

Impact of Obesity and Diabetes In Hypertension

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Disclosure of financial relationships

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Major stock shareholder:	None
Other:	None

CV Disease: Patients at Risk

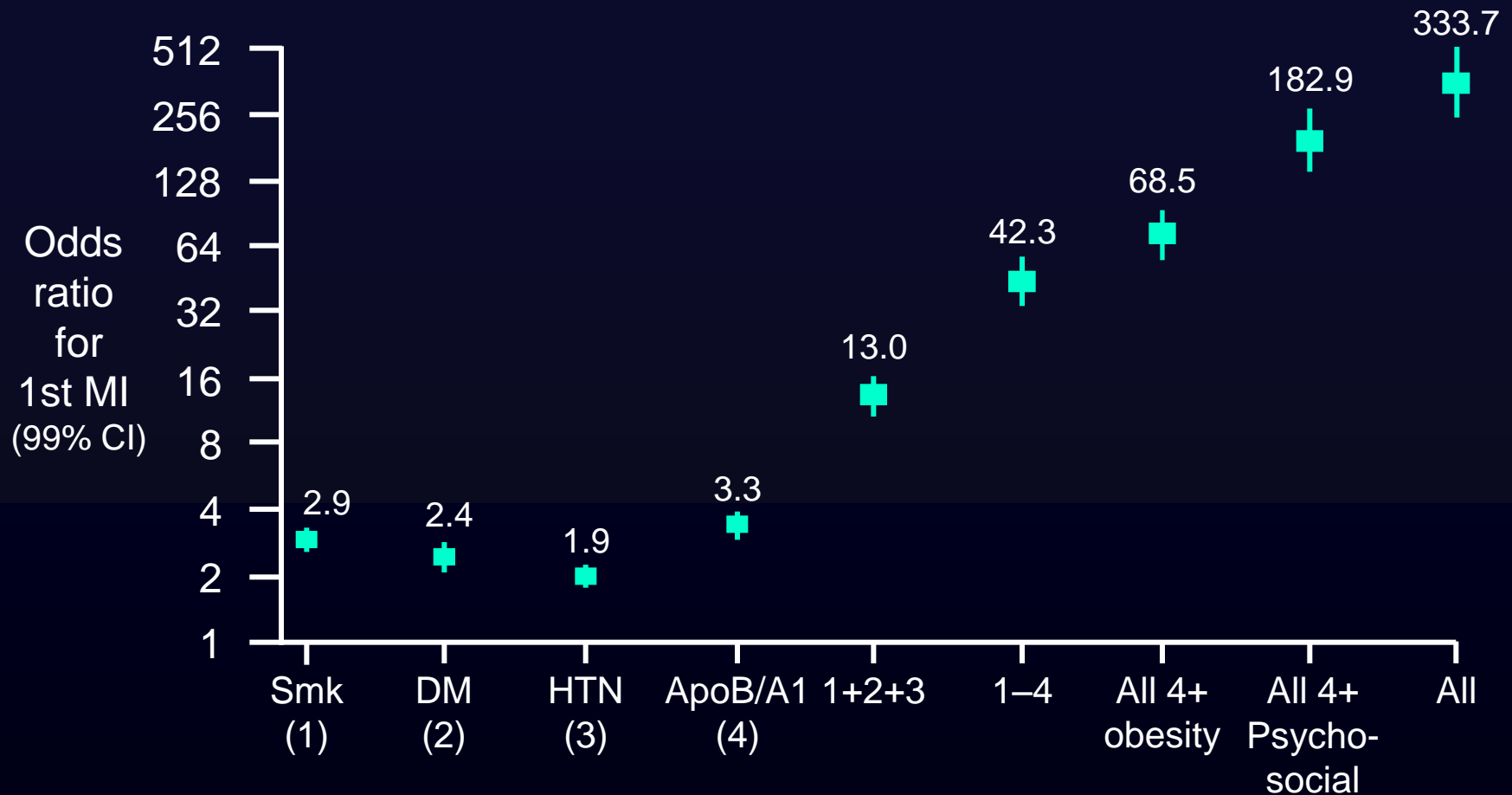
- 125 million with high cholesterol
- 76.4 million with hypertension
- 50 million with CMS
- 18.3 million with diagnosed DM
~8 million undiagnosed **



One death every 33 sec

Multiple Risk Factors Raise the Risk for MI

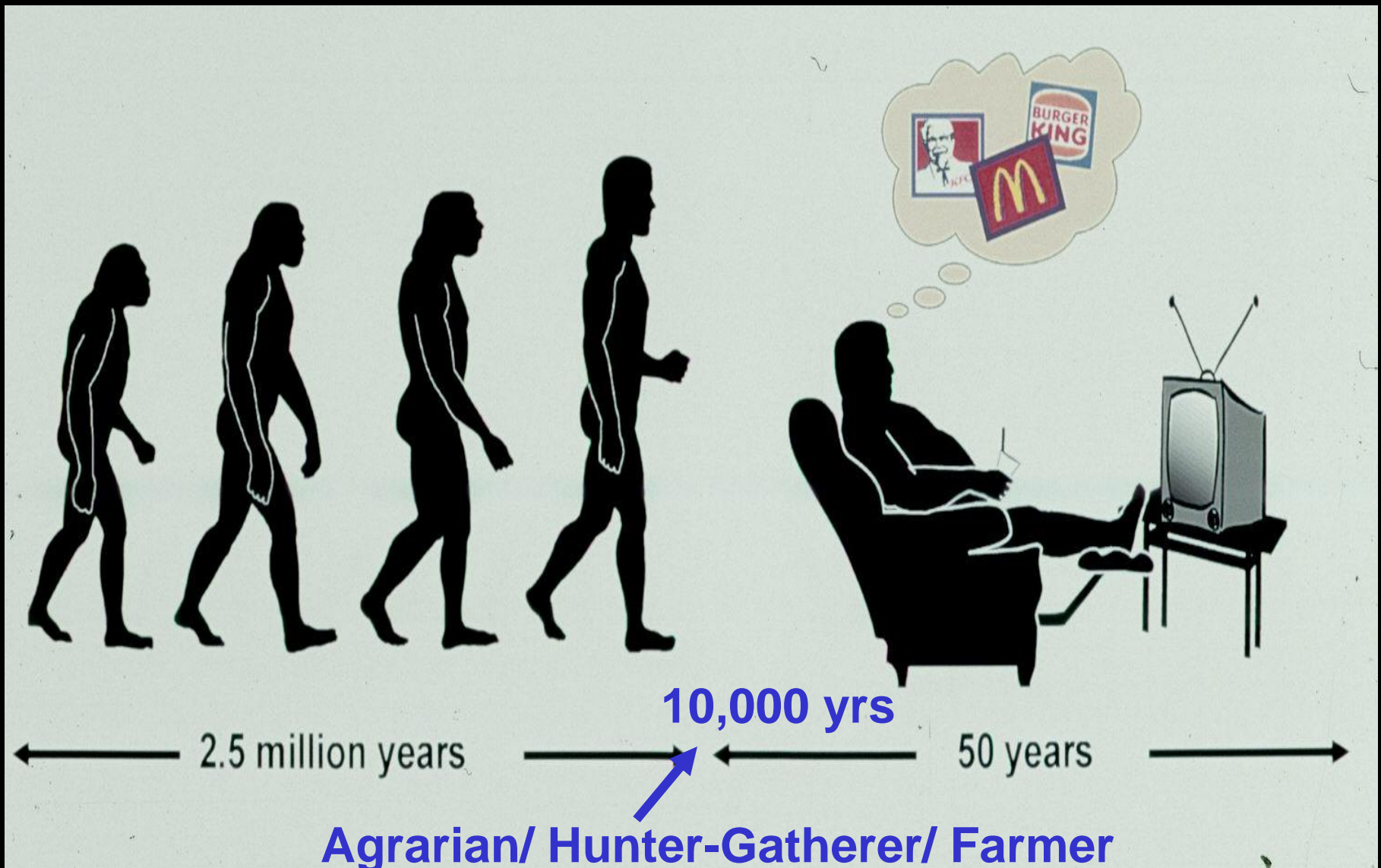
INTERHEART



Smk = smoking; DM = diabetes mellitus;
HTN = hypertension; Apo = apolipoprotein

Yusuf S et al. *Lancet*. 2004;364:937-952.

Evolution of Atherosclerotic Risk



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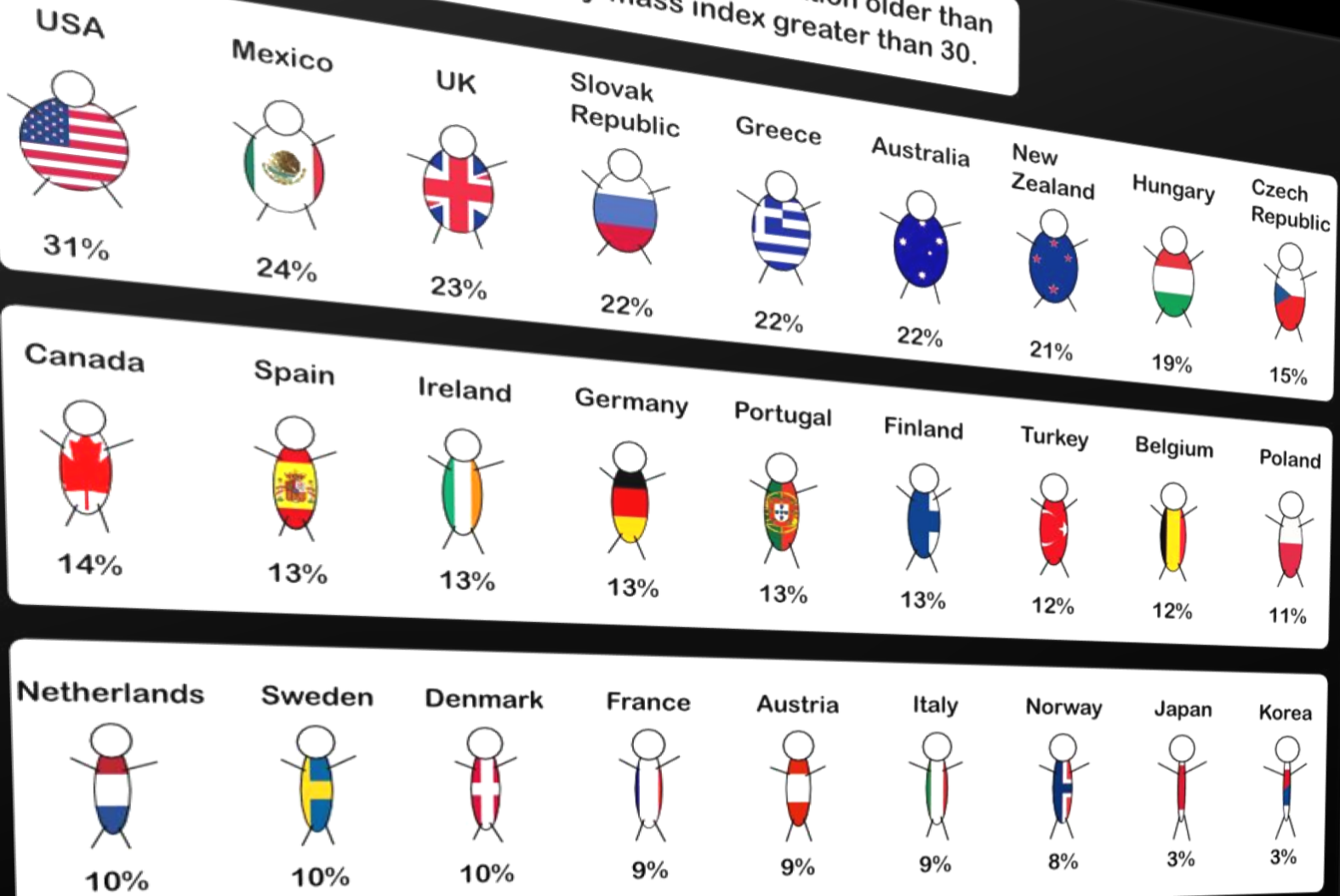
- 58% of overweight children have ≥ 1 CV risk factor
- 39% of obese and 50% of severely obese children have metabolic syndrome*

Freedman DS et al. *Pediatrics*. 1999;103:1175-82.

Weiss R et al. *N Engl J Med*. 2004;350:2362-74.

Obesity Worldwide

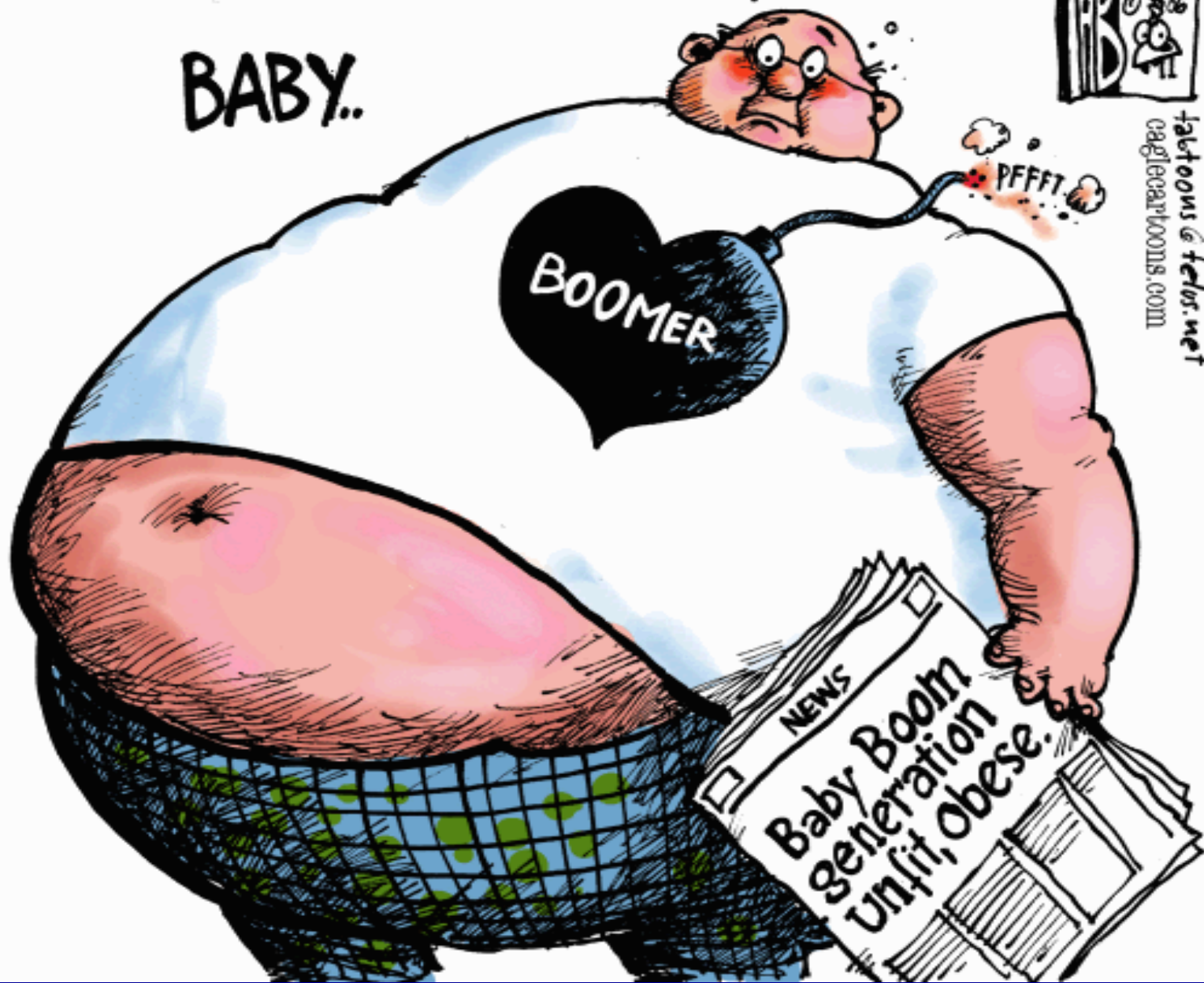
OBESITY: The percentage of the population older than 15 with a body-mass index greater than 30.



Data taken from:
<http://en.wikipedia.org/w/index.php?title=Image:Bmi30chart.png&oldid=107854217>

Drawing by:
<http://www.WellingtonGrey.net>

BABY..



fabtoons @ telus.net
cagflecartoons.com

Two Men Who Died of an MI at age 59 1960 vs 2008

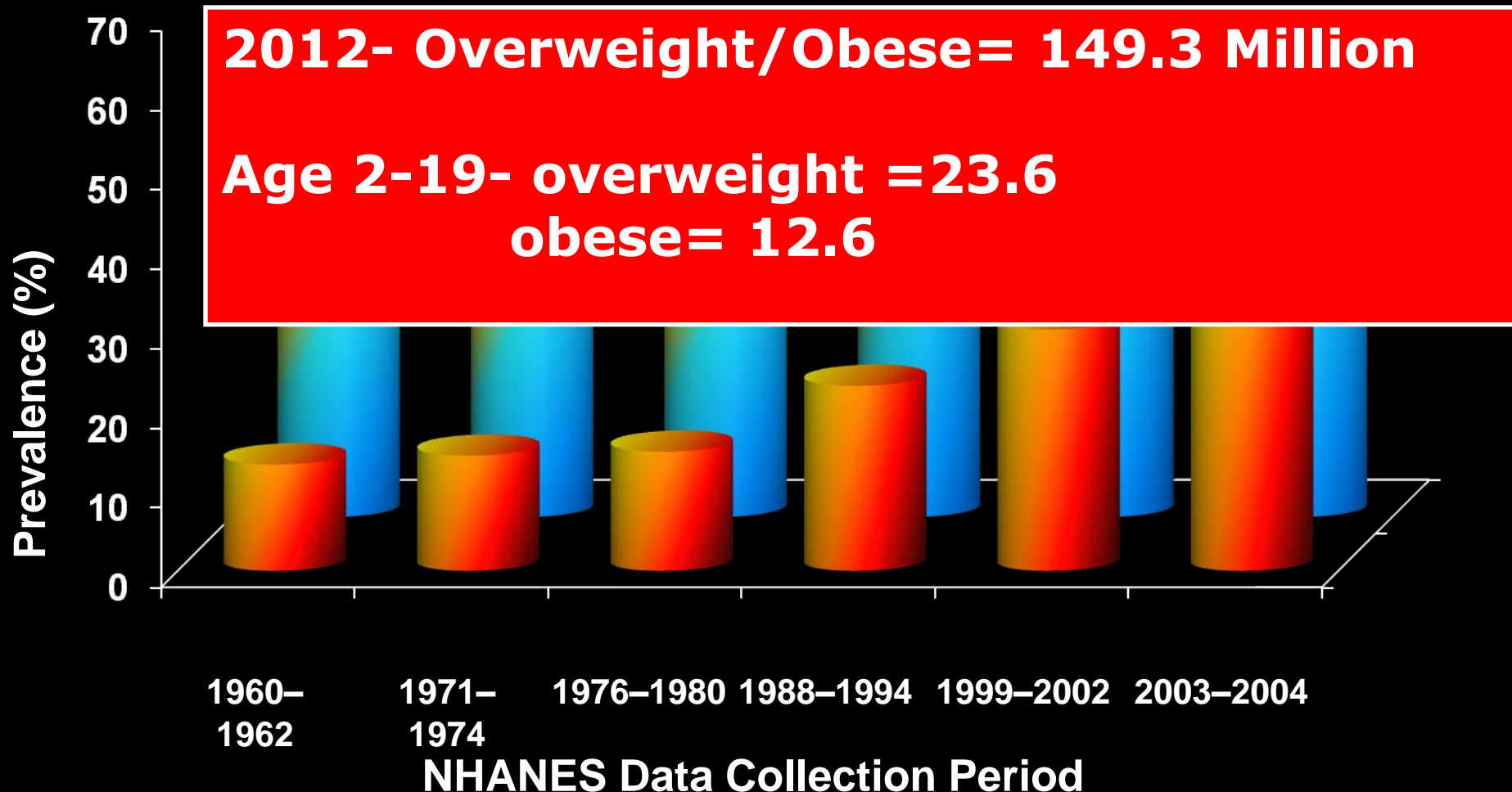


Clark Gable



Tim Russert (2008)

