The Optimal Treatment of Type 2 Diabetes: Life-Saving, Cost-Saving

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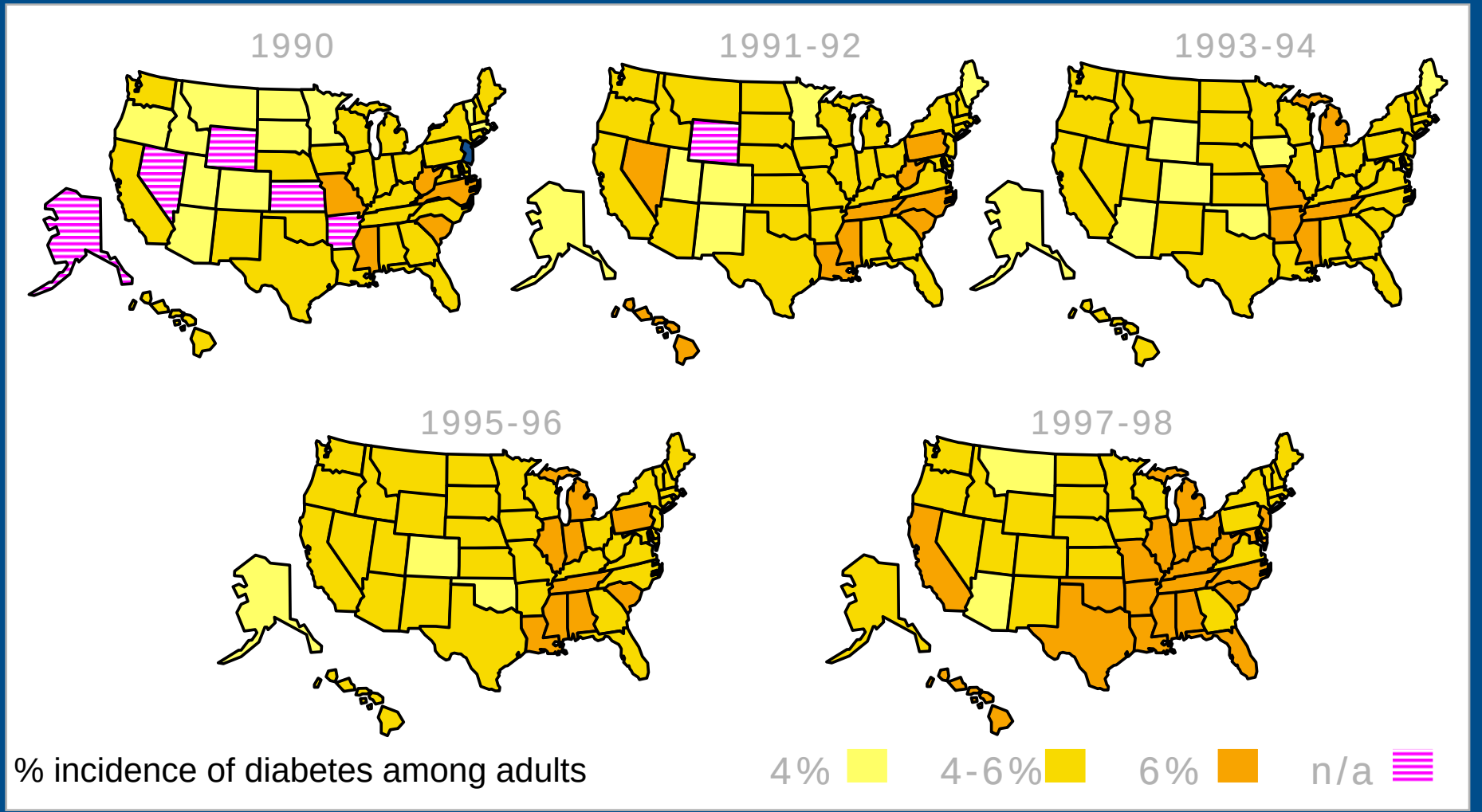
Diabetes Trends in the US, 1990-1998



Mokdad AH, et al. *Diabetes Care.* 2000;23:1278-83.

