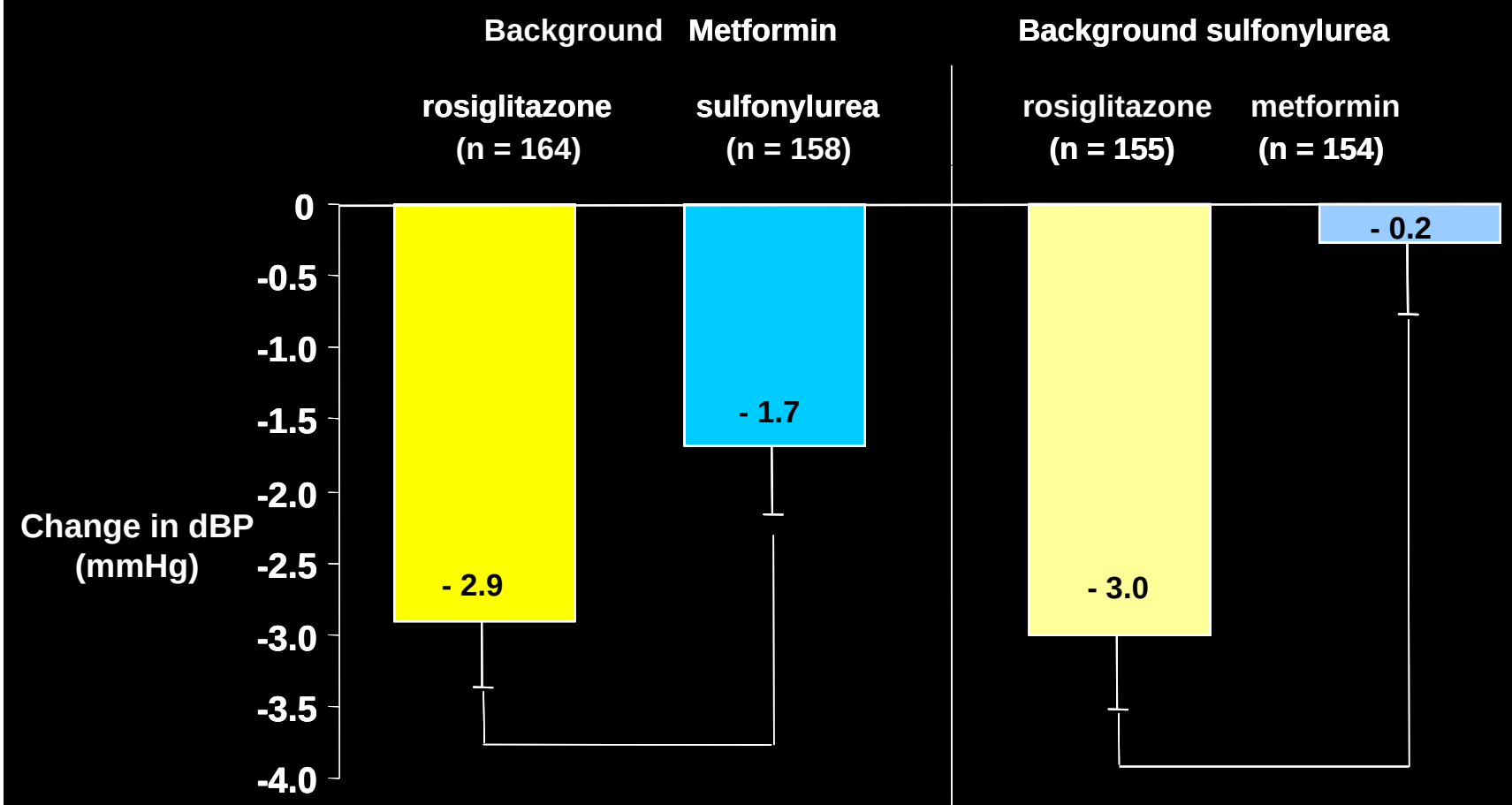


Difference: -1.6 (-3.7, +0.5) mm Hg. (NS) **Difference: -2.8 (-4.9, -0.6) mm Hg. (p = 0.013)**