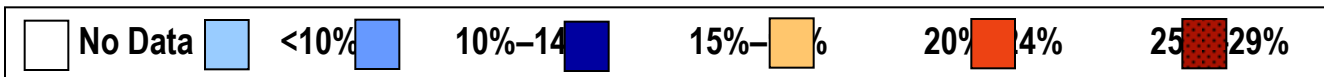
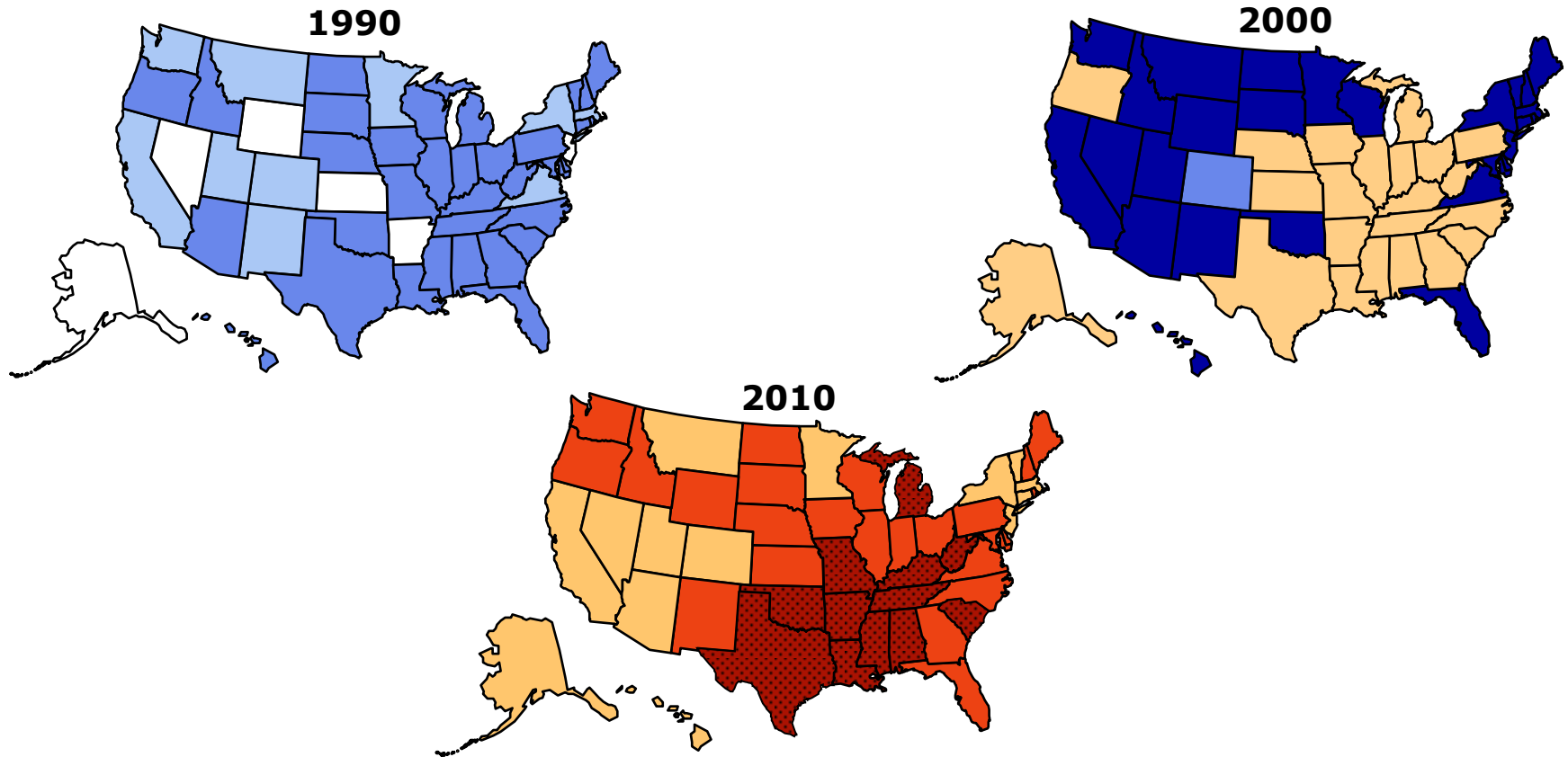
Overweight and Obesity among U.S. Adults



Obesity Trends* Among U.S. Adults

BRFSS, 1990, 2000, 2010

(*BMI ≥ 30 , or about 30 lbs. overweight for 5'4" person)

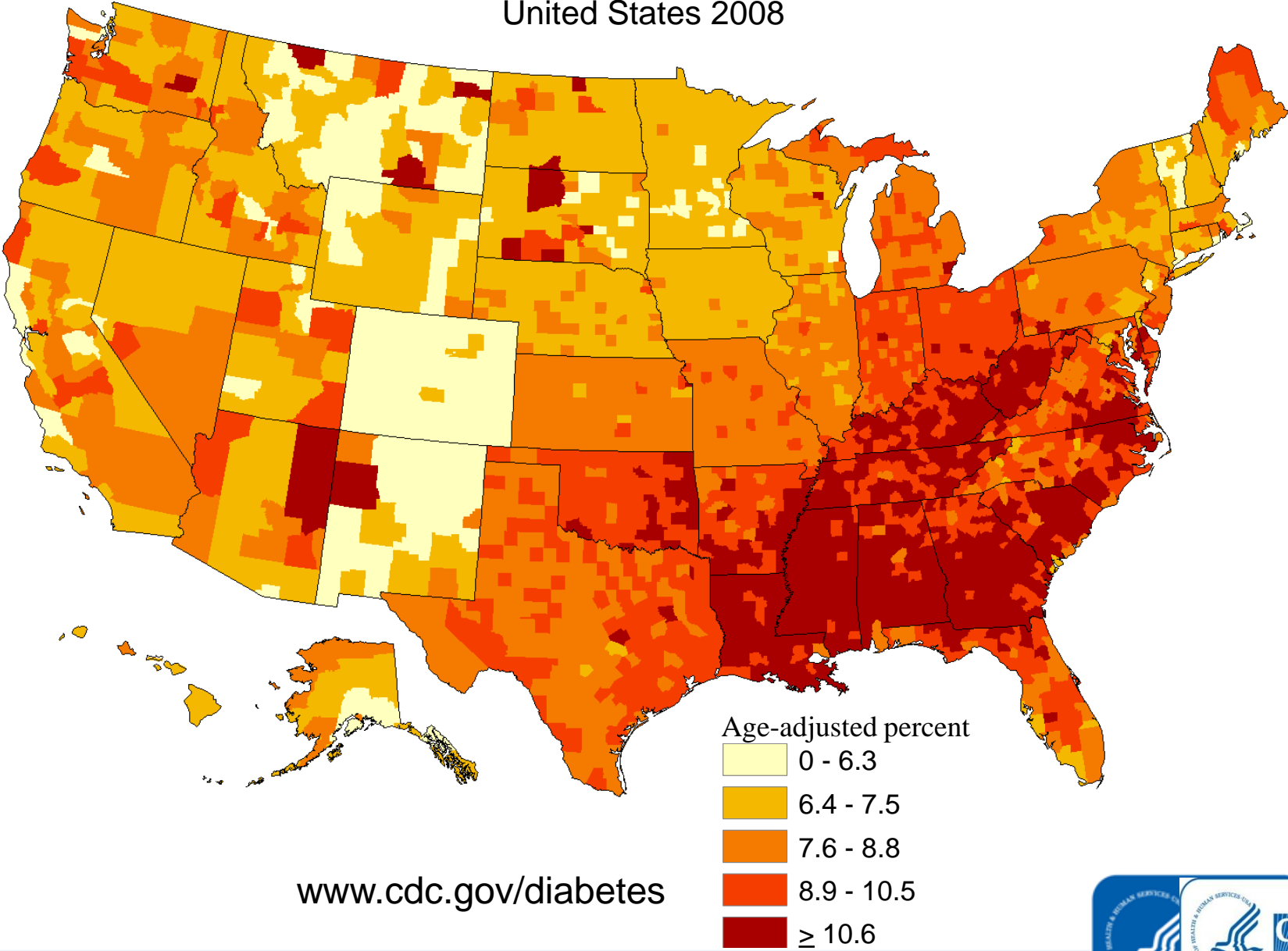


$\geq 30\%$



Source: Behavioral Risk Factor Surveillance System, CDC.

County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2008

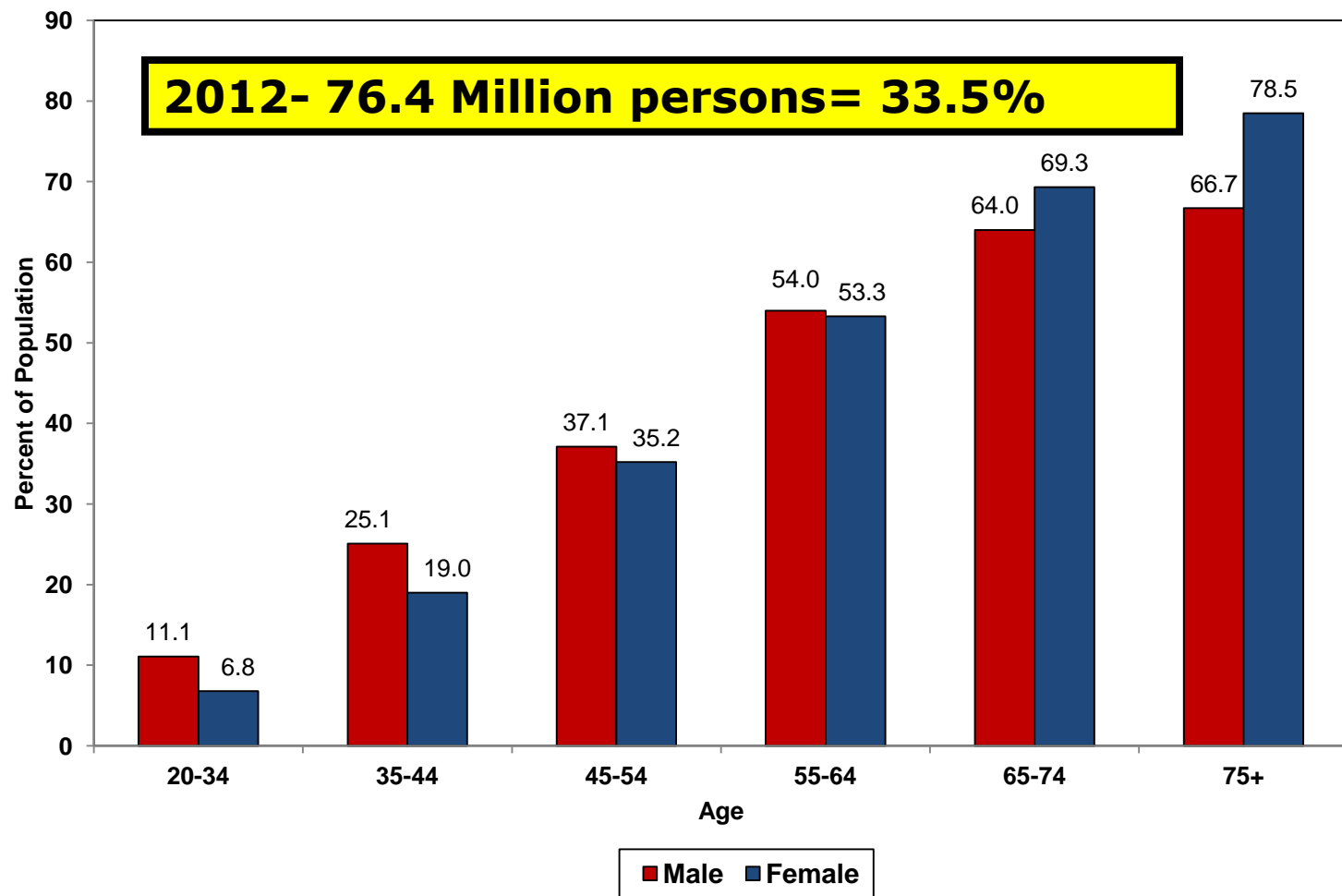


www.cdc.gov/diabetes

Source: Behavioral Risk Factor Surveillance System, CDC.

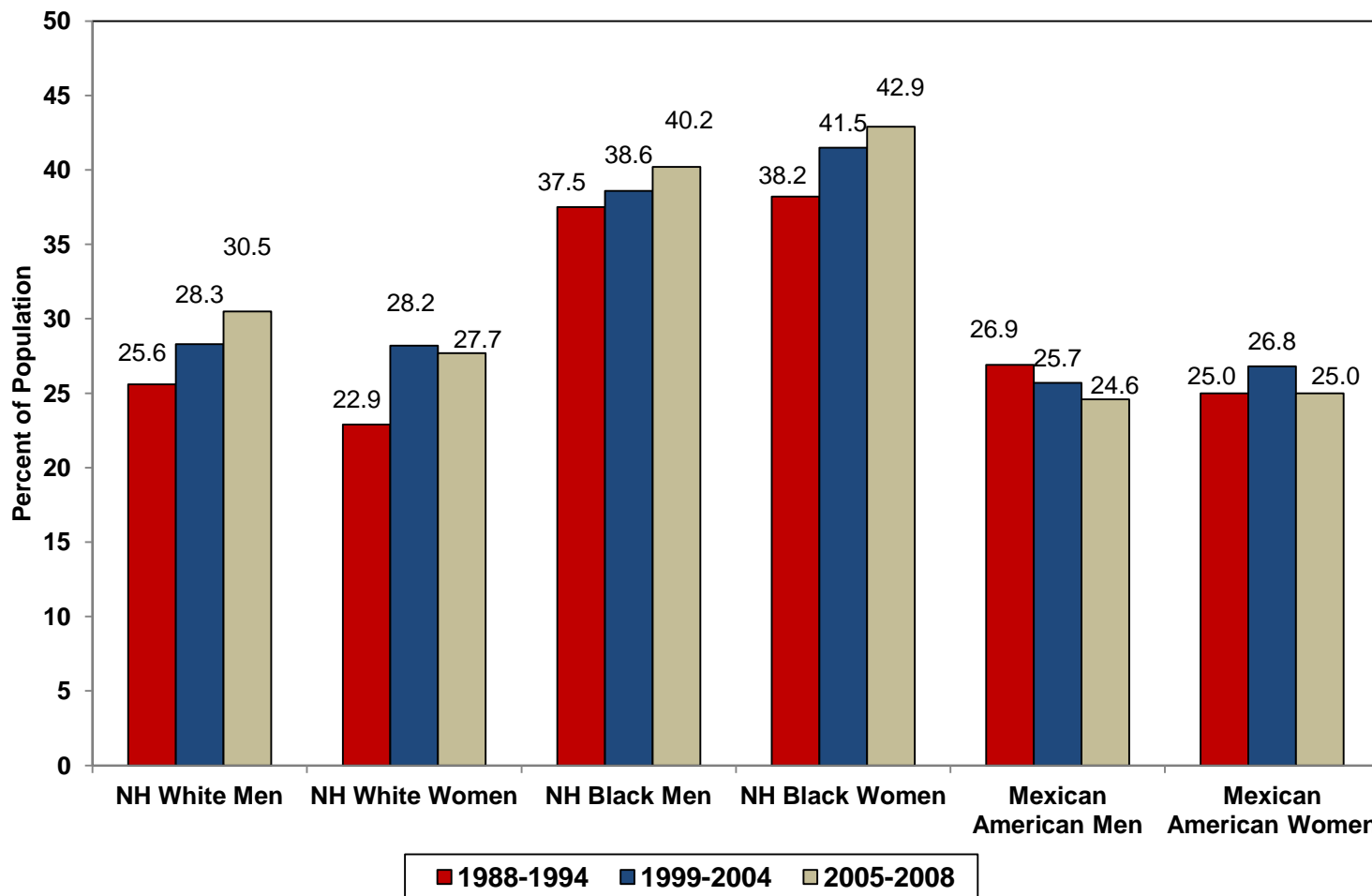


Prevalence of HBP in adults ≥ 20 years of age by age and sex (NHANES: 2005–2008).



Source: NCHS and NHLBI. Hypertension is defined as SBP 140 mm Hg or DBP 90 mmHg, taking antihypertensive medication, or being told twice by a physician or other professional that one has hypertension.

Age-Adjusted Prevalence Trends for HBP in Adults, ≥ 20 years of age by race/ethnicity, sex and survey (NHANES:1988-1994, 1999-2004 and 2005-2008).



Source: NCHS and NHLBI. NH indicates non-Hispanic.