Prevention of Type 2 Diabetes: The Trials

- Tuomilehto J, et al. *N Eng J Med* 2001;344:1343-1350.
  - Lifestyle modification: 58% reduction in progression from IGT to DM
- Diabetes Prevention Research Group *N Eng J Med* 2002;346:393-403 (metformin or lifestyle modification)
  - Lifestyle group: 58% reduction in progression from IGT to DM
  - Metformin group: 31% reduction in progression from IGT to DM
- Buchanan, TA, et al. Troglitazone unpublished data.
  - 56% reduction in emergence of DM in former GDM patients
    - Effect was maintained for 8 months after drug was discontinued
- Chiasson, JL, et al. Acarbose. *Lancet in press.*
  - 36% reduction in progression from IGT to DM

Adapted from ADA and NIDDK. *Diabetes Care.* 2002;25:742-749.

Prevention of Type 2 DM: Recommendations

- Inform high-risk individuals of the benefits of weight loss and exercise
- Screening for IFG or IGT in:
  - Individuals ≥45 y/o, especially if BMI ≥ 25
  - Younger individuals with BMI > 25 and at least one risk factor
    - Family hx of T2DM
    - Past hx of gestational DM or child > 9 lbs.
    - Dyslipidemia, HTN, or ethnicity
- Screening process: part of office visit
  - FPG or 2-hr OGTT; confirmation of positive test
- Intervention: weight loss/exercise; f/up q 1-2 yrs for possible DM, ↓ other risk factors for CVD, routine use of preventive drug tx is not recommended

Diabetes Care in an HMO Setting: Frequency of Assessments in 12 Months

Test or examination	Percent of patients tested or examined	ADA standard
≥ 2 Primary care visits	79	≥2 visits/y
Glycated hemoglobin	44	1-4 tests/y
Fasting plasma glucose	35	4-6 tests/y
Urinary protein *or* serum creatinine	48	yearly
Documented foot exam	8	at every regular visit
Documented retina examination or referral	26	at least yearly
Total cholesterol	56	at least yearly
LDL cholesterol	31	at least yearly

Peters AL, et al. *Diabetes Care.* 1996;19:601-606.

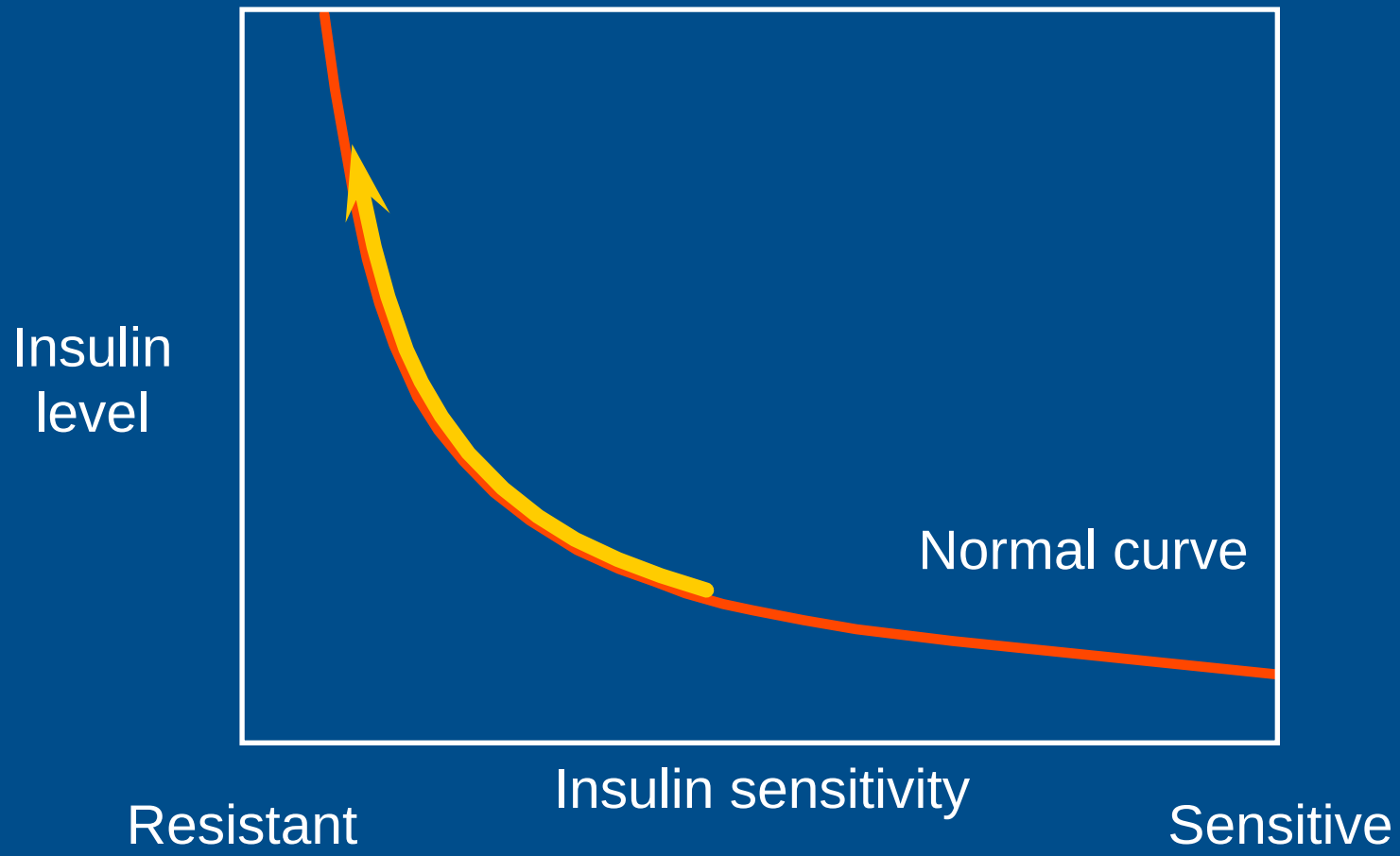
ADA and NCEP Goals for Patients With Diabetes