Baseline sbp (mm Hg)	**132±13**	**134±16**	**132±12**	**132±14**

K Oshinyemi et al EASD 2004 A1643

RECORD - Change in 24hr ambulatory diastolic blood pressure after 6 months

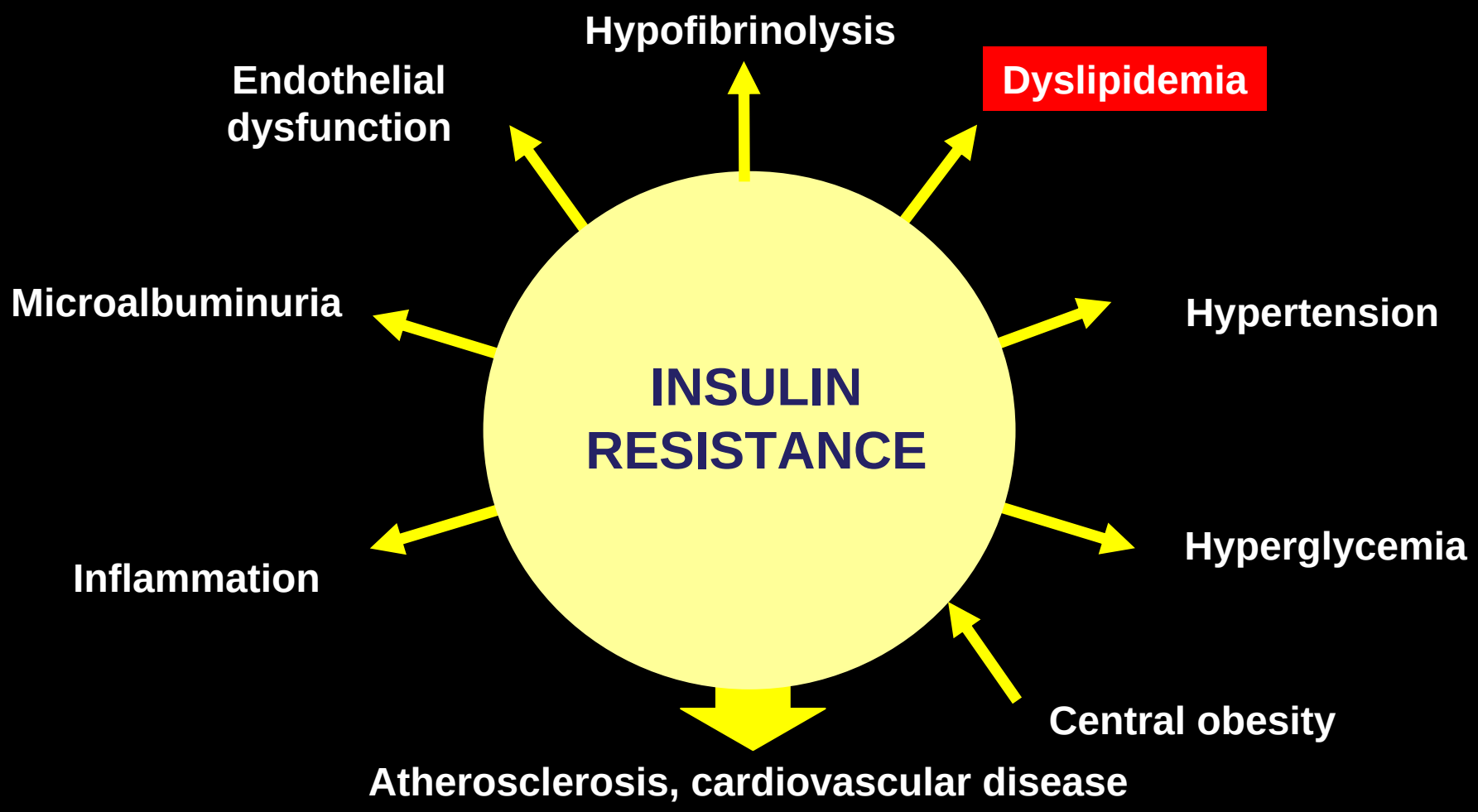


Difference: -1.2 (-2.5, +0.0) mm Hg. (p = 0.056) **Difference: -2.8 (-4.1, -1.5) mm Hg. (p <0.001)**

Baseline dbp (mm Hg)	**78±8**	**78±9**	**77±8**	**76±8**

K Oshinyemi et al EASD 2004 A1643

Insulin Resistance Syndrome

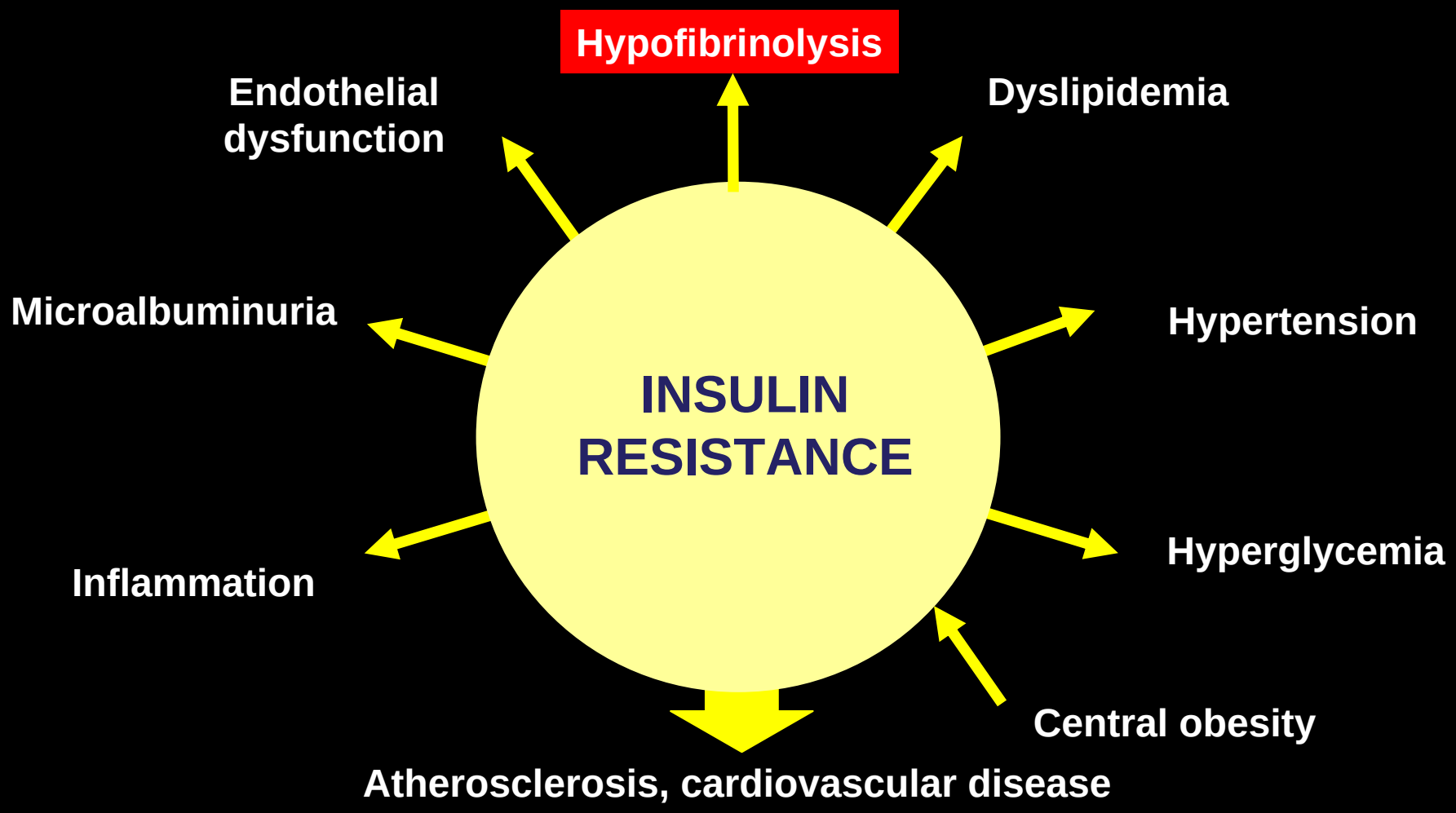


Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Thiazolidinediones influence diabetic dyslipidemia