Pathogenesis of Hypertension in Obesity

- Elevation in cardiac output with relatively normal systemic vascular resistance
- Increased activation of the renin-angiotensin-aldosterone system
- Hyperinsulinemia and insulin resistance
- Sympathetic nervous system activation
- Leptin elevation
- Increased renal sodium re-absorption
- Endothelial dysfunction
- Decreased cardiac natriuretic peptide
- Upregulation of angiotensin II receptors

Mechanisms in which hyperinsulinemia may lead to development of hypertension

- ④ Sympathetic nervous system activation**
- ④ Decreased Na⁺/K⁺ ATPase activity**
- ④ Increased Na⁺/H⁺ pump activity**
- ④ Increased intra-cellular Ca²⁺ accumulation**
- ④ Stimulation of growth factors**
- ④ Increased renal Na⁺/water reabsorption**

EVOLUTIONARY MISADVENTURES: ANGIOTENSIN and VASCULAR DISEASE



SHORT-TERM



**VASOCONSTRICTION,
INCREASED BP**



**ARTERIAL
EFFECTS**



**VOLUME
RESTORATION**



**RENAL/HORMONAL
EFFECTS**

**VASCULAR
INTEGRITY**



**INHIBITION OF
FIBRINOLYSIS**

EVOLUTIONARY MISADVENTURES: ANGIOTENSIN and VASCULAR DISEASE



SHORT-TERM



LONG-TERM

**VASOCONSTRICTION,
INCREASED BP**

**VOLUME
RESTORATION**

**VASCULAR
INTEGRITY**

**ARTERIAL
EFFECTS**

**RENAL/HORMONAL
EFFECTS**

**INHIBITION OF
FIBRINOLYSIS**

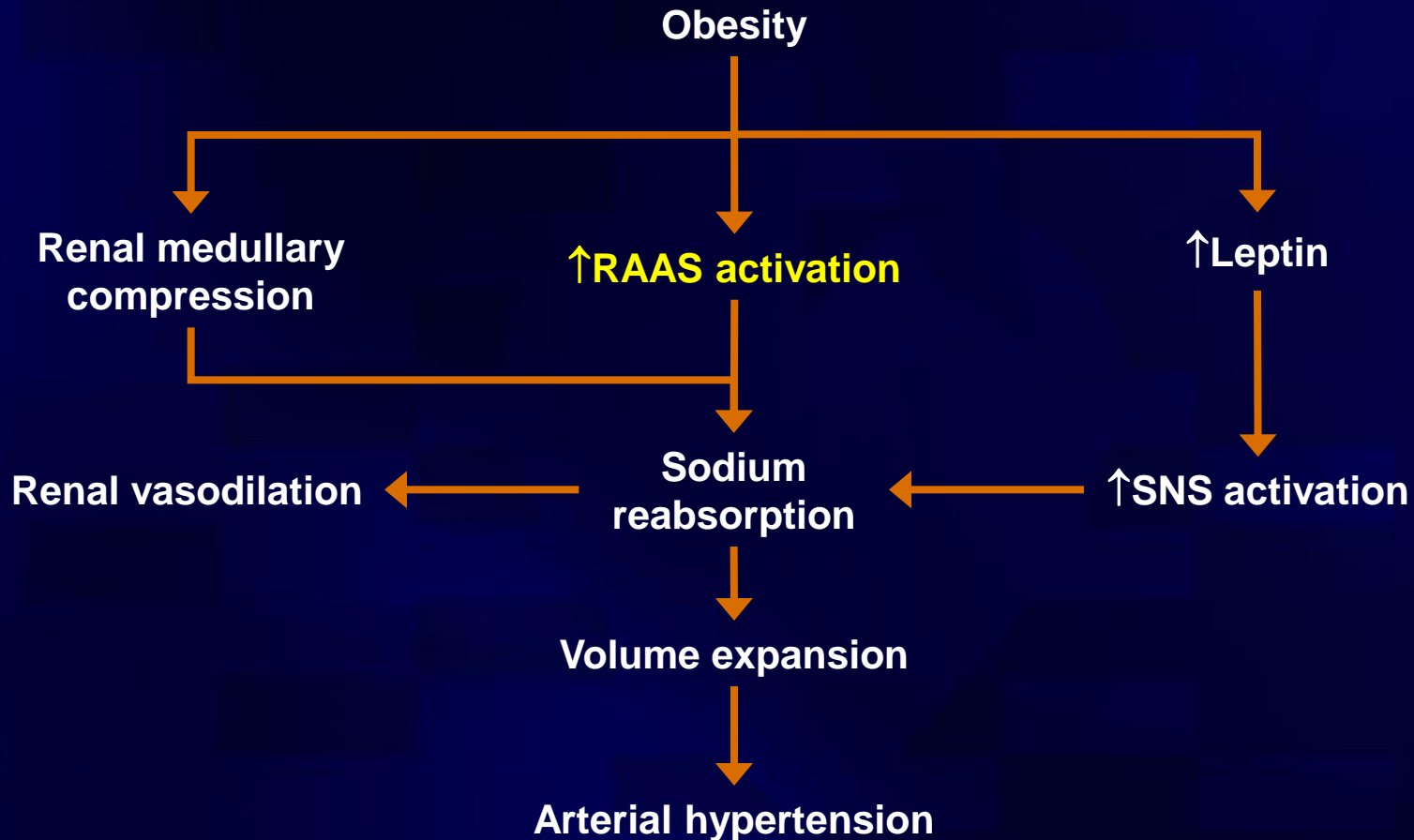
**VASCULAR
HYPERTROPHY,
ATHEROSCLEROSIS**

**INCREASED VOLUME
FIBROSIS**

**PROTHROMBOTIC,
PROGRESSION OF
VASCULAR LESIONS**

Vaughan, D 2003

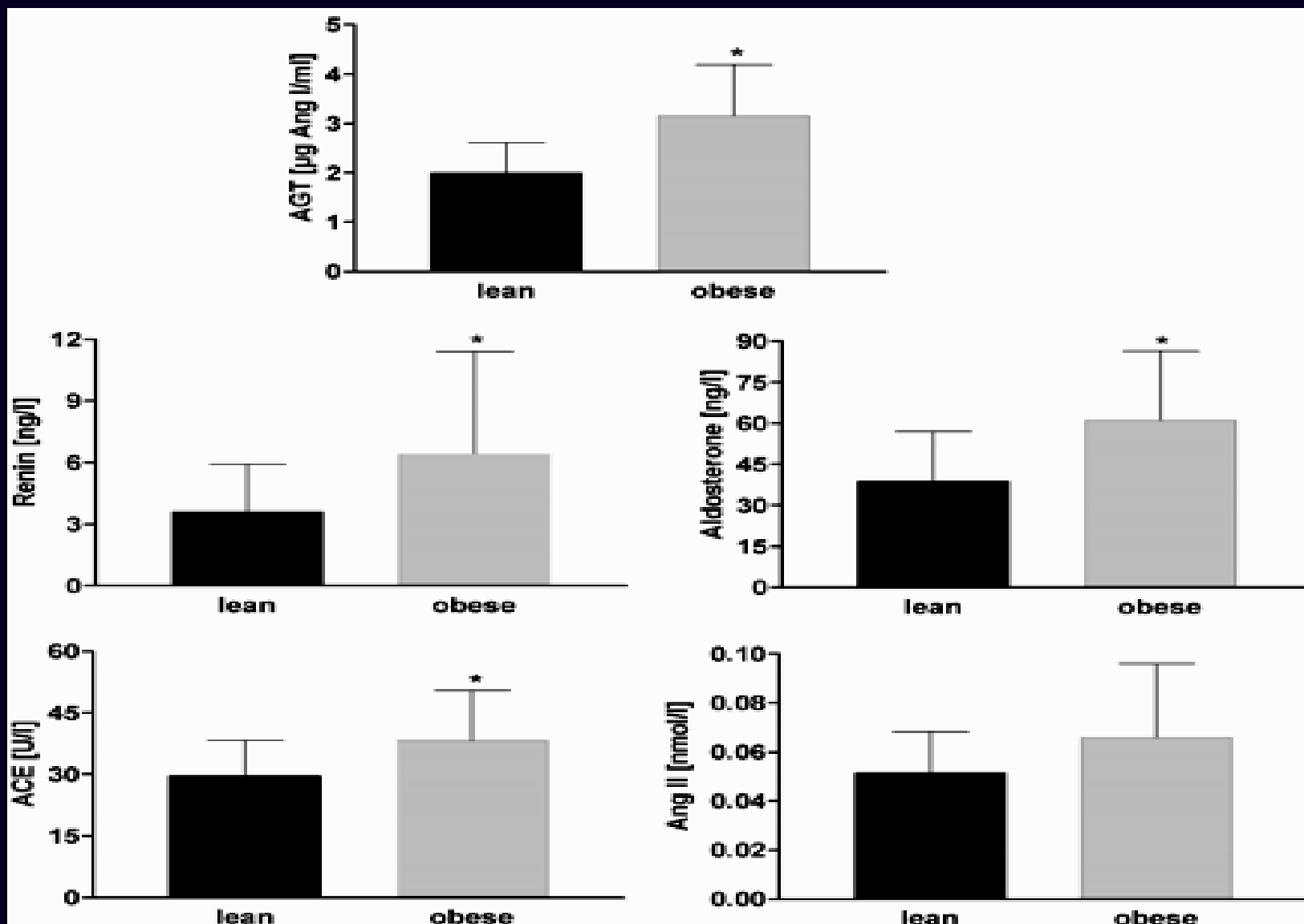
RAAS activation contributes to obesity-related hypertension



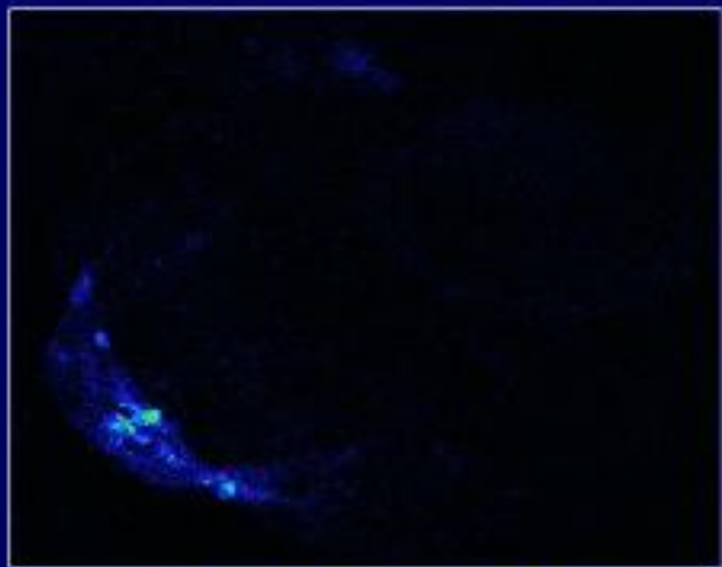
SNS = sympathetic nervous system

Sharma AM. *Hypertension*. 2004;44:12-19.