Biochemical index	Normal	Goal	Action suggested
Fasting/preprandial plasma glucose (mg/dL)	<110	90-130	<90 or >150
Bedtime plasma glucose (mg/dL)	<120	110-150	<110 or >180
Hemoglobin A_{1c} (%)*	4-6	<7	>8
Blood pressure (mm Hg)	<120/80	<130/80	>130/80
LDL-c cholesterol (mg/dL)	<100	<100	>100
HDL-c cholesterol (mg/dL)	40-60	>40	<40
Triglycerides (mg/dL)	<150	<150	>150

American Diabetes Association. *Diabetes Care*. 2000;22(Suppl 1):S23-S51.

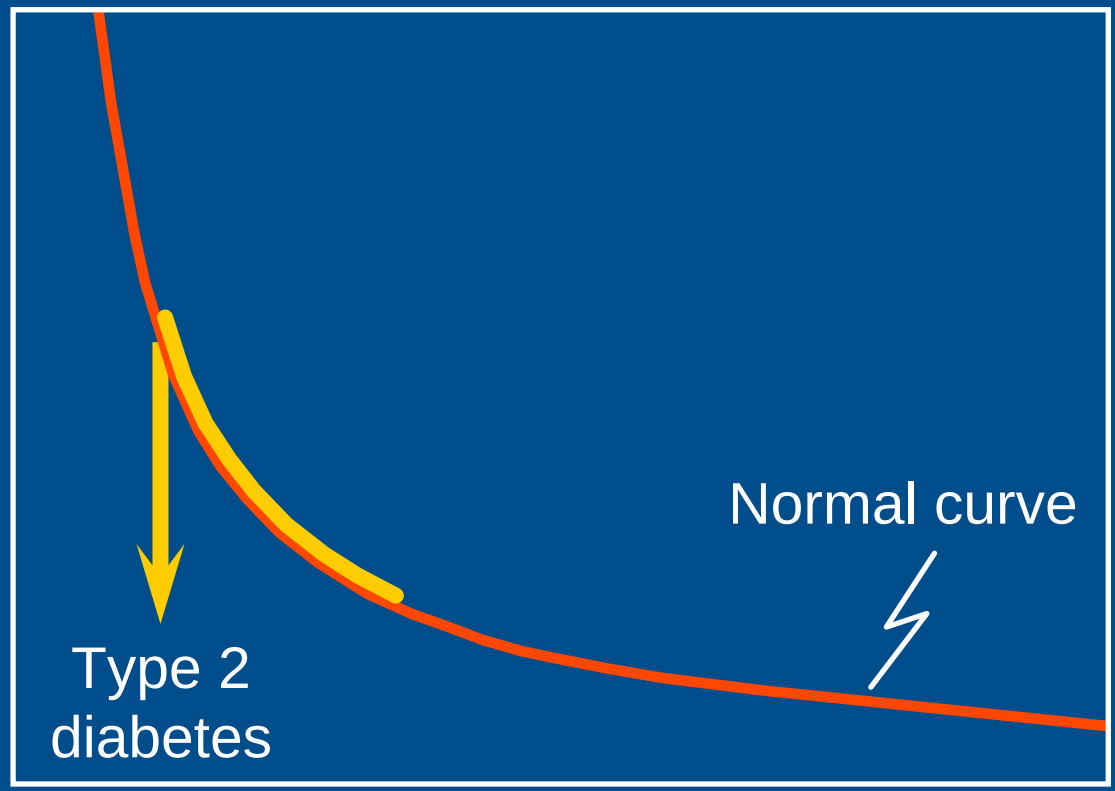
Insulin Resistance with Normal β Cells

‘Climbing the Curve’