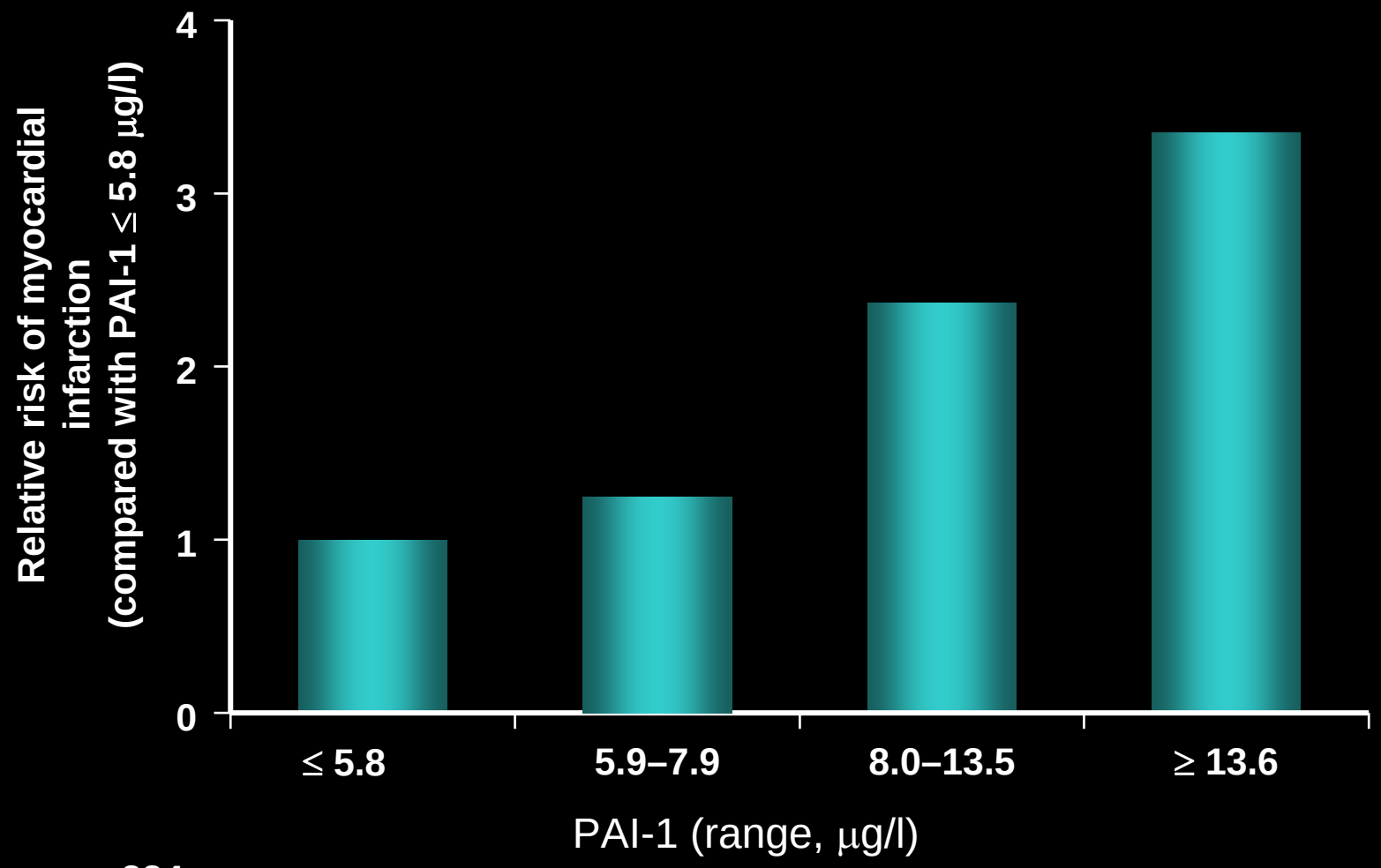
- Increase total HDL (up to 20%)
  - preferential increase in cardioprotective HDL_2
- No change, or small increase in total LDL, but Reduction in LDL particle density
  - (small dense LDL carries bulk of atherogenic risk)
- Reduce hypertriglyceridemia
- Reduce elevated free fatty acids

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Elevated PAI-1, an inhibitor of fibrinolysis, predicts cardiovascular disease