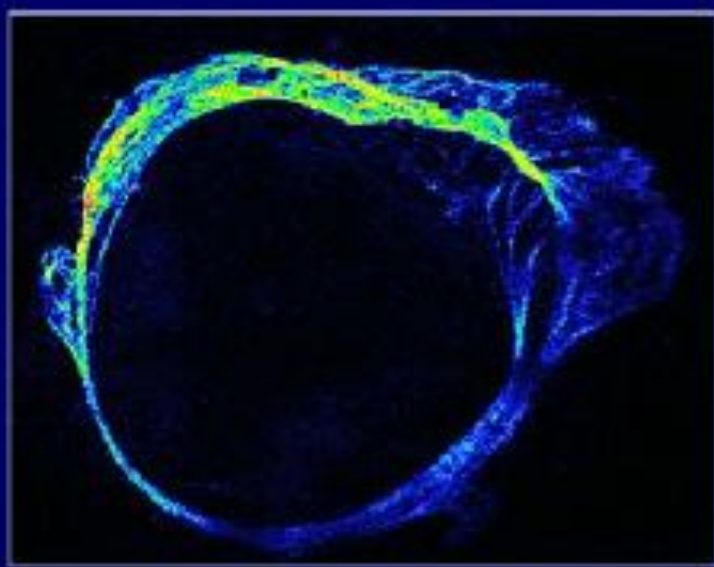
Impact of Obesity on the RAS



AT₁- Receptors are Expressed on Human Adipocytes



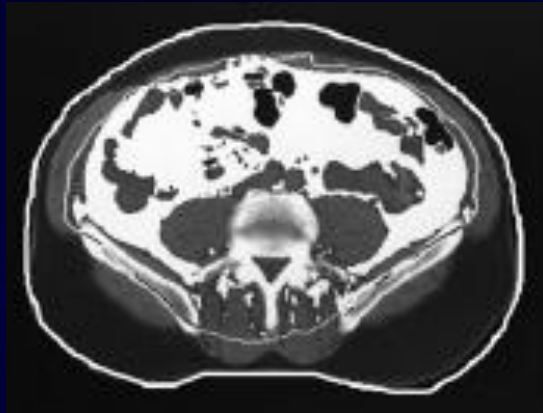
negative control



AT₁-expression

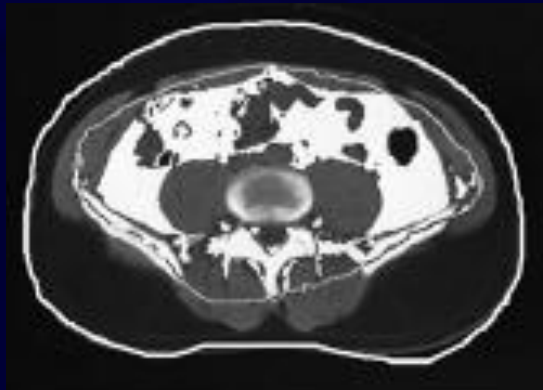
Visceral vs subcutaneous adiposity

CT scans matched for BMI and total body fat



Visceral obesity

Fat mass: 19.8 kg
VFA: 155 cm²

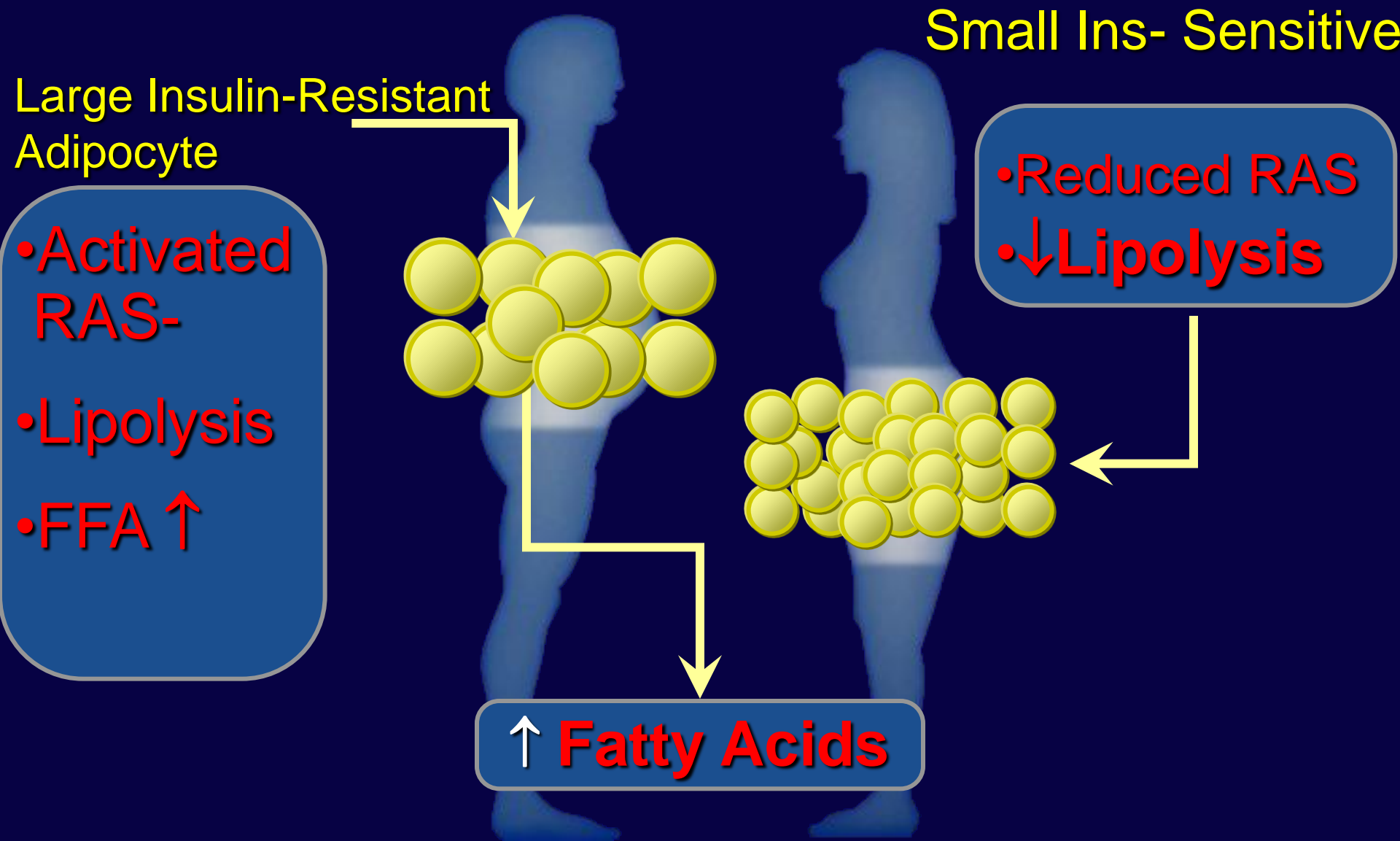


Subcutaneous (sc) obesity

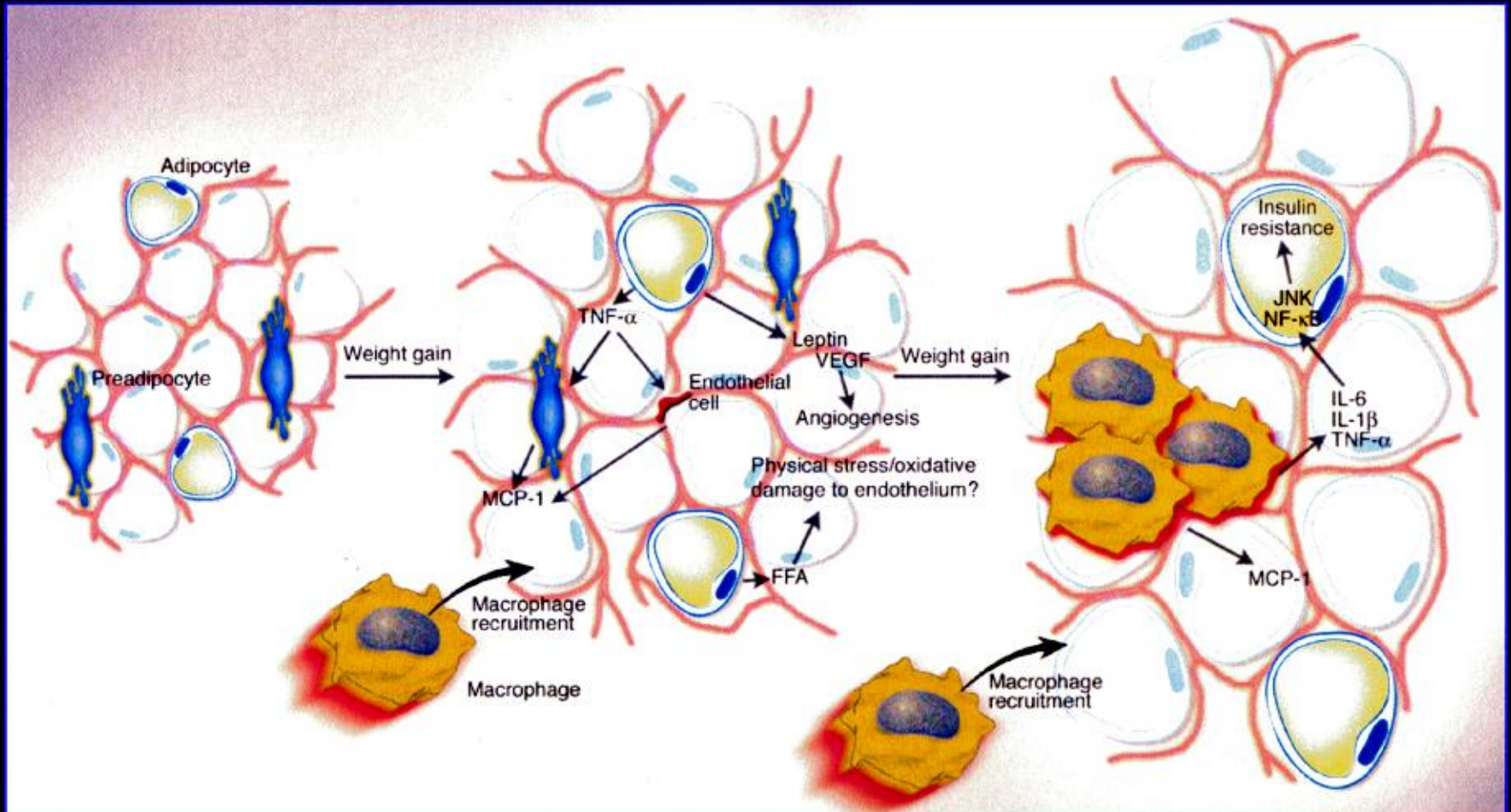
Fat mass: 19.8 kg
VFA: 96 cm²

White = VFA
Black = sc fat

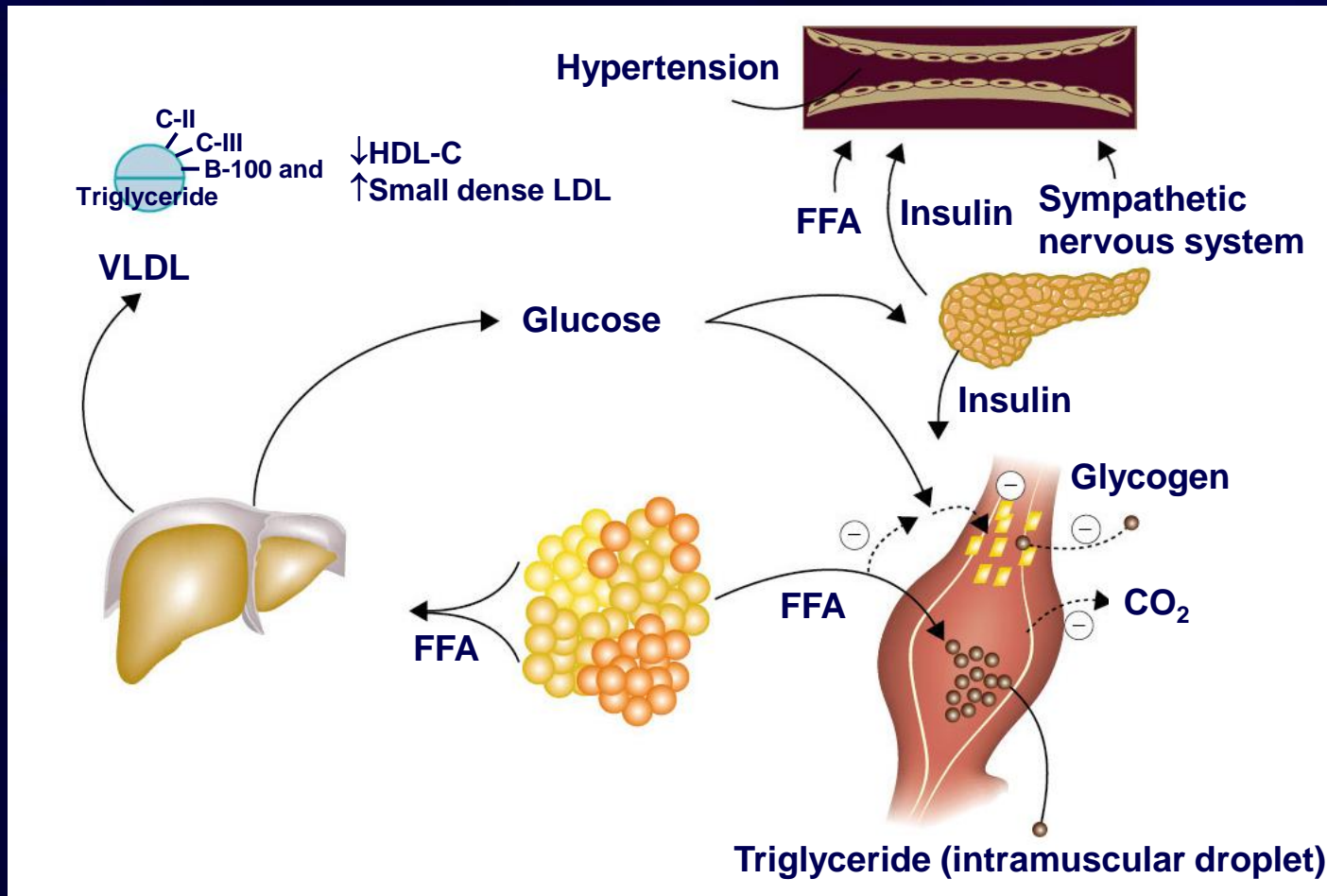
Fat Cells Are Not Created Equal



Obesity induces inflammatory changes in adipose tissue



Elevated FFA contribute to hypertension, dyslipidemia, and insulin resistance

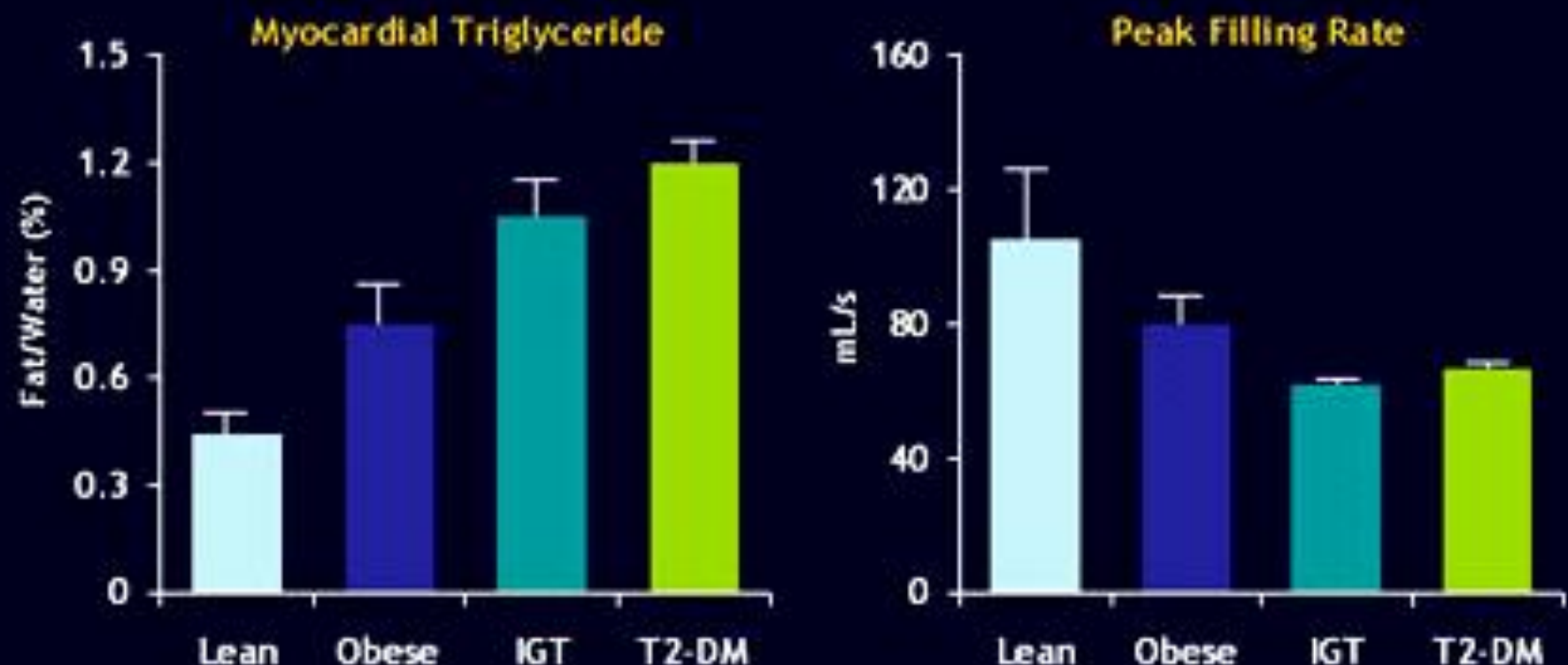


VLDL = very low density lipoproteins

Eckel RH et al. *Lancet*. 2005;365:1415-28.

Cardiac Steatosis in Prediabetic Humans: A Spectrum of Alterations From Obesity to DM

- Translational study in 134 humans evaluating myocardial fat accumulation
- MR imaging and spectroscopy used to quantify cardiac TG and diastolic function
- Cardiac lipotoxicity is a factor in cardiomyopathy in obesity-related disorders



Angiotensin II is Central to the Development of Atherosclerosis

Oxidative Stress

- ↑NAD (P)H oxidase activity
- ↑Reactive oxygen species
- ↑LDL peroxidation, LOX-1
- ↓Nitric oxide
- ↑Vasoconstriction
- ↑PAI-1 activation
- ↑Platelet aggregation

Endothelial Dysfunction

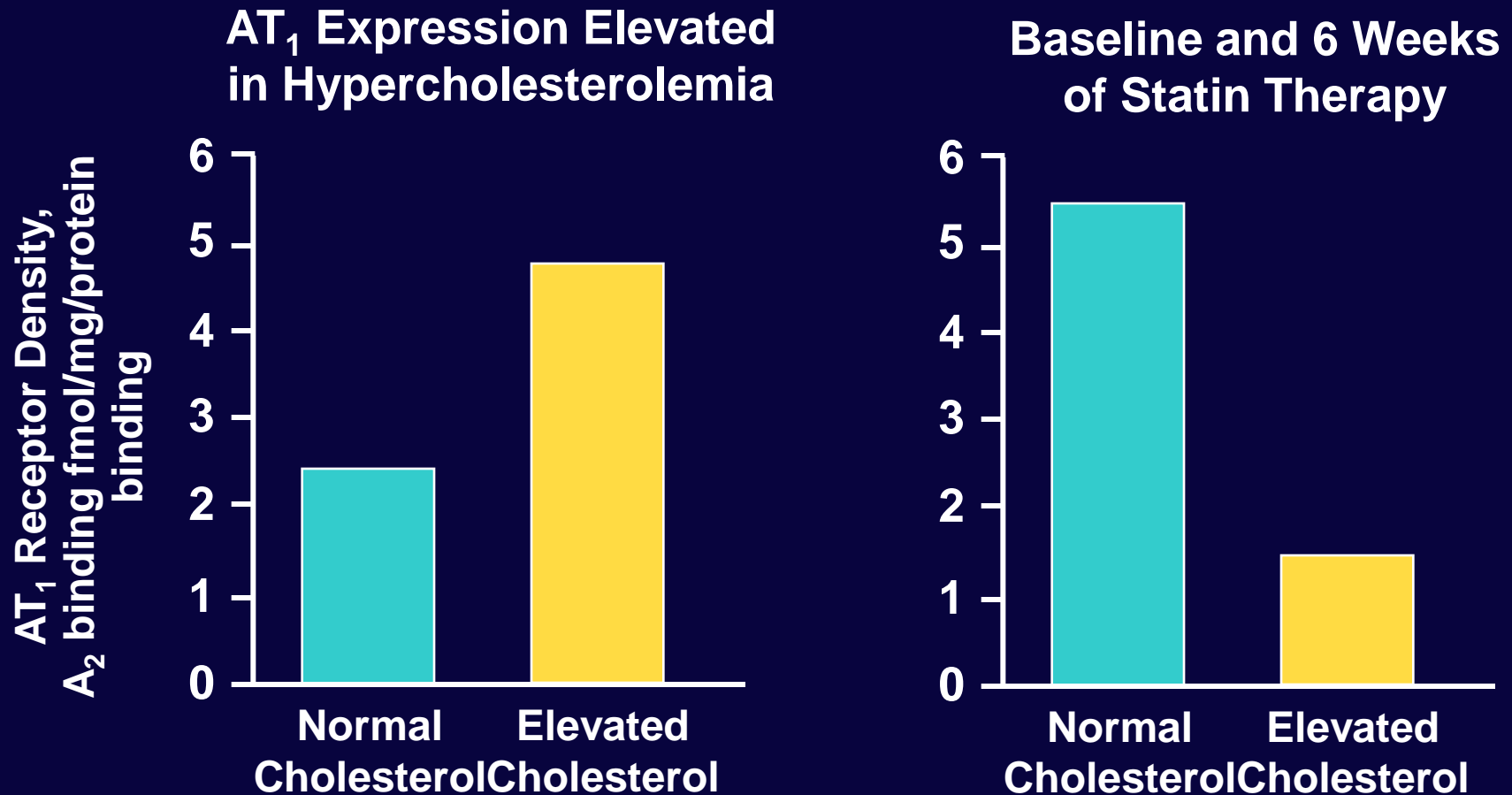
Inflammation

- ↑Vascular permeability
- ↑Leucocyte infiltration
- ↑Signaling pathways (NF κ B)
- ↑Inflammatory mediators
- ↑VSMC proliferation
- ↑Matrix deposition
- ↑MMP activation

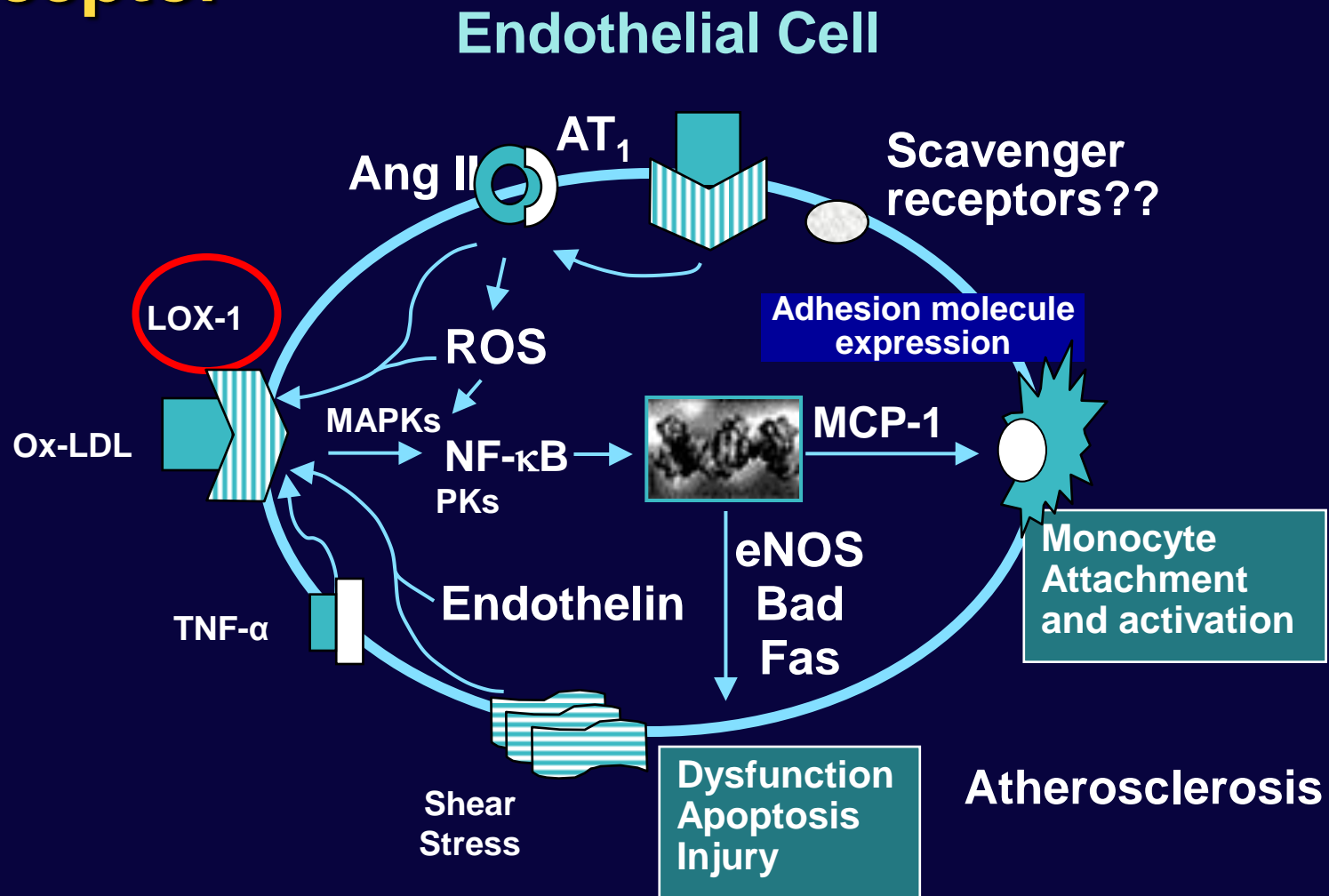
Tissue Remodeling

Ang II

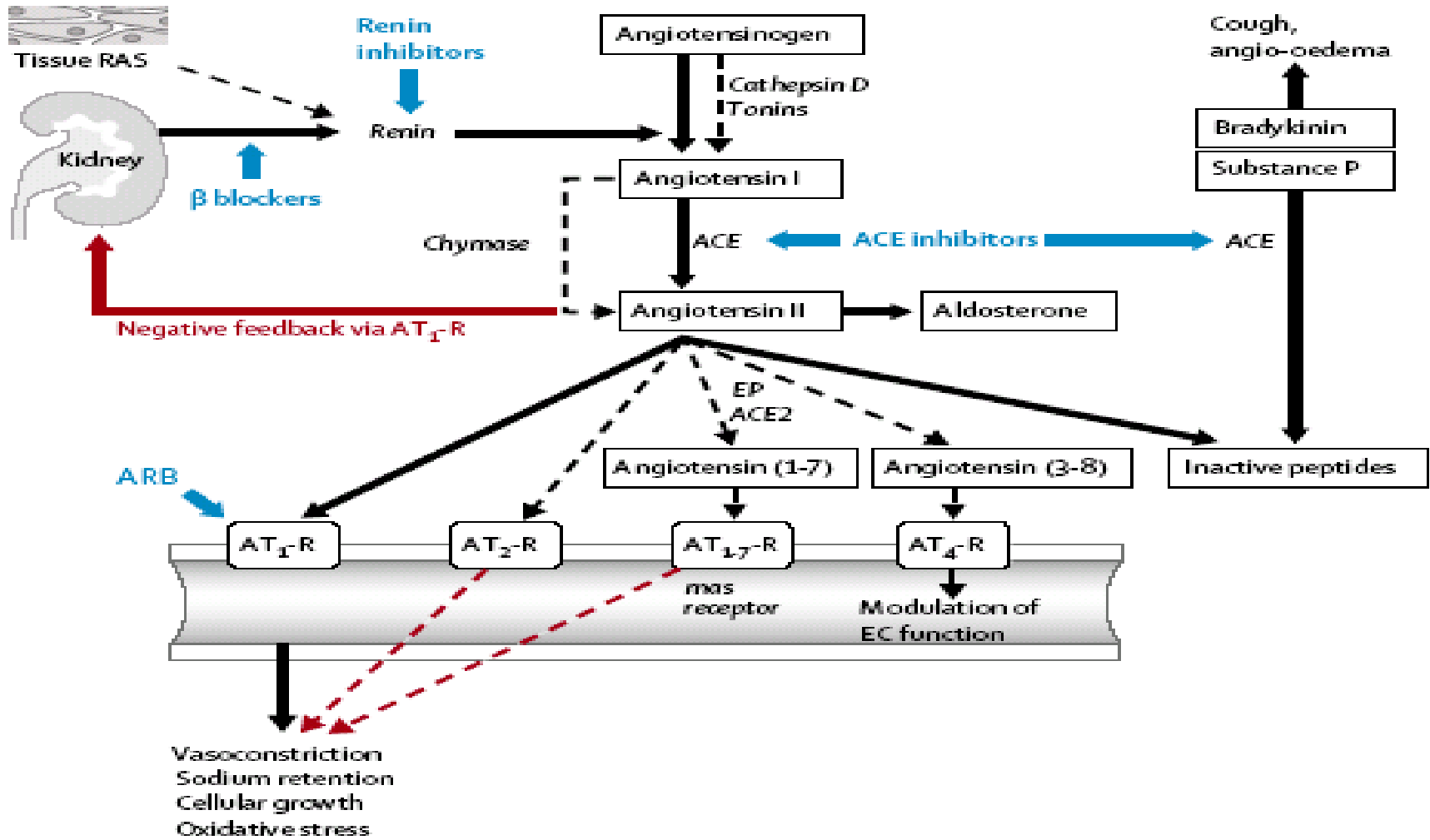
AT₁ Receptor Density Is Upregulated in Hypercholesterolemia and Downregulated by Statin Therapy



Implications of Activation of the LOX-1 Receptor



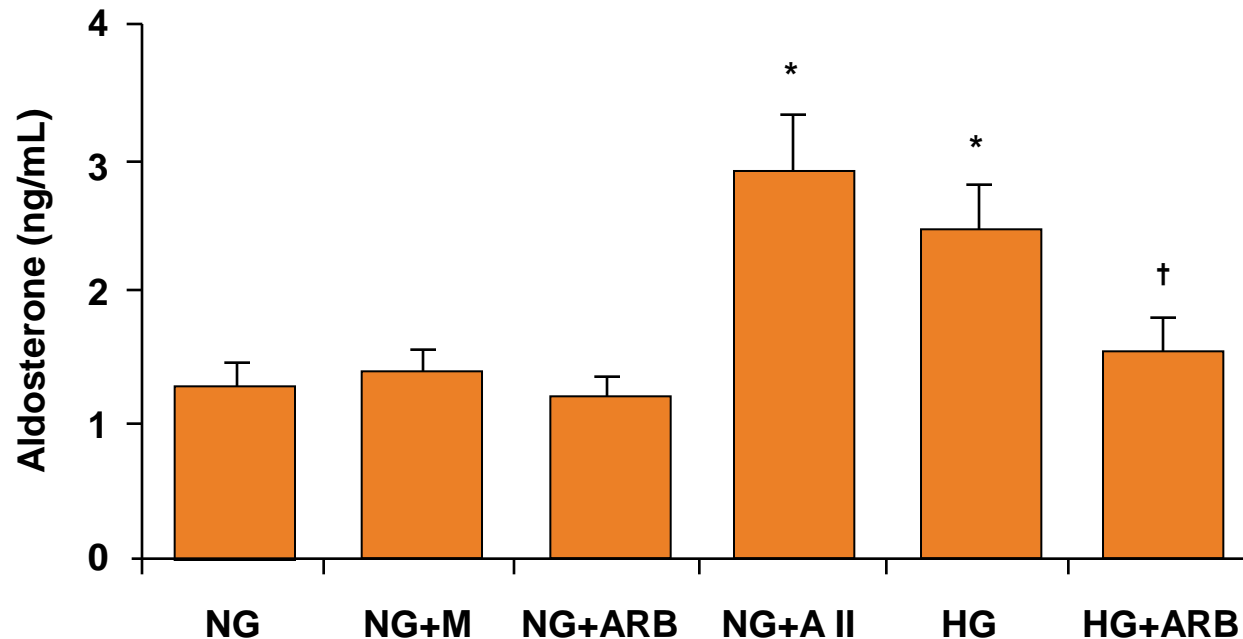
Implications of RAAS Activation



Aldosterone and Glucose

Cultured Mouse Podocytes

High Glucose Upregulates Aldosterone and Its Receptor at the Tissue Level

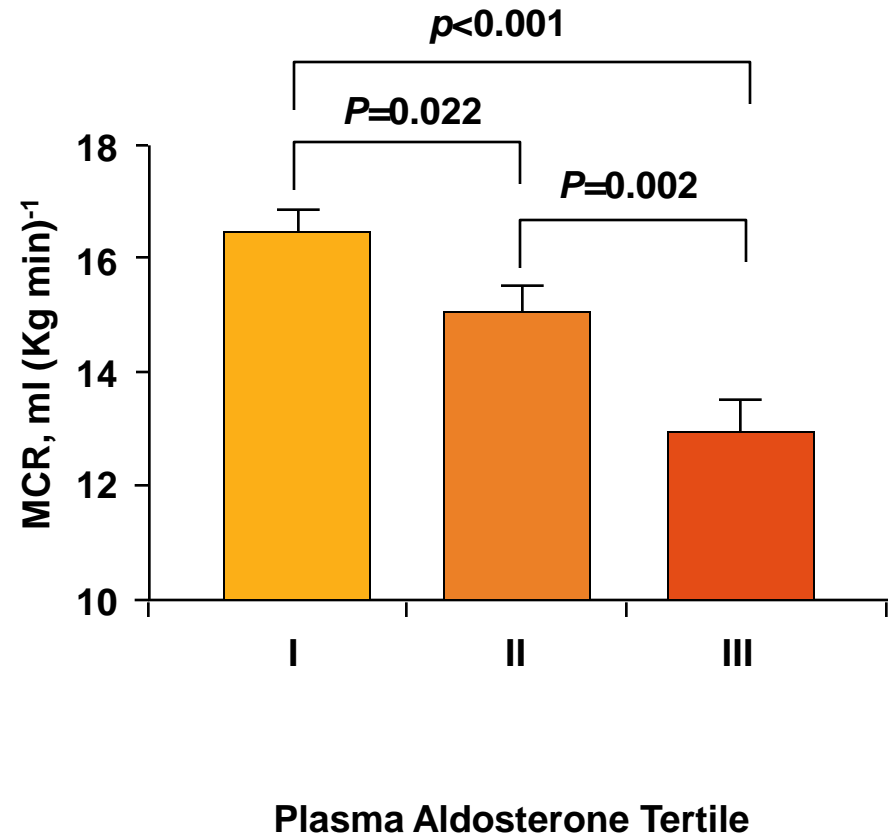


ARB: angiotensin receptor blocker; A II: angiotensin II; HG: high glucose; M: mannitol; NG: normal glucose
* $p < 0.01$ vs NG, NG+M, and NG+ARB groups; † $p < 0.05$ vs HG group.
Lee et al. *Am J Physiol Renal Physiol.* 2009;297:F1381.

Insulin Resistance and Aldosterone Levels

In Patients with Hypertension

- Patients with hypertension (BL BP 160/100 mm Hg) and FPG 91 mg/dL
- Euglycemic clamp to assess glucose clearance rate
- Independent association between insulin resistance (HOMA) and plasma aldosterone levels ($p=0.009$)
- Elevated aldosterone was associated with insulin resistance in patients with hypertension

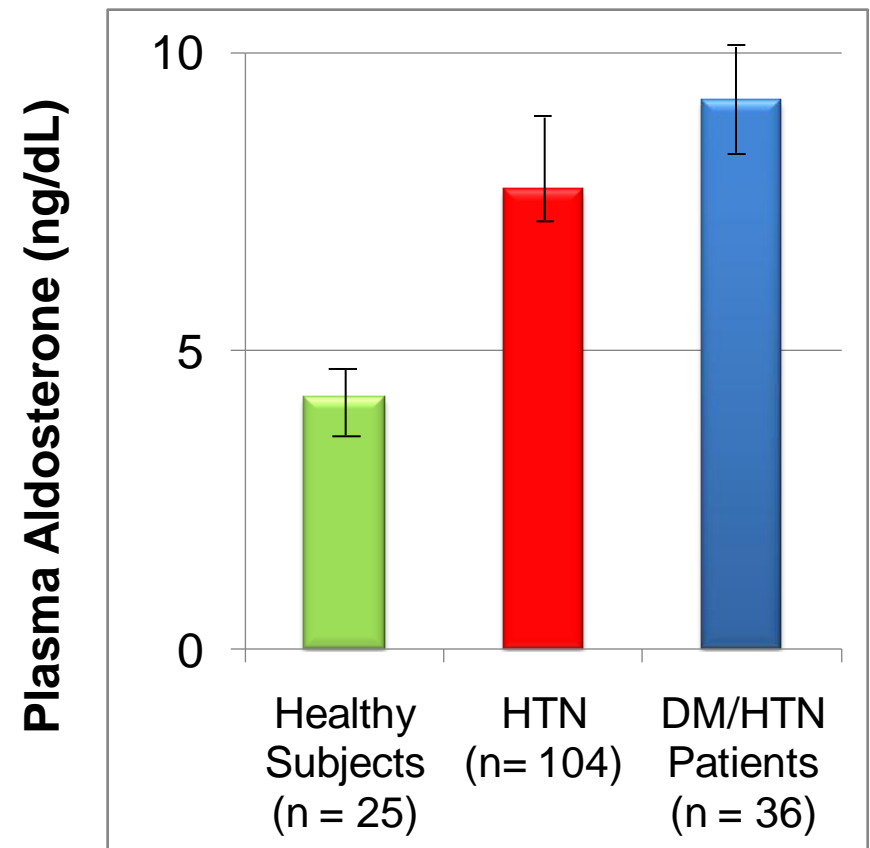
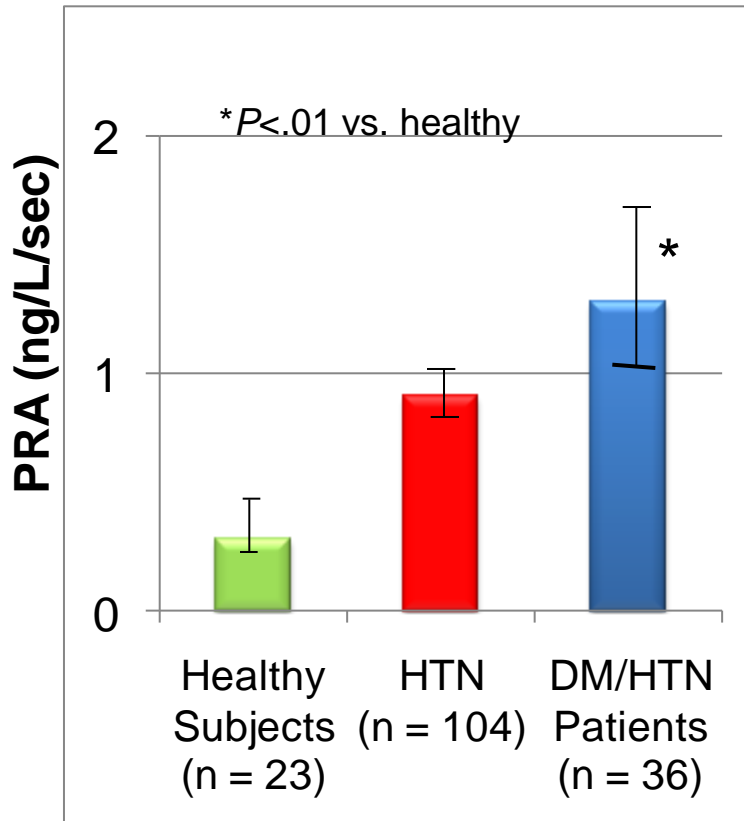


Plasma aldosterone levels: Tertile 1 68 ± 22 pg/ml; Tertile 2 130 ± 24 pg/ml; Tertile 3 293 ± 132 pg/ml
Bar graph showing the glucose metabolic clearance rate, as assessed during a euglycemic-hyperinsulinemic clamp, across plasma aldosterone tertiles in patients with essential hypertension (n 356). Comparisons were done by one-way ANOVA ($P < 0.001$) followed by group-to-group comparisons. MCR, metabolic clearance rate.

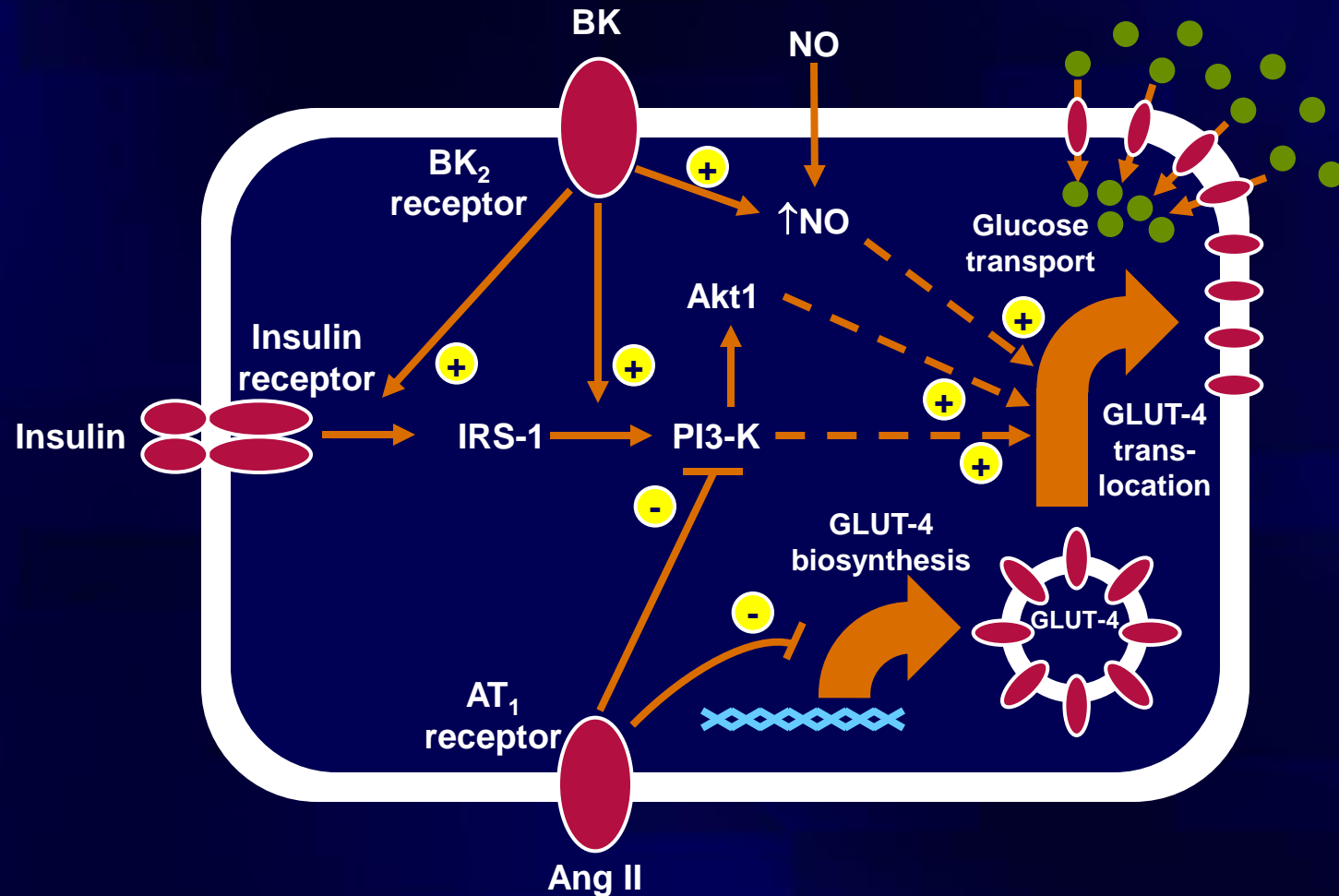
RAAS Responsiveness in Patients with HTN and T2DM

RAAS suppression is impaired in patients with HTN and DM.

- High-salt diet, patients in recumbent position



Role of Ang II in insulin resistance: Focus on signaling pathways



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 10, 2008

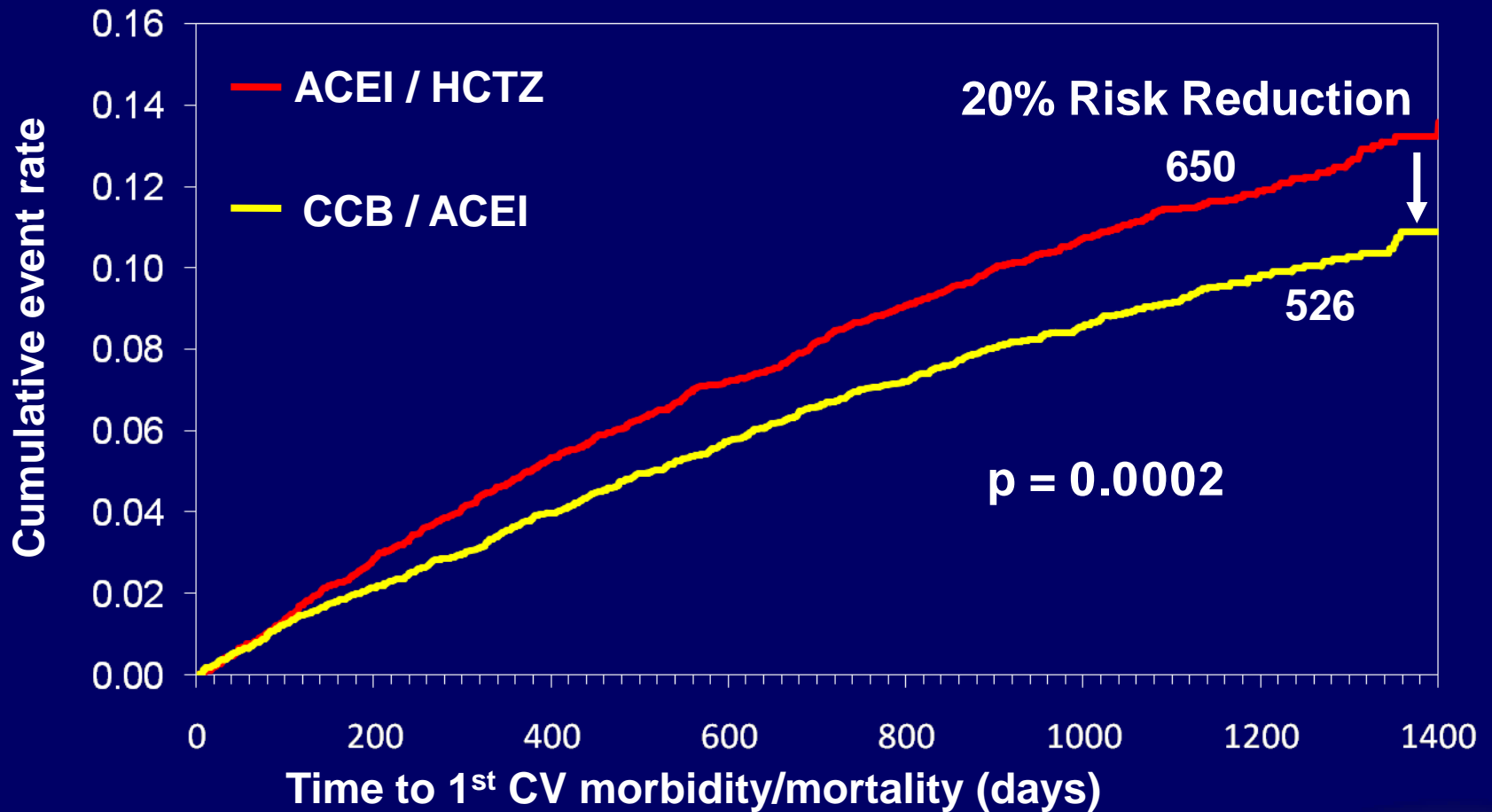
VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

	Ramipril	Telmisartan	Combination		
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)

PRIMARY ENDPOINT



CVD, NFMI, NFCVA, Hosp for Angina, Resuscitation post SCD, Revasc

HR (95% CI): 0.80 (0.72, 0.90)