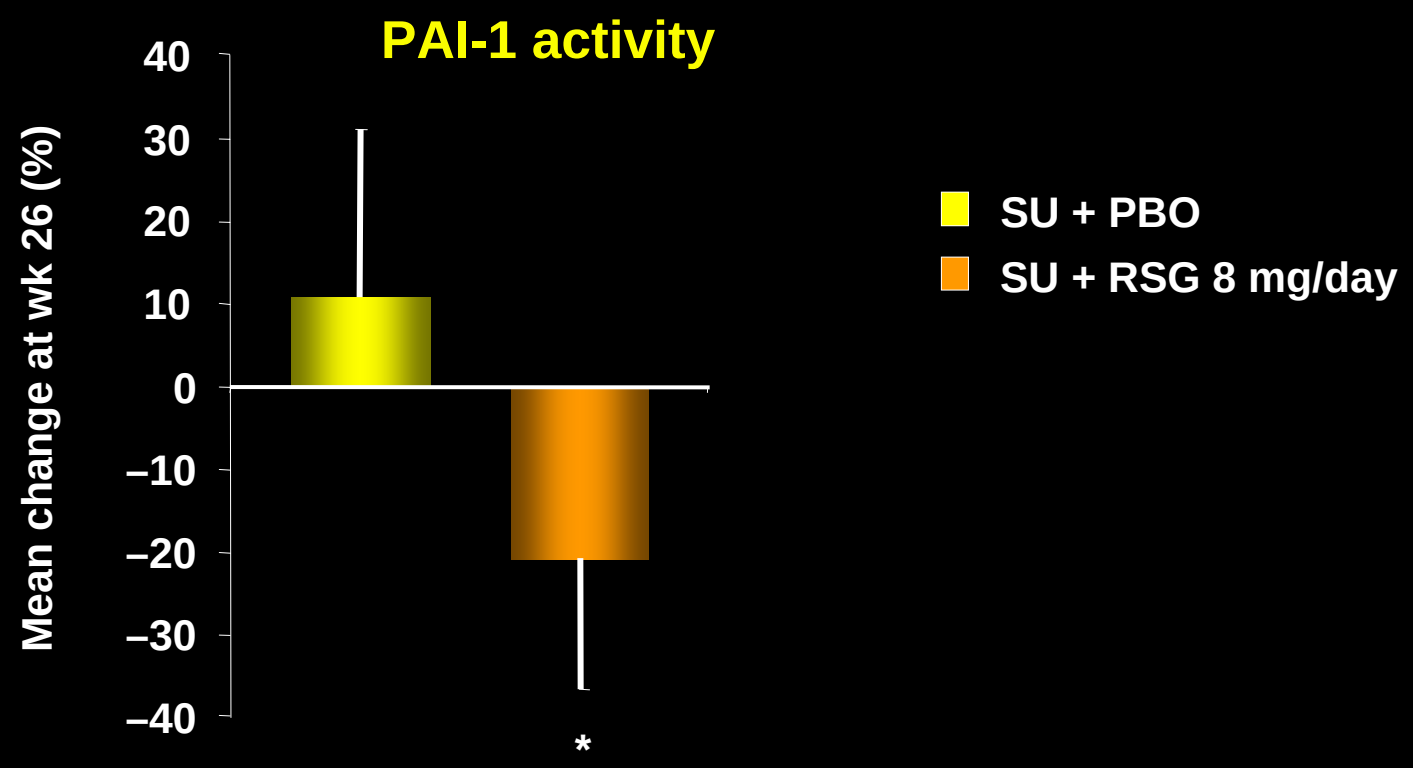


n = 234

***P* = 0.002**

Thögersen AM, *et al*. *Circulation* 1998; 98:2241–2247.