INTERIM RESULTS Mar 08



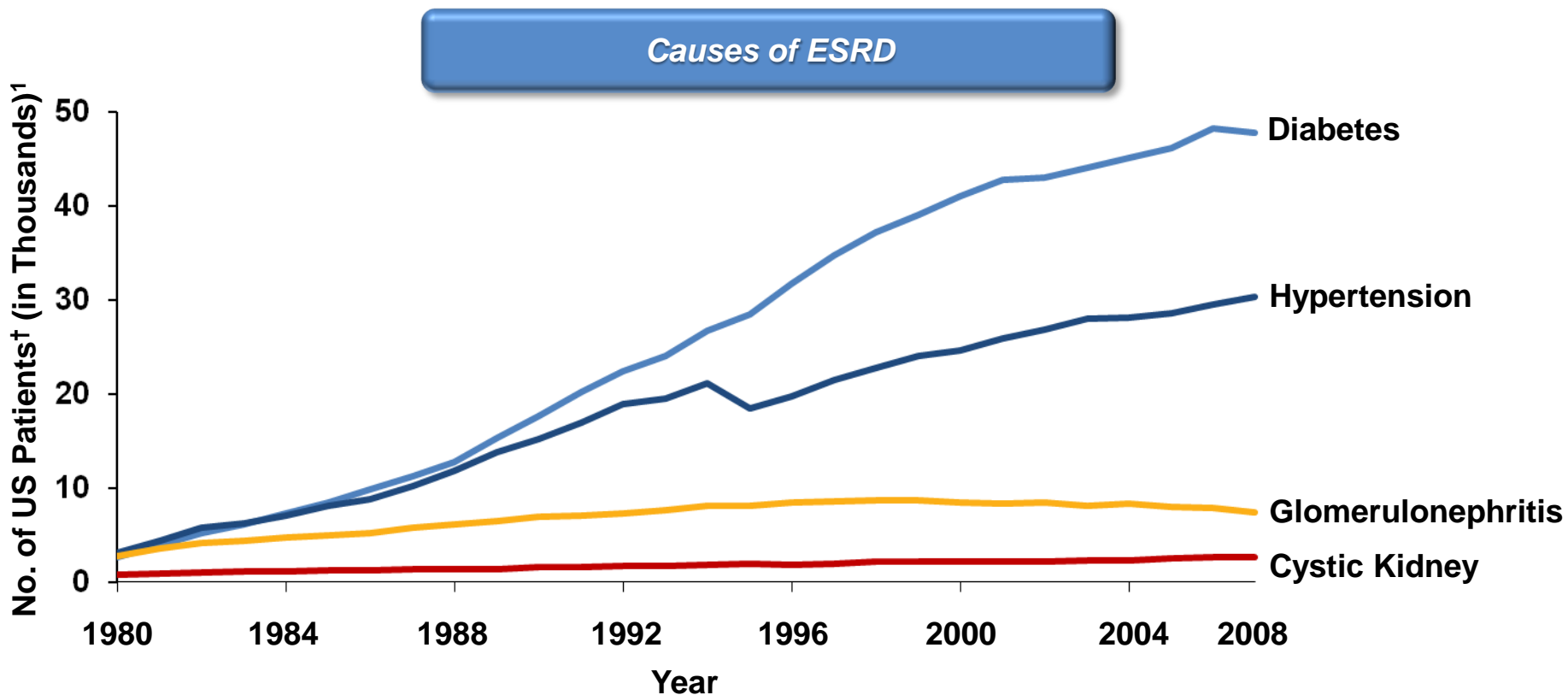
ACCOMPLISH- Renal Outcomes in the intention-to-treat population

End point	Benazepril plus amlodipine (n=5744), %	Benazepril plus hydrochlorothiazide (n=5762), %	Hazard ratio (95% CI)
Progression to CKD (primary end point)	1.97	3.73	0.52 (0.41–0.65)
Doubling of serum creatinine	1.83	3.61	0.51 (0.39–0.63)
Dialysis	0.12	0.23	0.53 (0.21–1.35)
eGFR <15 mL/min/1.73 m ²	0.31	0.30	1.06 (0.54–2.05)
Progression to CKD and cardiovascular death	3.83	5.99	0.63 (0.53–0.74)
Progression to CKD and all-cause mortality	6.02	8.07	0.73 (0.64–0.84)

Bakris GL et al. *Lancet* 2010

Diabetes and Hypertension

Association with End Stage Renal Disease (ESRD)



In Patients with Diabetes and Hypertension, the Risk of Developing ESRD Is 5 to 6 Times Greater Than in Individuals with Hypertension Alone²

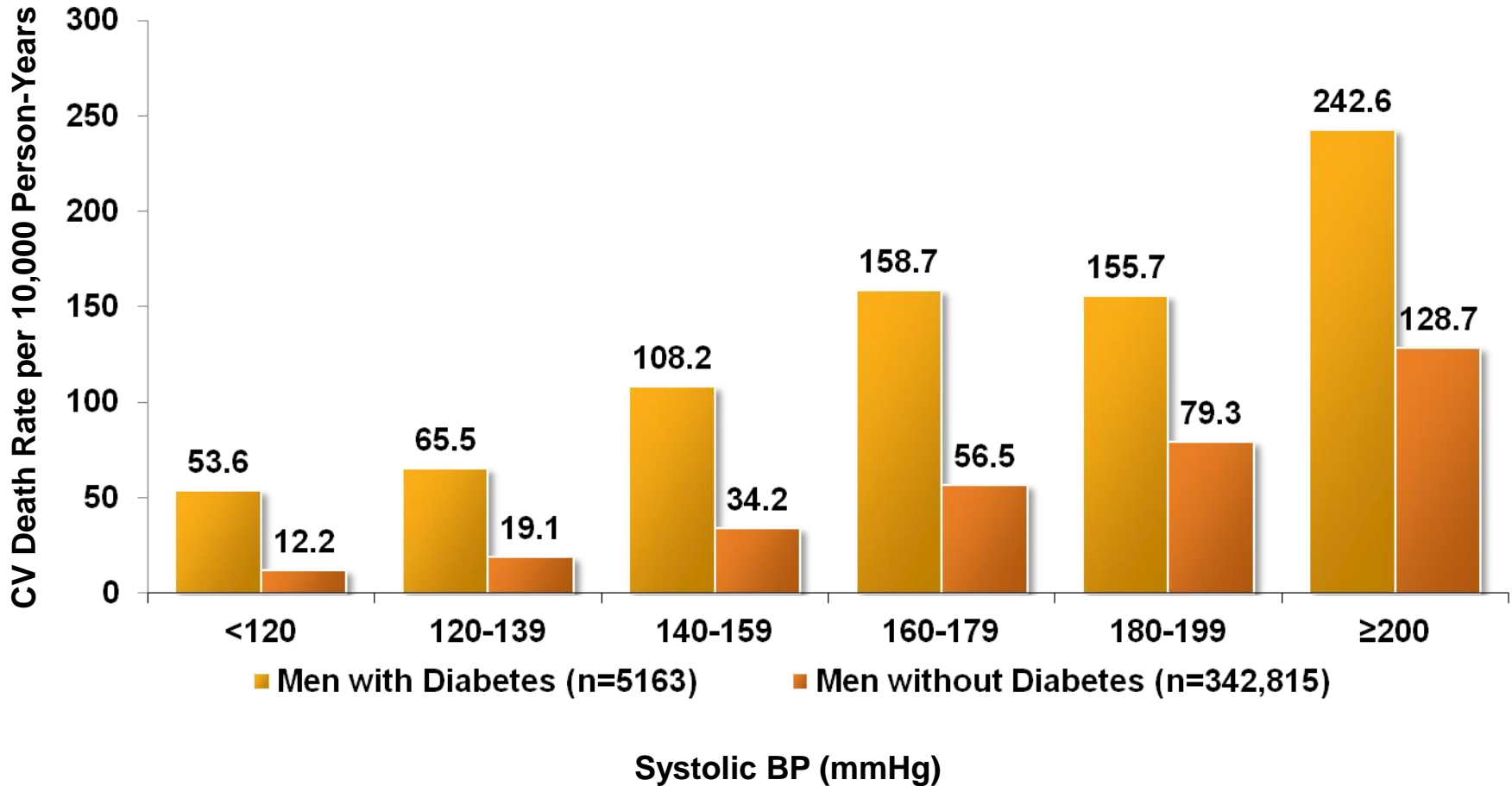
¹Incident ESRD patients; rates adjusted for age, gender and race;

1. USRDS 2009 Annual Data Report. NIH/NIDDKD, Bethesda, MD, 2009

2. Bakris et al. Am J Kidney Dis 2000;36:646-61

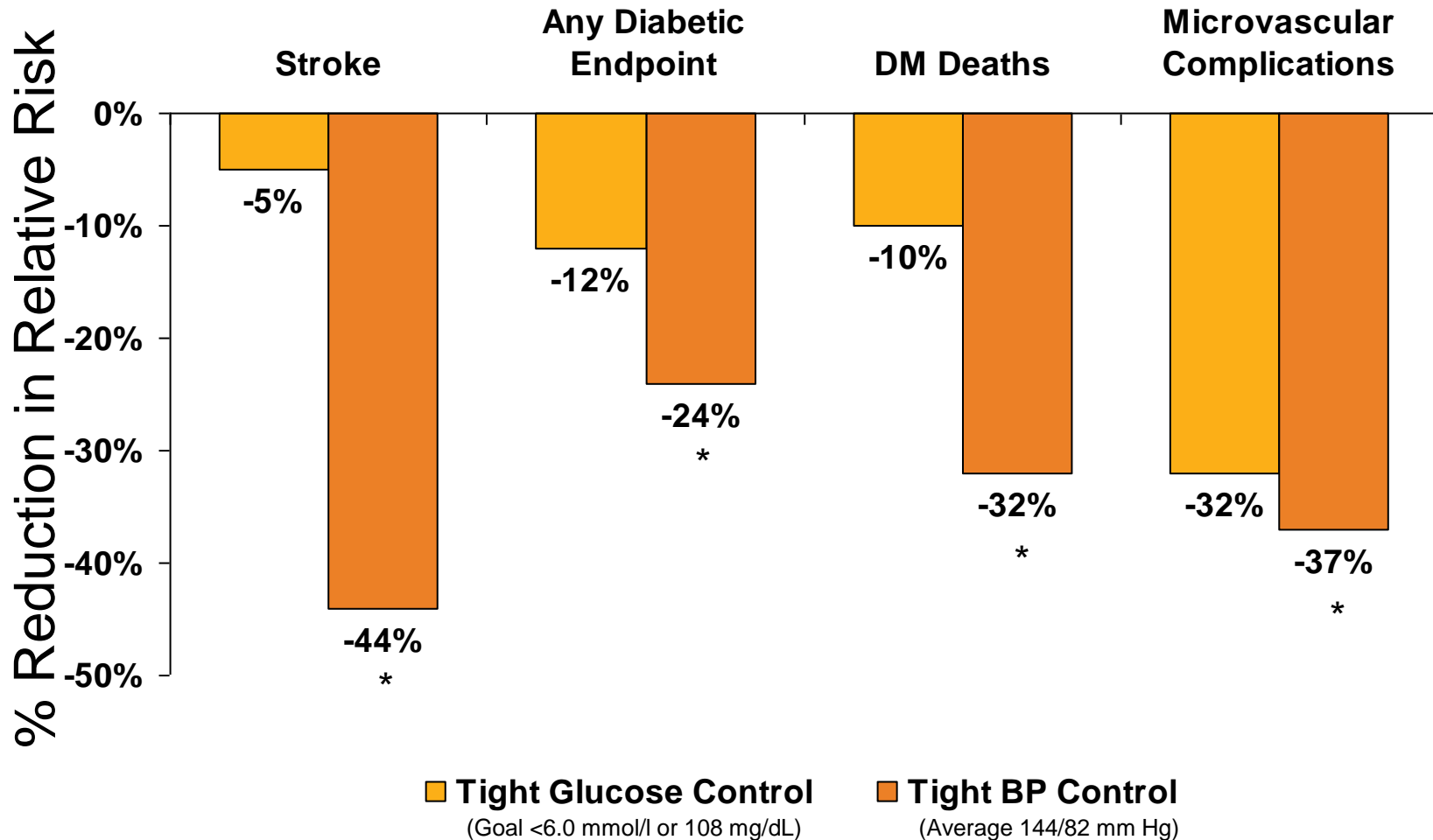
MRFIT Trial

Patients with Hypertension and Diabetes and Risk of CV Mortality



BP = blood pressure;
MRFIT = Multiple Risk Factor Intervention Trial
Stamler et al. *Diabetes Care* 1993;16:434-444

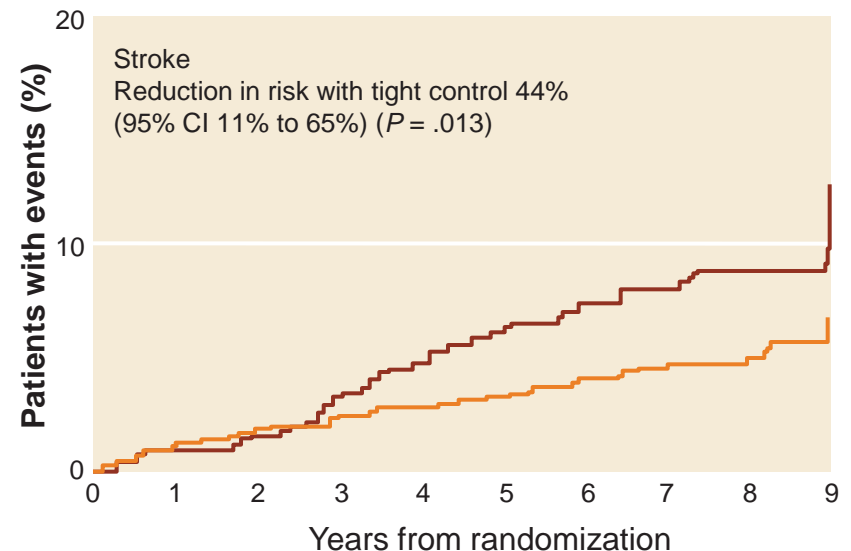
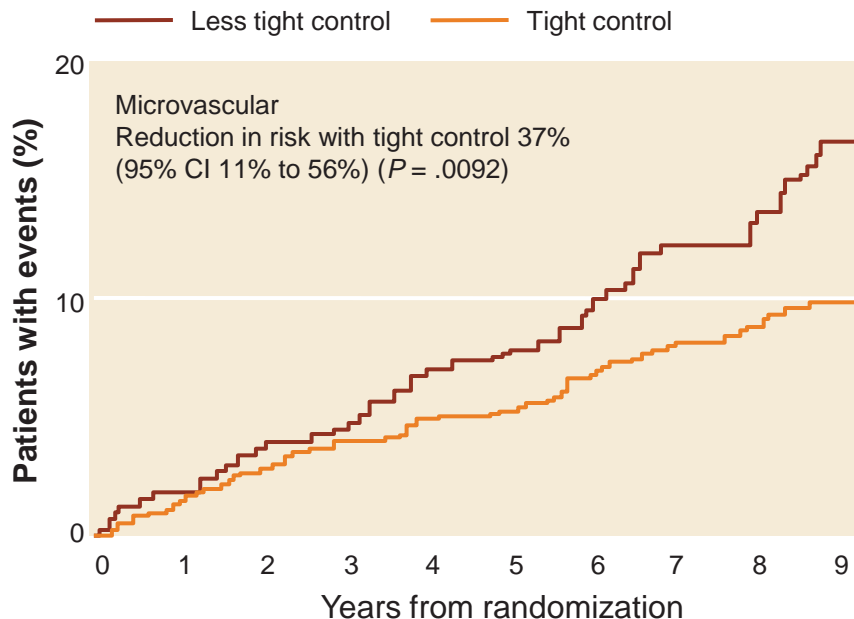
Diabetes: Tight Glucose vs Tight BP Control and CV Outcomes in UKPDS



* $p < 0.05$ compared to tight glucose control. There were no differences between ACEi and Beta-blockers in study
Bakris GL, et al. *Am J Kidney Dis.* 2000;36(3):646-661.

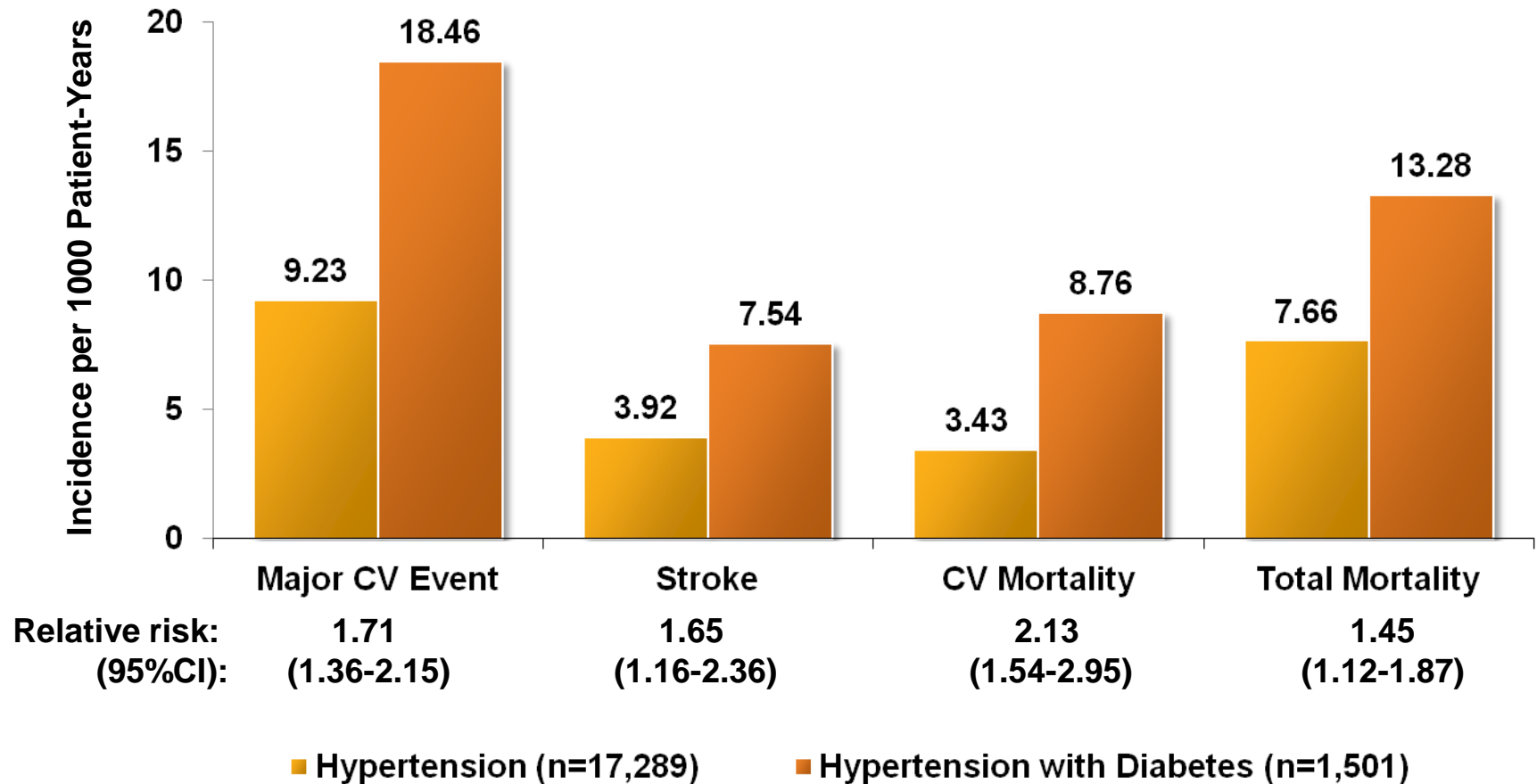
UKPDS Results

- Patients assigned to tight BP control (aim <150/85 mm Hg) compared with those assigned to less tight BP control (aim <180/105 mm Hg) had:
 - nonsignificant reduction in risk of 21% in the aggregate end point for MI
 - 44% reduction in risk of stroke (fatal and non-fatal)
 - 37% reduction in risk of microvascular disease
 - 32% reduction in risk of mortality from diseases substantially increased by diabetes ($P=.019$), two-thirds of which were CV diseases



HOT Study

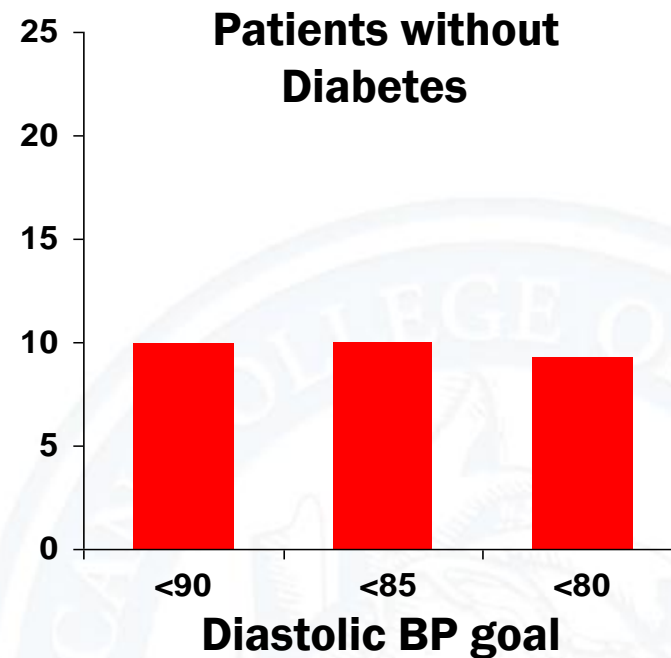
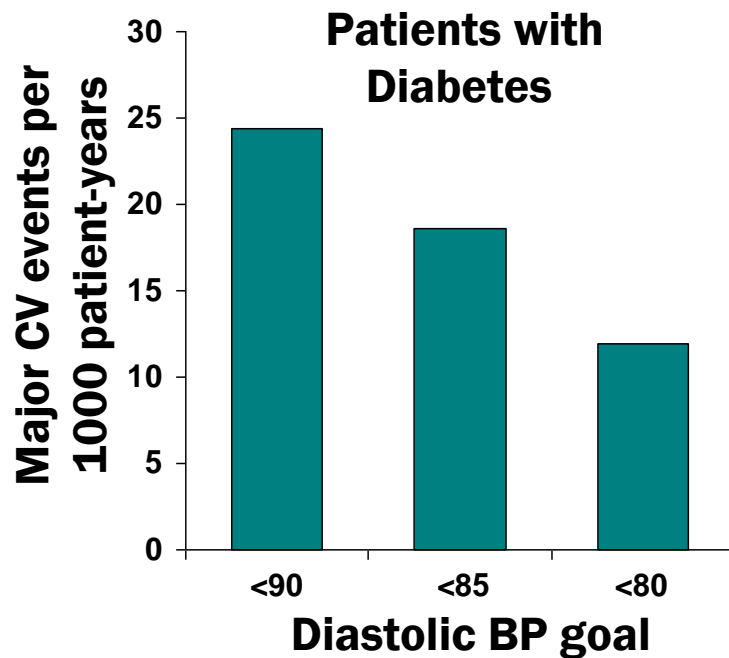
Co-Morbid Diabetes and Risk of CV Events in Patients with Hypertension:



Blood Pressure Lowering Therapy Evidence: Effect of Intensive Blood Pressure Control

Hypertension Optimal Treatment (HOT) Study

18,790 patients with a baseline diastolic BP of 100-115 mm Hg randomized to a target diastolic BP of ≤ 90 mm Hg, ≤ 85 mm Hg, or ≤ 80 mm Hg



More intensive blood pressure control provides greater benefit in diabetics

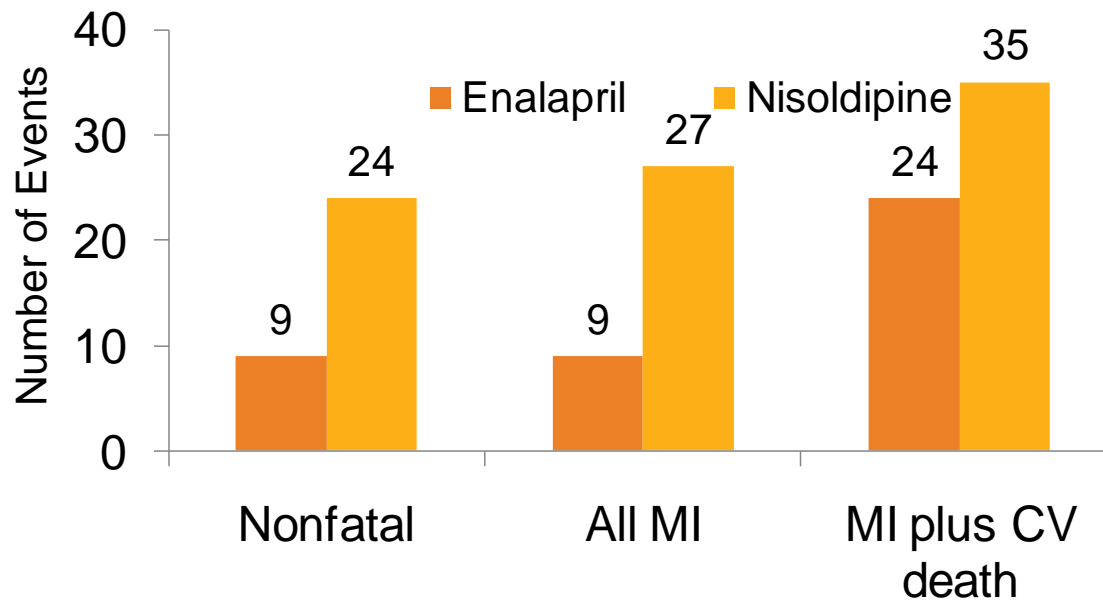


Helping Cardiovascular Professionals
Learn. Advance. Heal.

Source: Hansson L et al. *Lancet*. 1998;351:1755-1762.

ABCD Results

Patients with hypertension and diabetes assigned to enalapril had significantly fewer CV complications than those assigned to nisoldipine.

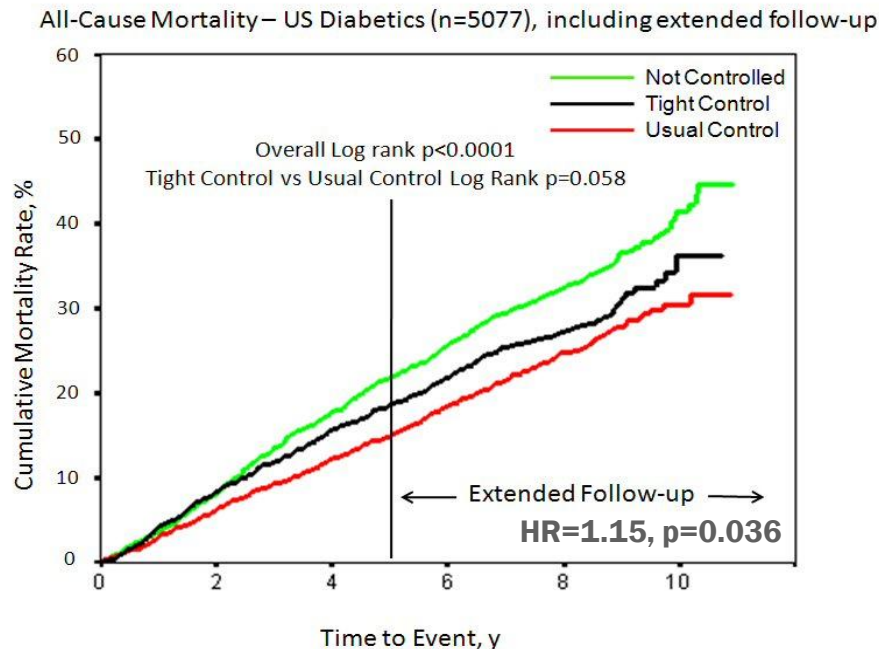


- All-cause mortality over the 5 years of the hypertensive ABCD study was significantly lower in the intensive than in the moderate BP control group (5.5% vs. 10.7%; $P < .037$).

Blood Pressure Lowering Therapy Evidence: Effect of Intensive Blood Pressure Control

International Verapamil-Trandolapril Study (INVEST)—DM Substudy

6,400 diabetic patients from the INVEST study grouped by tight (<130 mm Hg), usual (\geq 130 to <140 mm Hg), or uncontrolled (>140 mm Hg) blood pressure



Tight BP control is not associated with reduced adverse CV events



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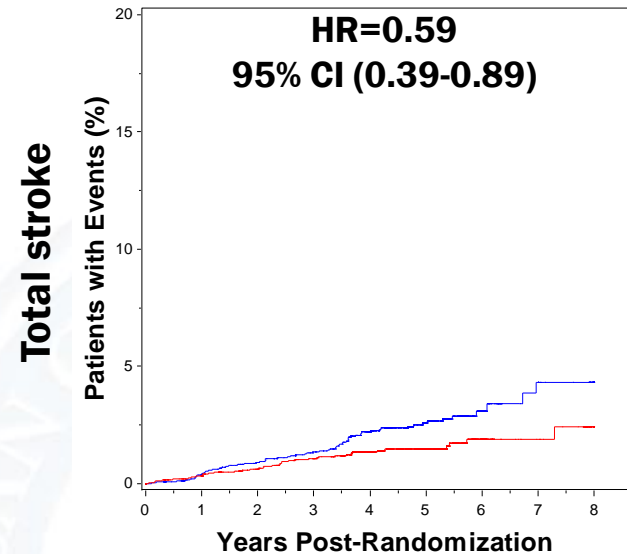
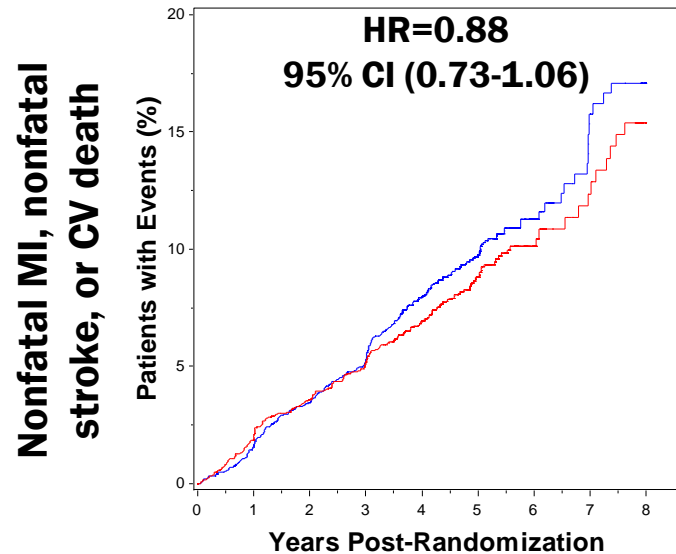
BP=Blood pressure, CV=Cardiovascular

Source: Cooper-DeHoff RM et al. Presented at the 2010 ACC Scientific Sessions, Orlando, Florida

Blood Pressure Lowering Therapy Evidence: Effect of Intensive Blood Pressure Control

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years



Intensive BP control in DM does not reduce a composite of adverse CV events, but does reduce the rate of stroke



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Learn. Advance. Heal.*

BP=Blood pressure, DM=Diabetes mellitus,
HR=Hazard ratio, SBP=Systolic blood pressure
ACCORD study group. *NEJM* 2010;362:1575-85.

Action in Diabetes and Vascular Disease: ADVANCE

- **5-year blinded randomized factorial design study comparing intensive vs standard BP and Glucose control with perindopril/indapamide and Gliclazide (modified release).**
- **The BP lowering part of the study completed in June 2007. BP lowering alone (intensive cohort msSBP 135.5 mmHg vs standard treatment cohort 137.9 mmHg) demonstrated a reduction in major vascular events and death, regardless of the initial BP. Over 5 years, one death due to any cause would be averted among every 79 patients assigned active treatment**
- **There were no interaction between blood pressure intervention and the blood glucose intervention for primary outcomes ($p>0.50$)**
- **After 3 years of follow-up, event rates (in the two groups combined) were lower than expected. The protocol was amended to extend the period of treatment and follow up by 12-months to increase power**

The ADVANCE Collaborative Group. 2008, NEJM 358 (24): 2560

Dluhy RG, McMahon GT. 2008 NEJM 358 (24): 2630

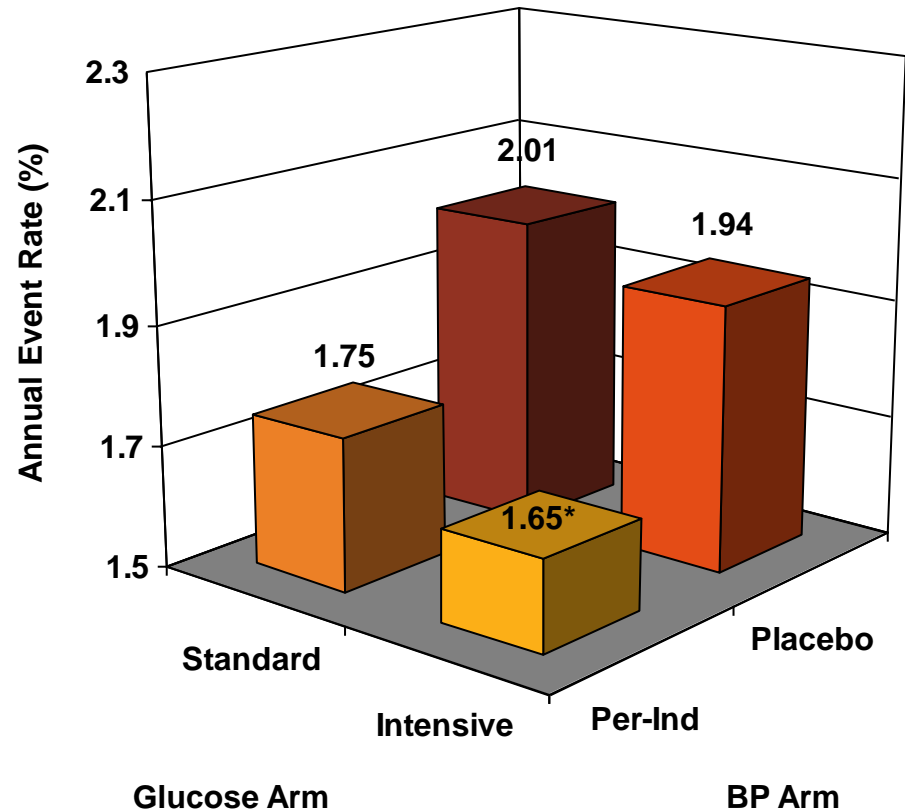
Cefalu WT, 2008 NEJM 358 (24): 2633

The ADVANCE Collaborative Group. 2007 Lancet 370: 829

Zoungas S., De Galan BE et al. 2009 Diabetes Care 32 (11):2068

Effect on Nephropathy and Proteinuria in ADVANCE Trial

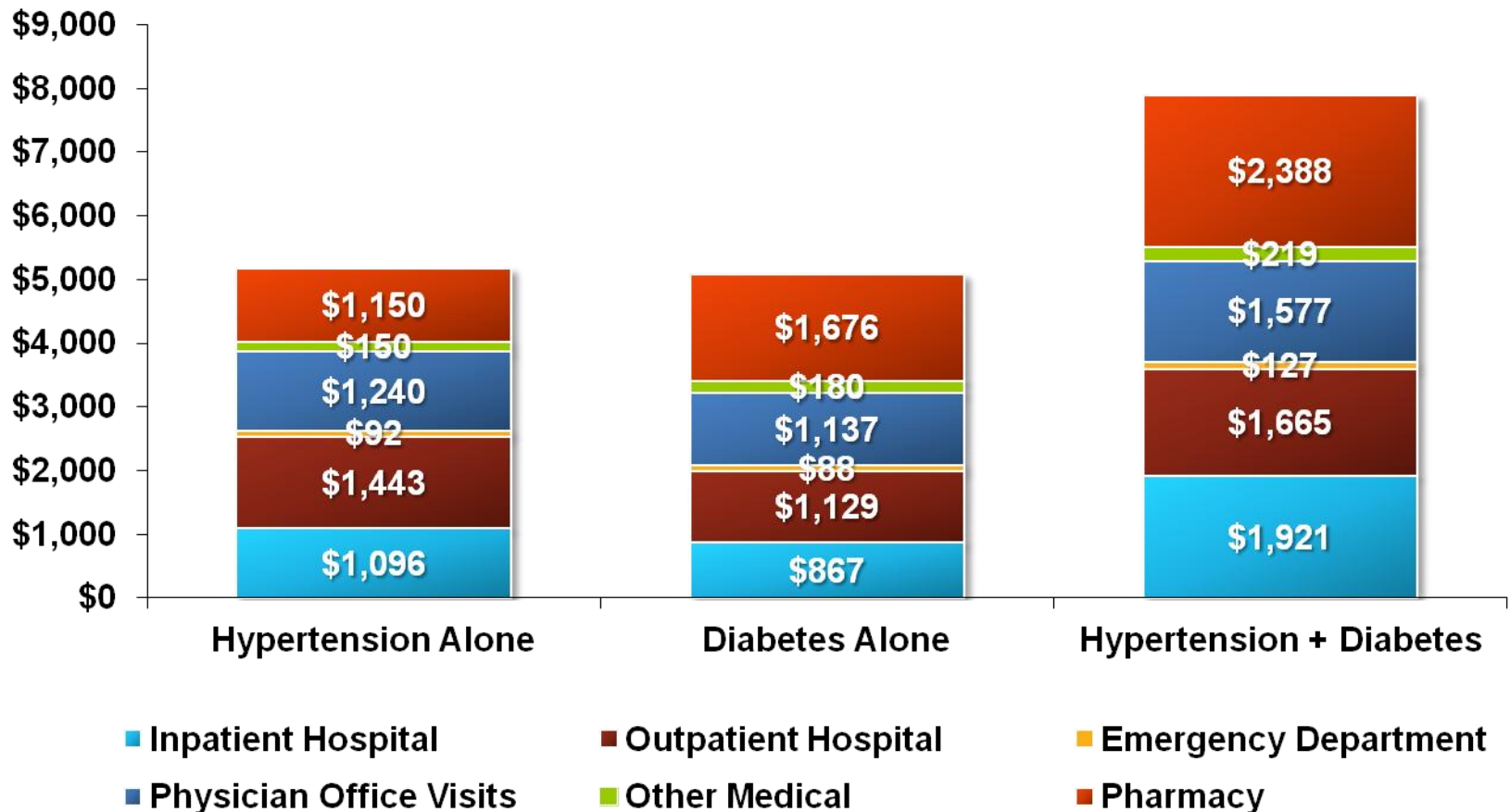
- **Intensification of Glycemic Control to achieve A1C $\leq 6.5\%$ augments the benefits obtained with Blood Pressure treatment, particularly in respect to renal events**
 - **33% reduction in the risk of new or worsening nephropathy ($p=0.005$)**
 - **54% reduction in the risk of onset of macroalbuminuria ($p<0.0001$)**
 - **25% reduction in the risk of new onset of microalbuminuria ($p<0.001$)**



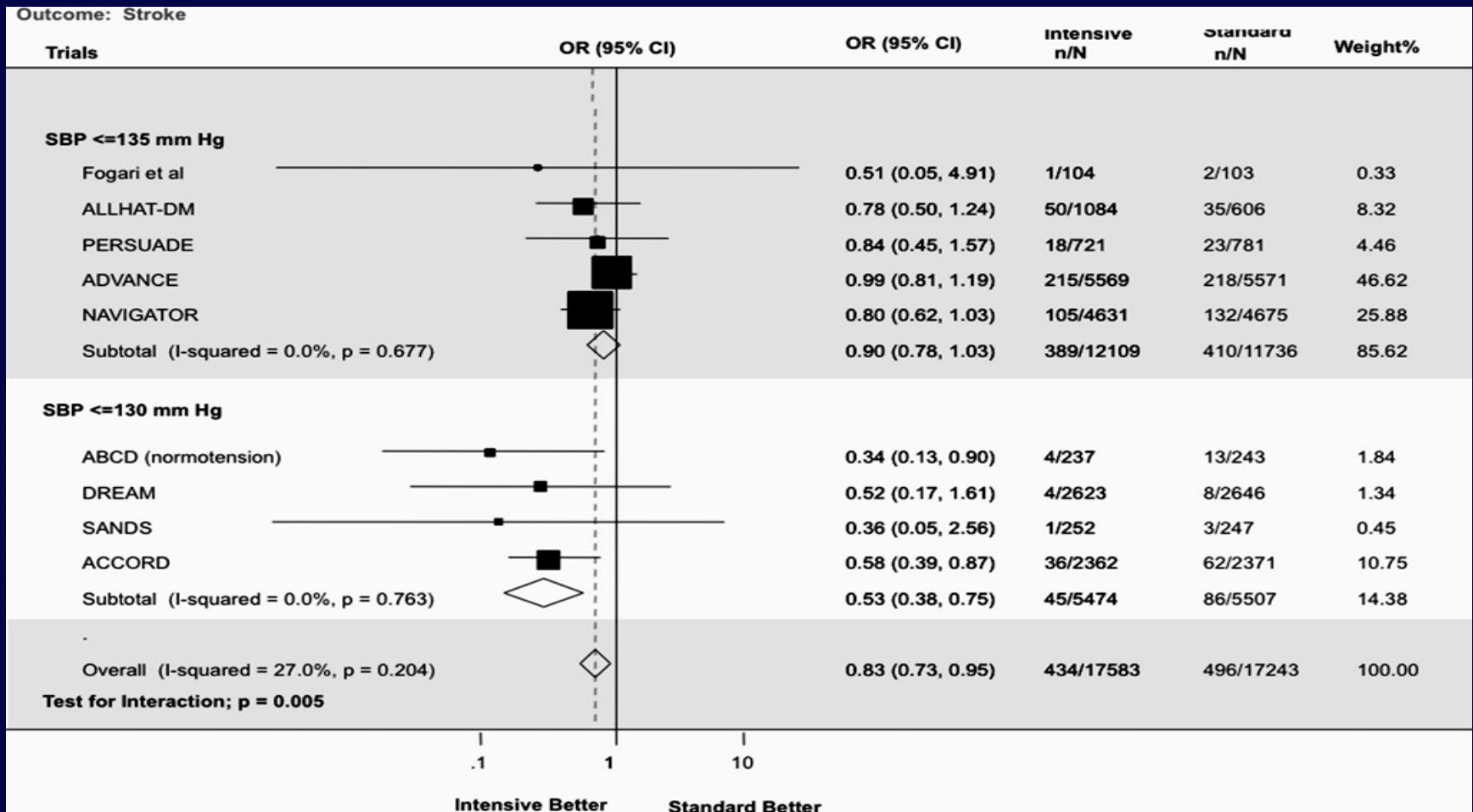
*RRR 18% (95% CI 1-32), $p=0.04$ vs the group of standard and placebo.
RRRs, relative risk reductions.
Zoungas S, et al. *Diabetes Care*. 2009;32(11):2068-2074.