Thiazolidinediones reduce PAI-1



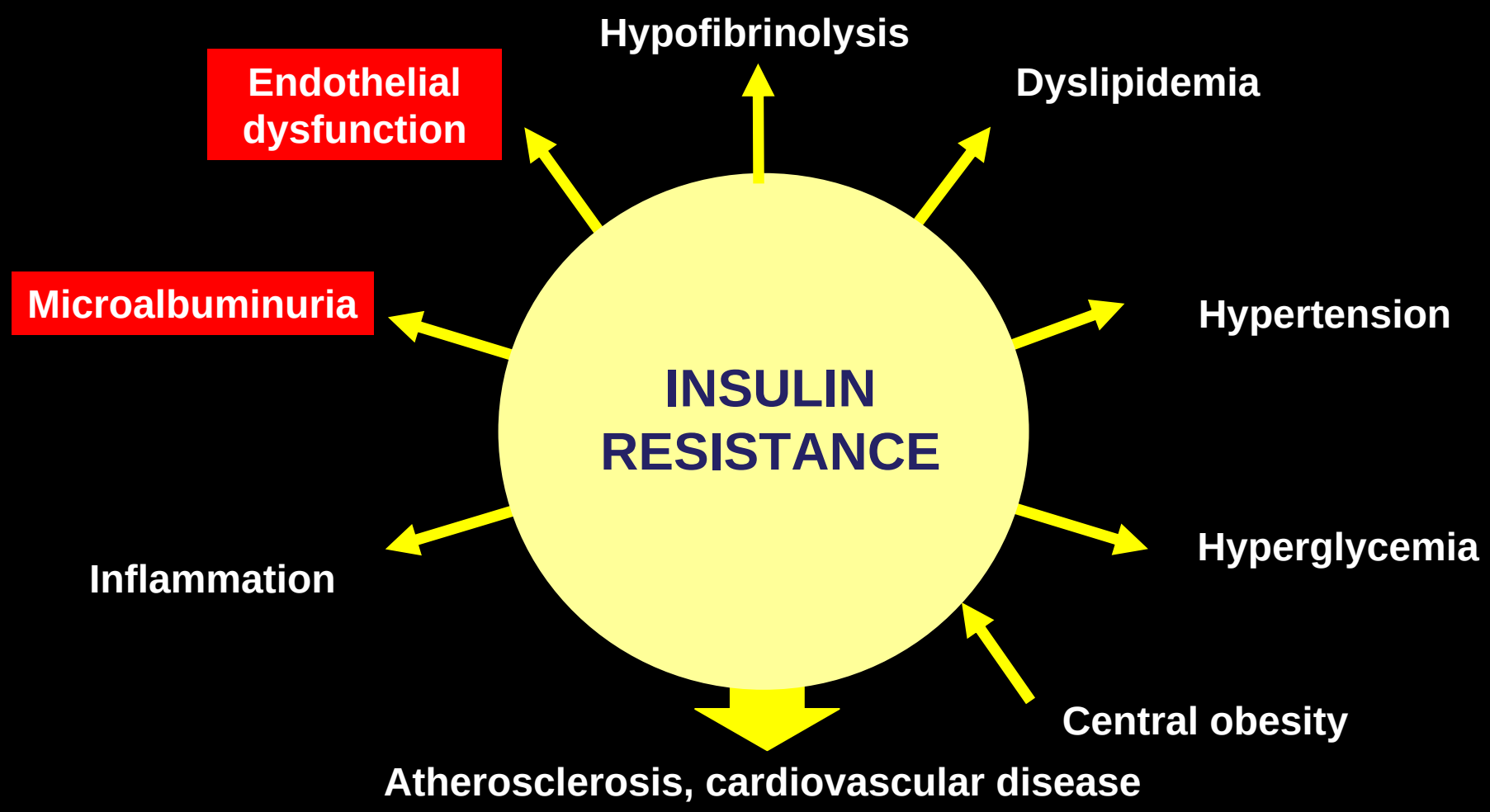
n = 114

**P* = 0.006 compared with placebo

Error bars = 95% CI

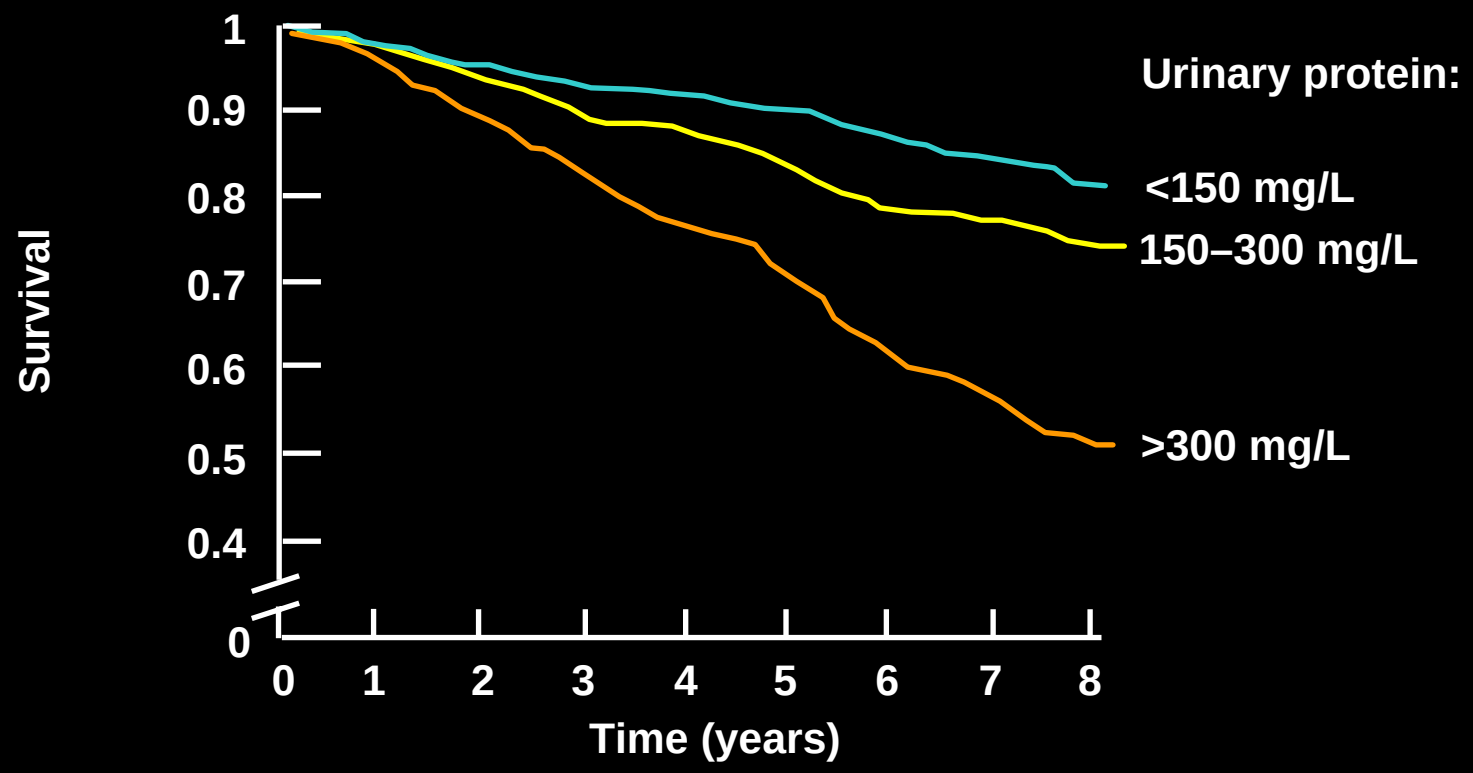
Freed M, *et al. Diabetologia* 2000; 43 (Suppl 1):A267.

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

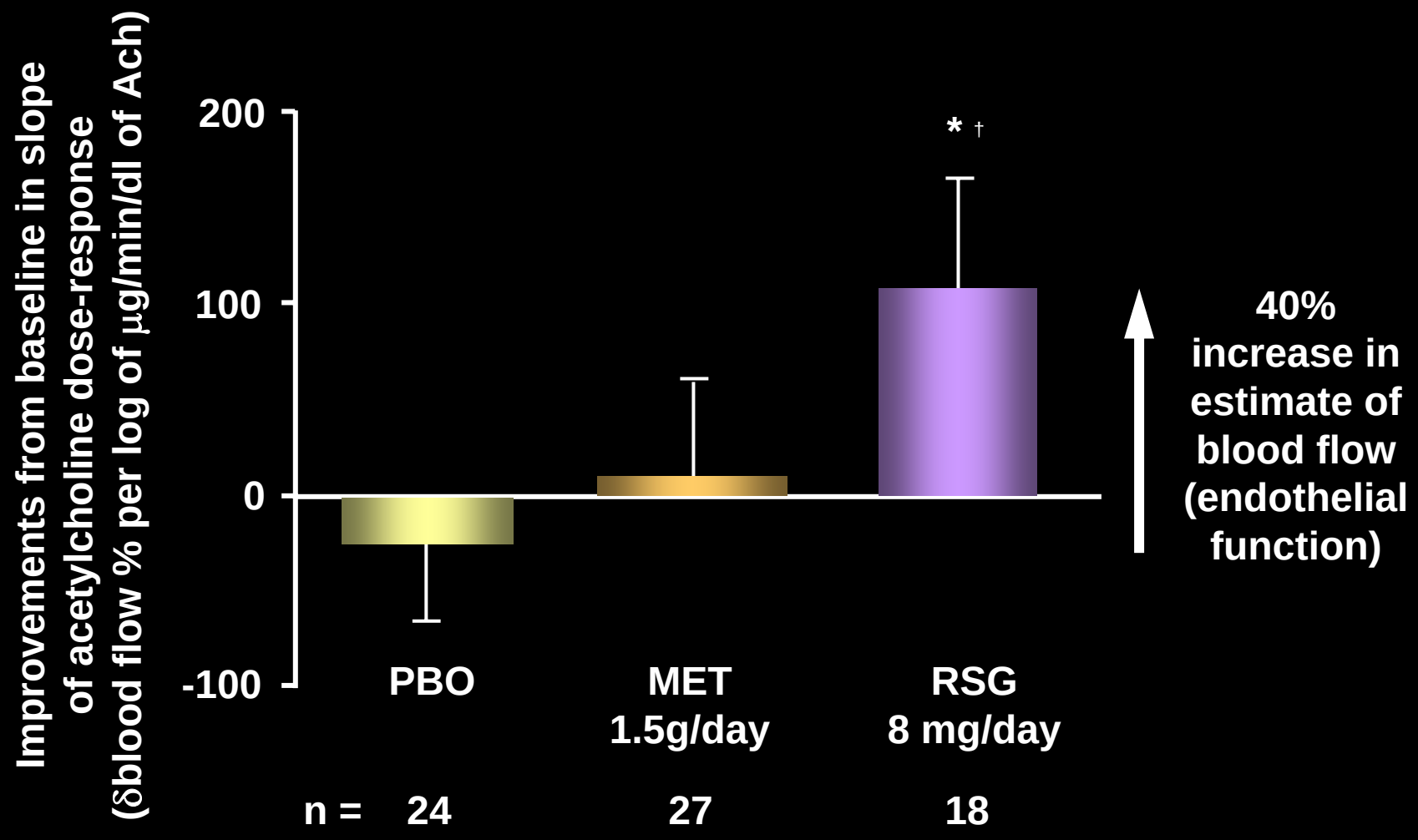
Cardiovascular mortality correlates with the severity of proteinuria – a marker of endothelial dysfunction