Cost of Comorbid Hypertension and Diabetes

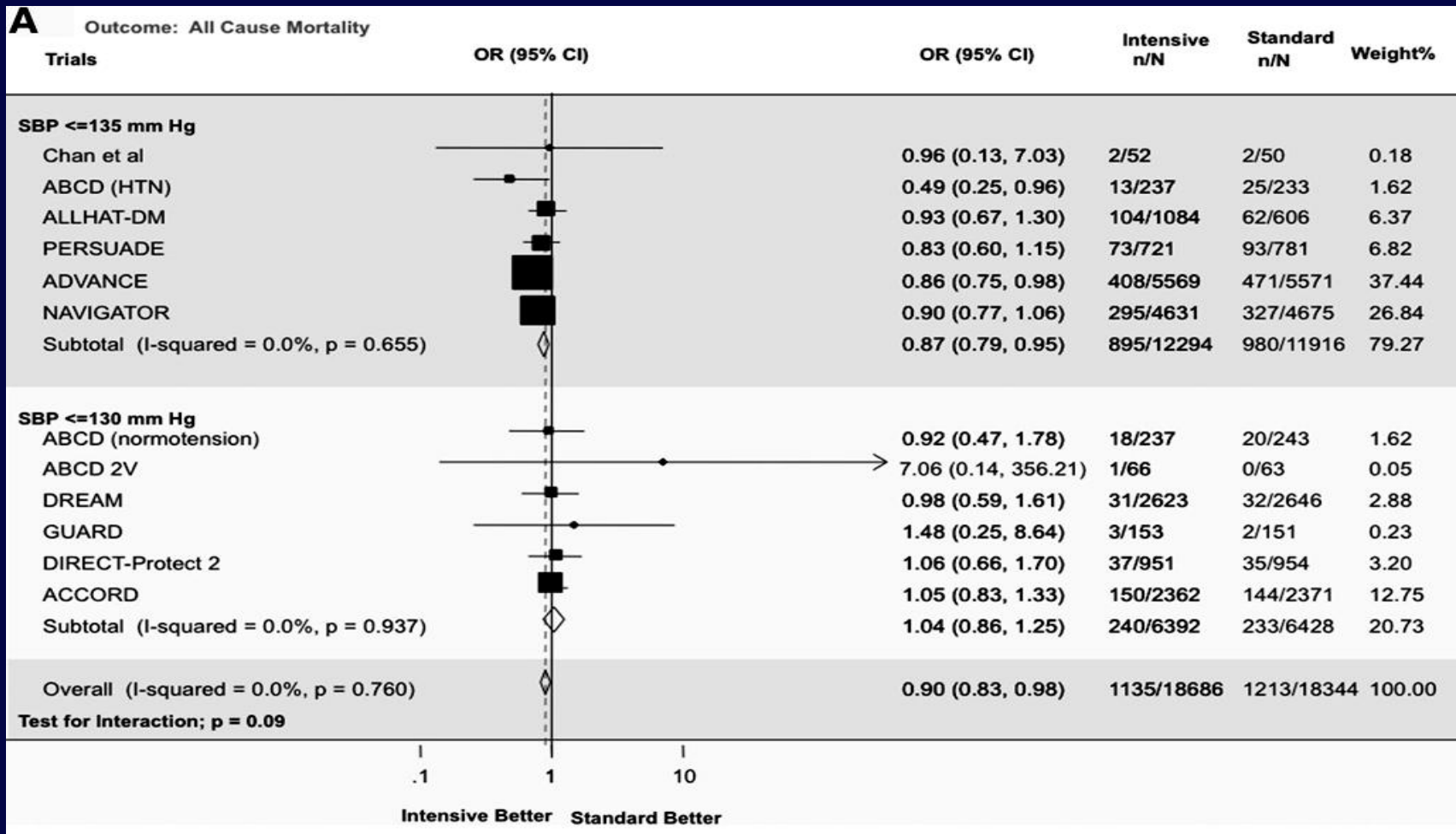
Average 12-Month Healthcare Cost for Patients with Comorbid Diabetes



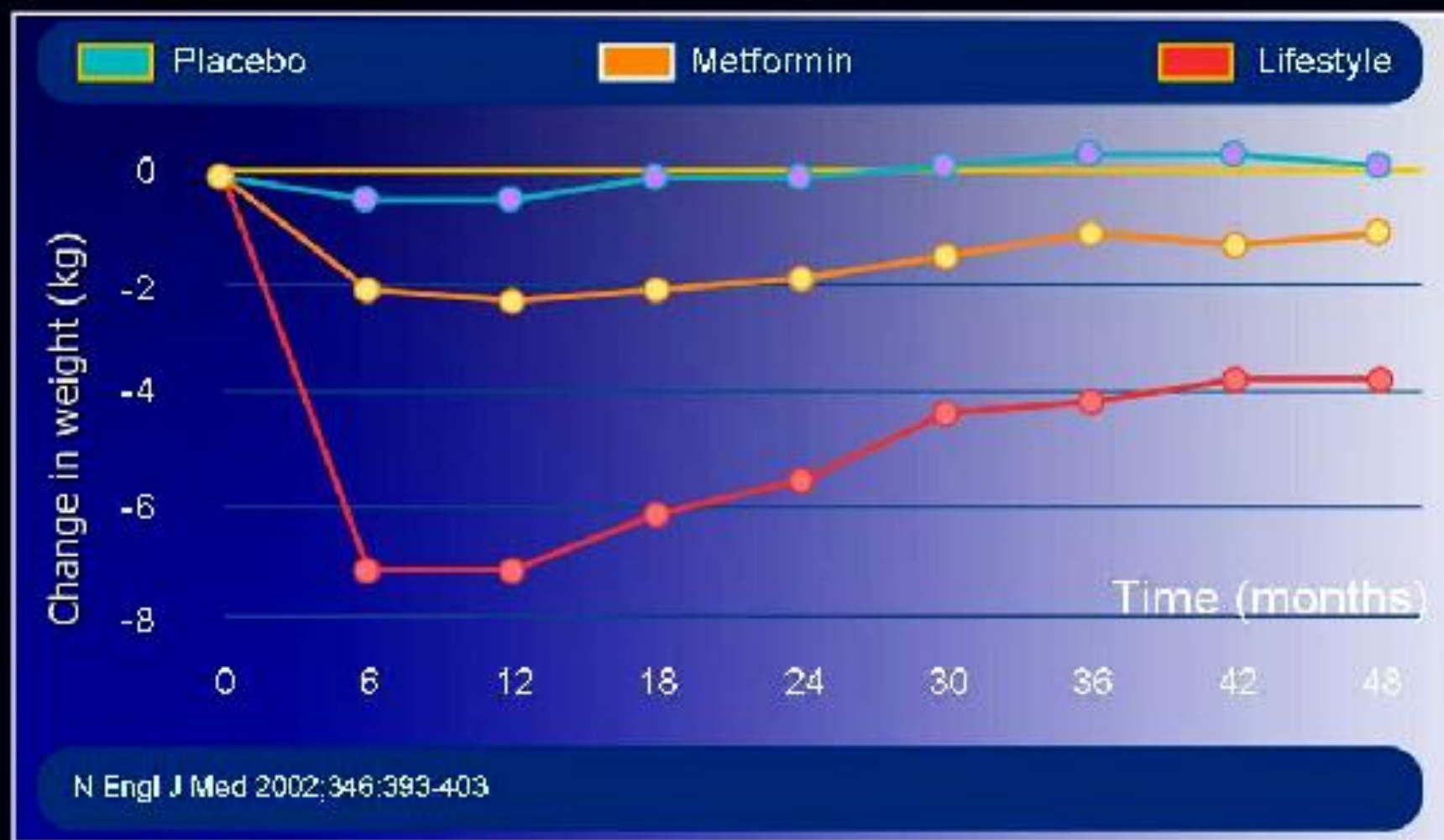
Impact of Intensive BP Lowering on Stroke



Impact of Intensive BP Lowering on All Cause Mortality



DPP: Effect of Interventions on Weight

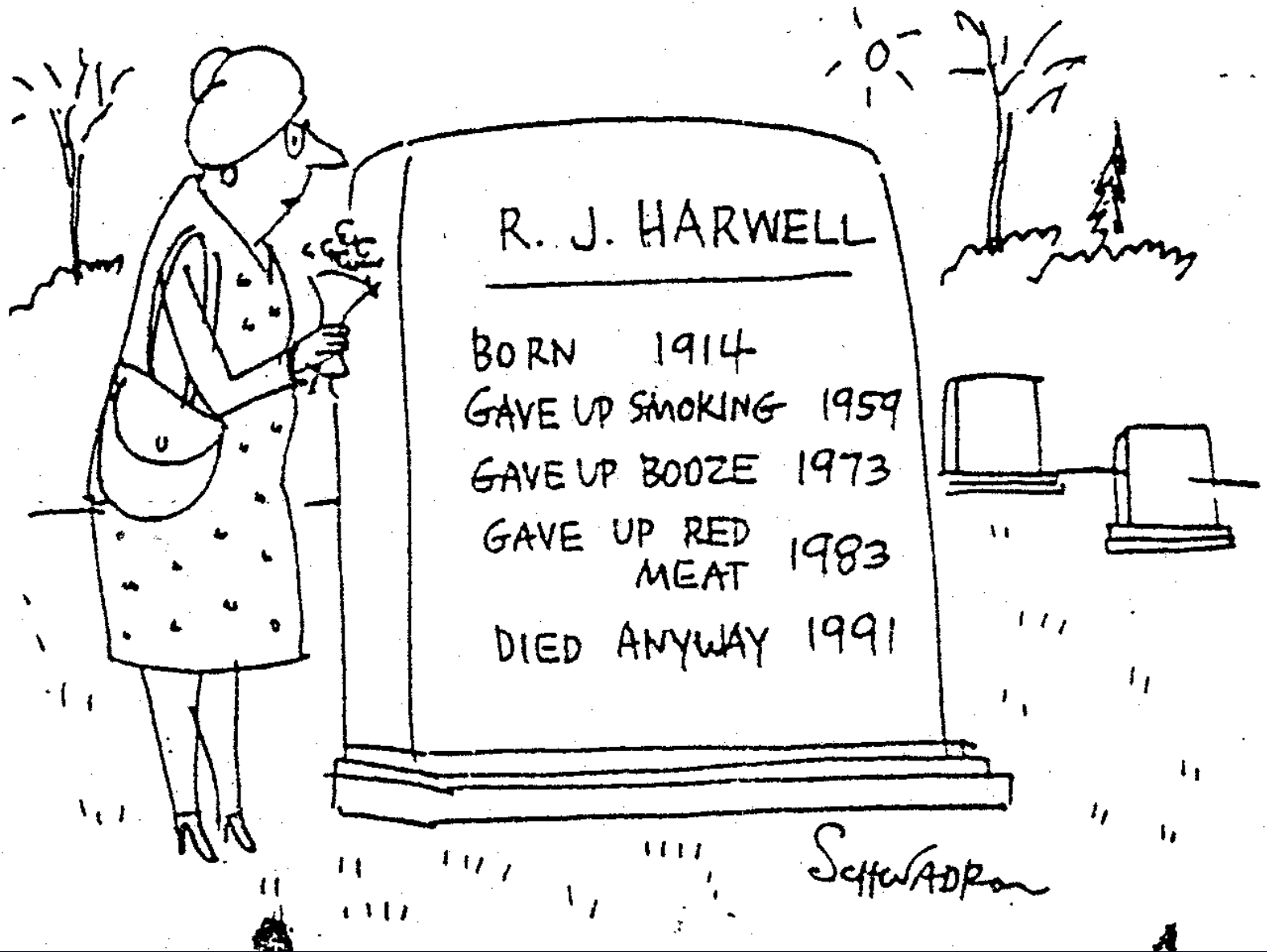


Aldosterone Decreases During Caloric Restriction and Weight Reduction



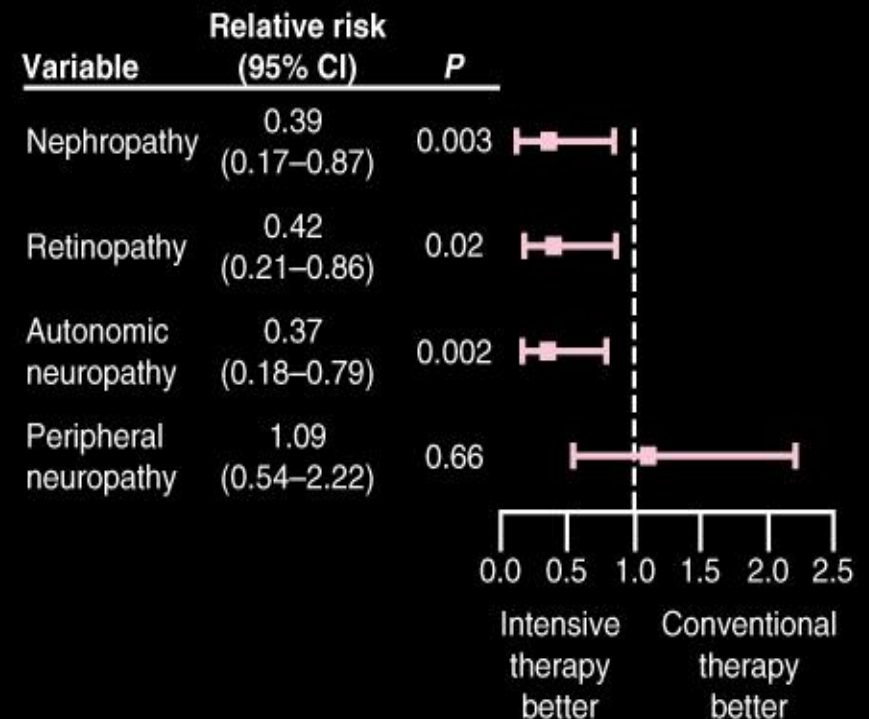
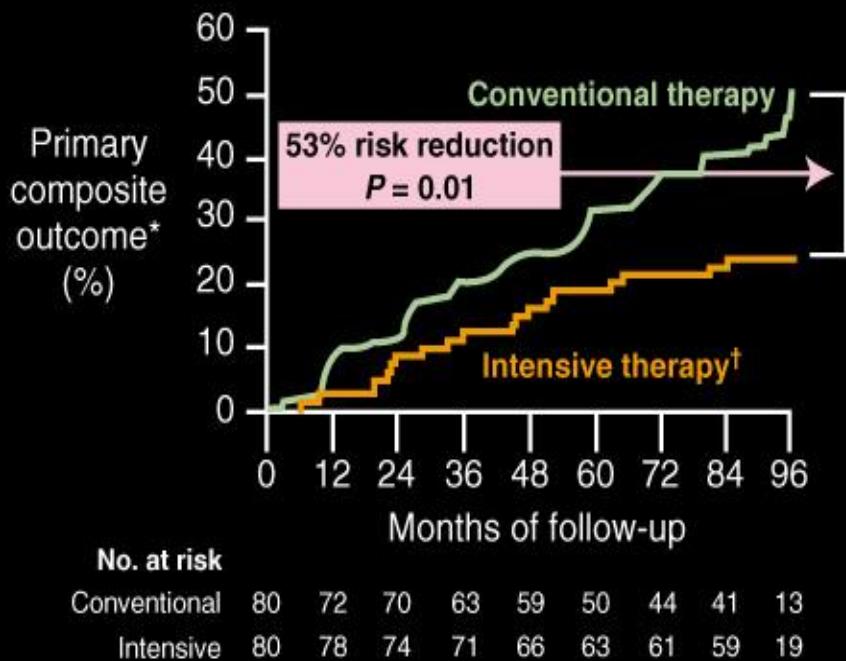
Mean Change in Blood Pressure





Steno-2: Effects of multifactorial intervention on macrovascular and microvascular outcomes

160 patients with type 2 diabetes and microalbuminuria



*CV death, MI, stroke, revascularization, amputation

[†]Total fat intake <30%, >30 min exercise 3–5x weekly, ACE inhibitor, aspirin, BP <130/80 mm Hg, total-C <175 mg/dL, TG <150mg/dL, A1c <6.5%

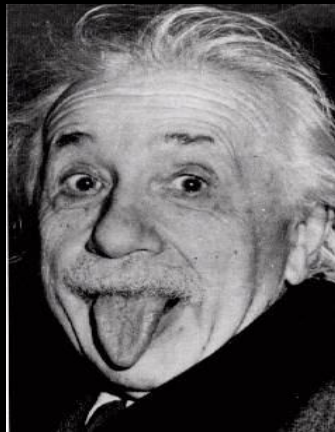
Gaede P, et al. *N Engl J Med.* 2003;348:383-393.

“Insanity:

Doing the same thing

over and over again

and expecting different results.”



Albert Einstein