n = 2431

Miettinen H, *et al. Stroke* 1996; 27:2033–2039.

Rosiglitazone improves measures of endothelial function

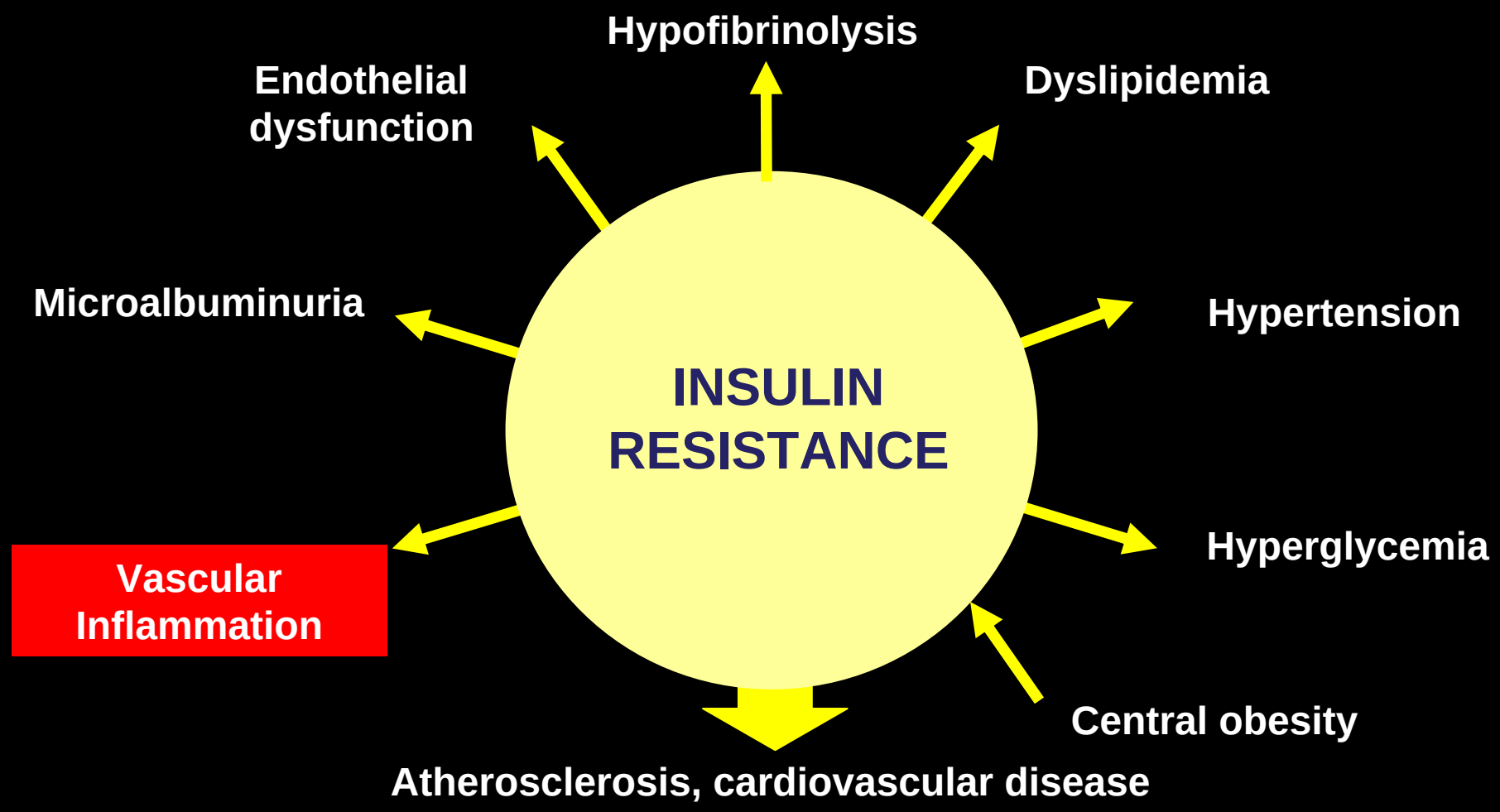


*$P < 0.05$ vs baseline
† $P < 0.005$ vs placebo

Error bars = 95% CI

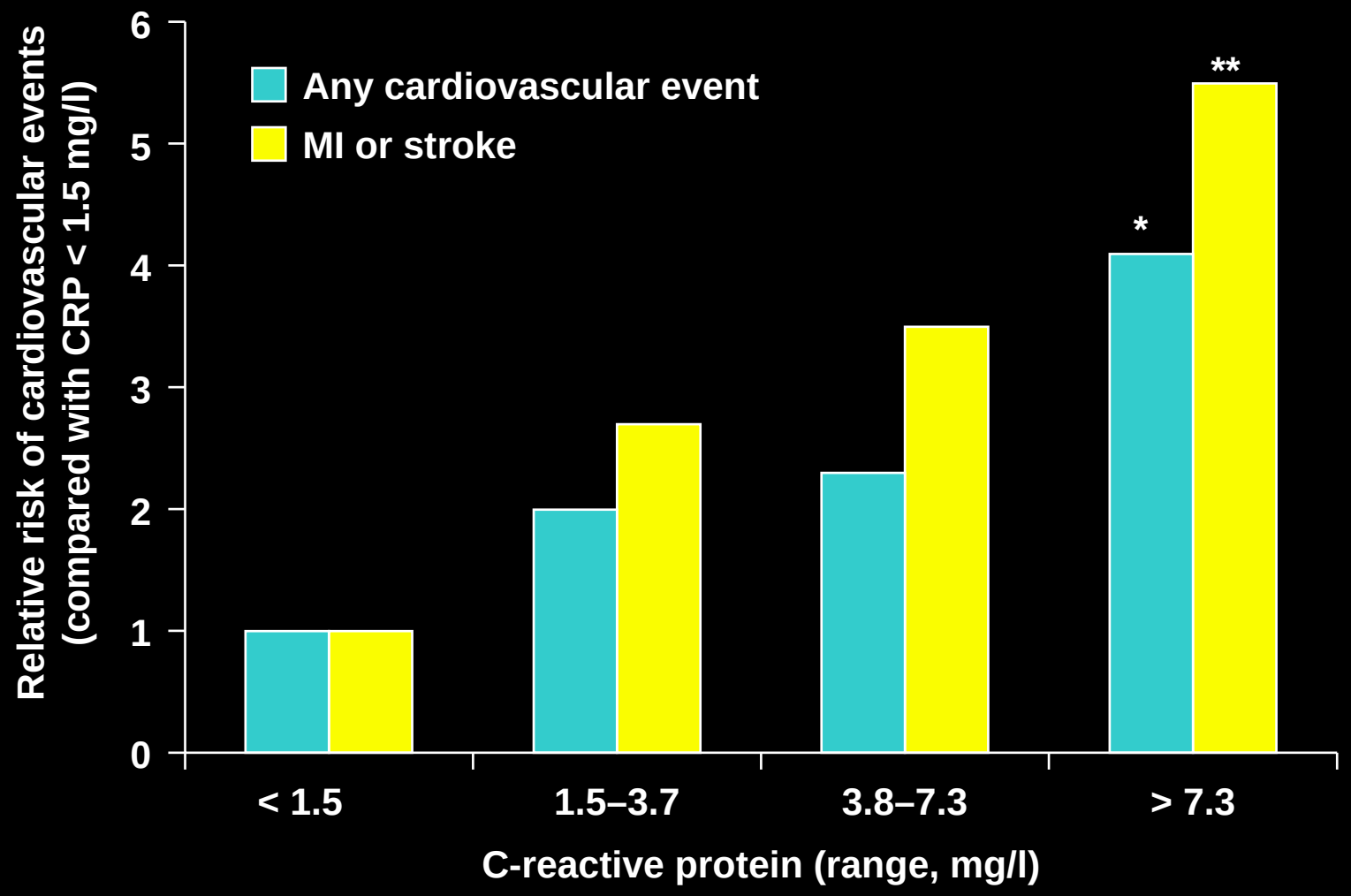
Adapted from Natali A, *et al. Diabetes Care* 2004; 27 1349-1357

Insulin Resistance Syndrome



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.

Elevated CRP, an inflammatory marker, predicts cardiovascular disease



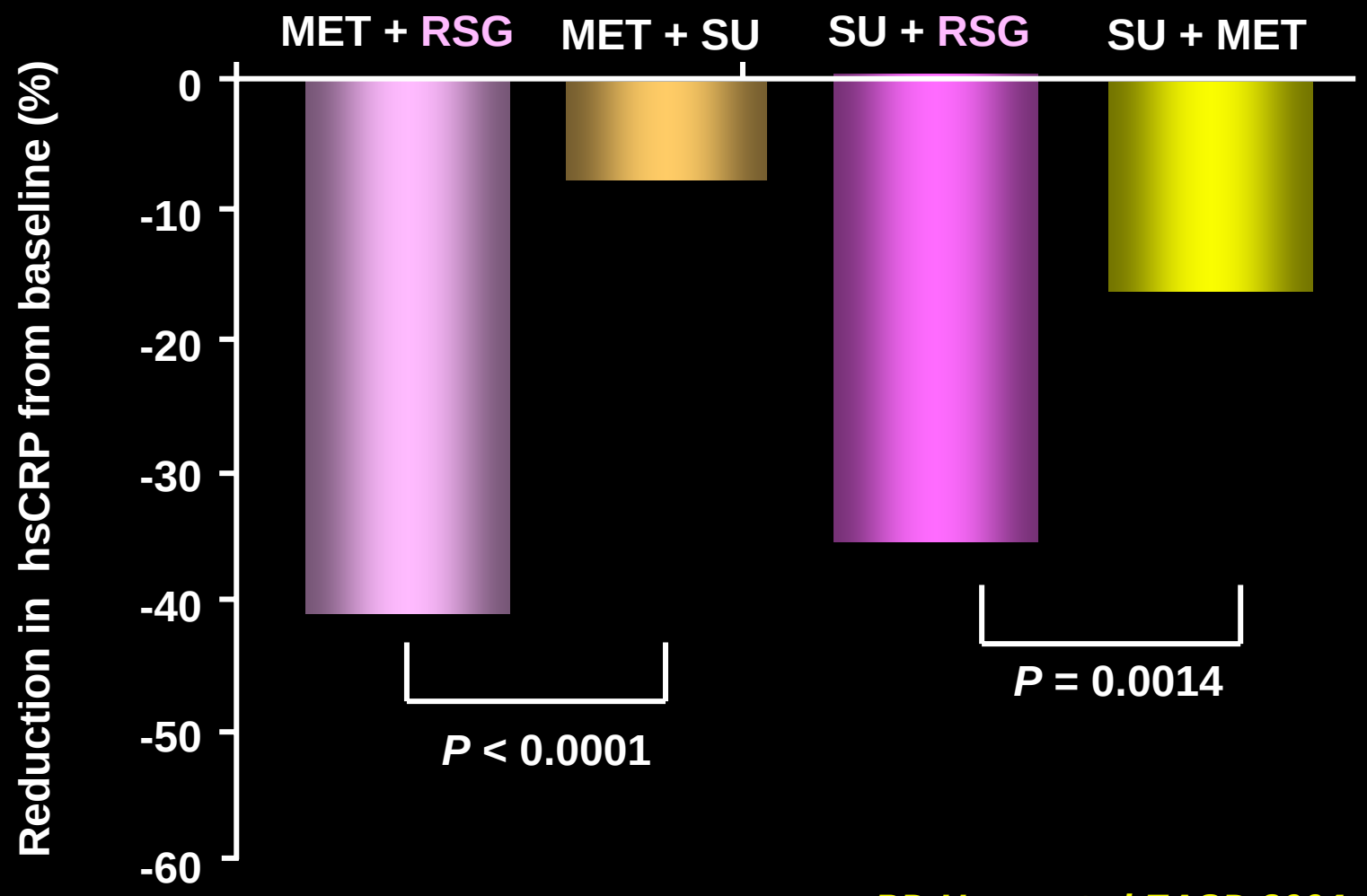
n = 366

*P = 0.001 compared with CRP < 1.5 mg/l

**P = 0.002 compared with CRP < 1.5 mg/l

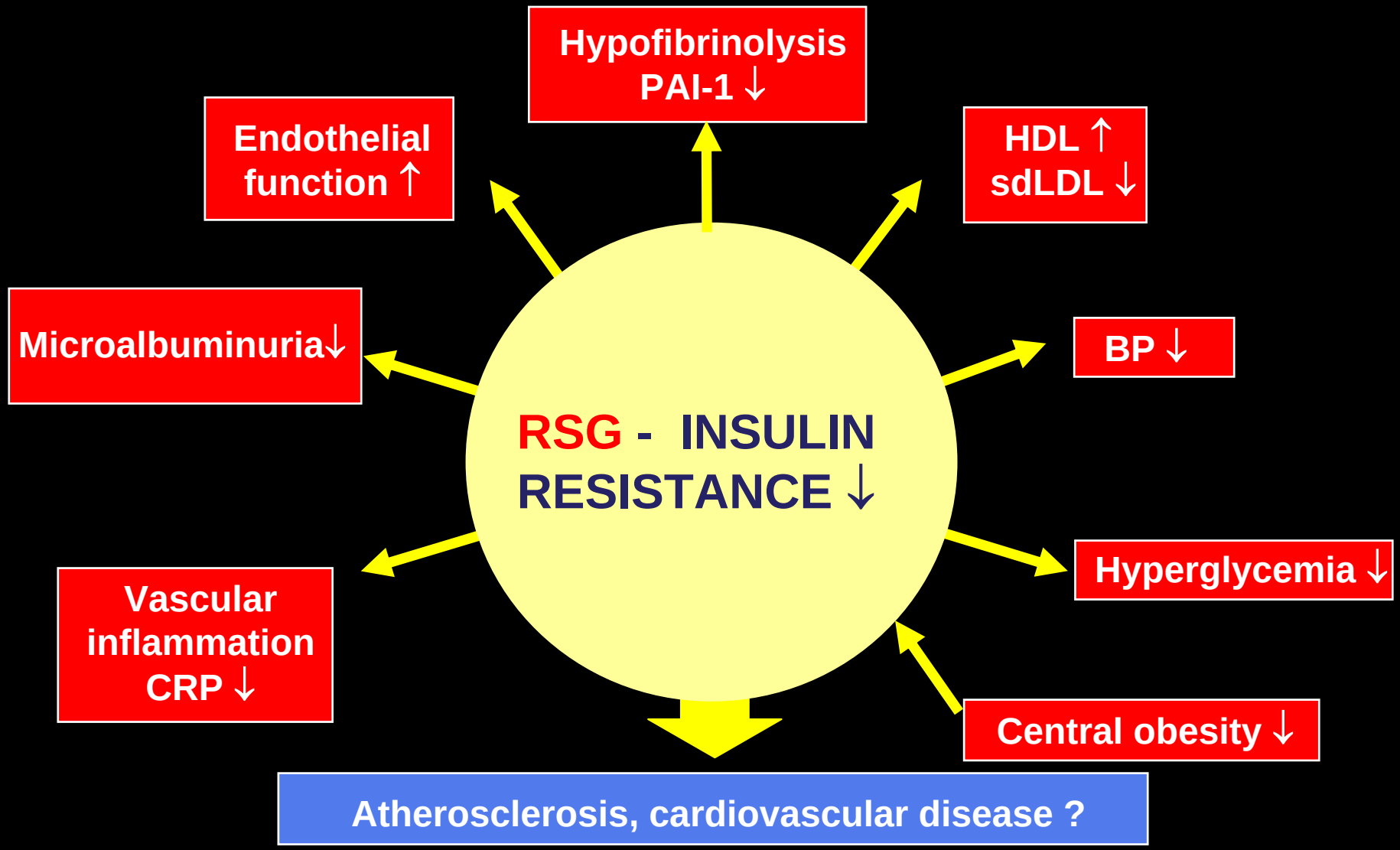
Ridker PM, *et al*. *Circulation* 1998; 98:731–733.

RECORD: comparison of effects on CRP



PD Home et al EASD 2004 A1580

Thiazolidinediones: potential to impact on CVD risk



Festa A *et al. Circulation* 2000; 102:42–47; Reaven GM *et al. Annu Rev Med* 1993; 44:121–131.