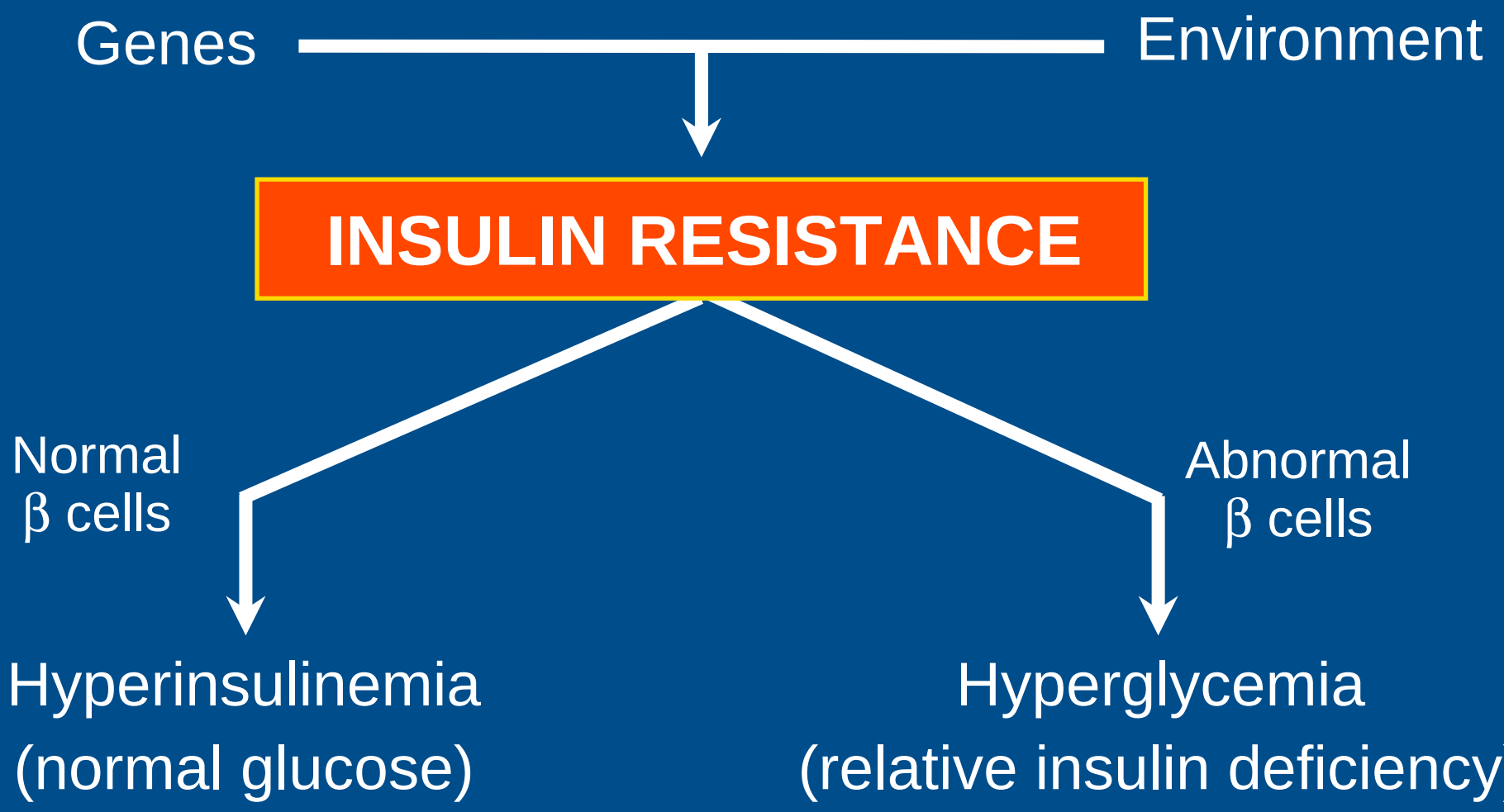
Pathogenesis of Type 2 Diabetes

‘Falling Off the Curve’



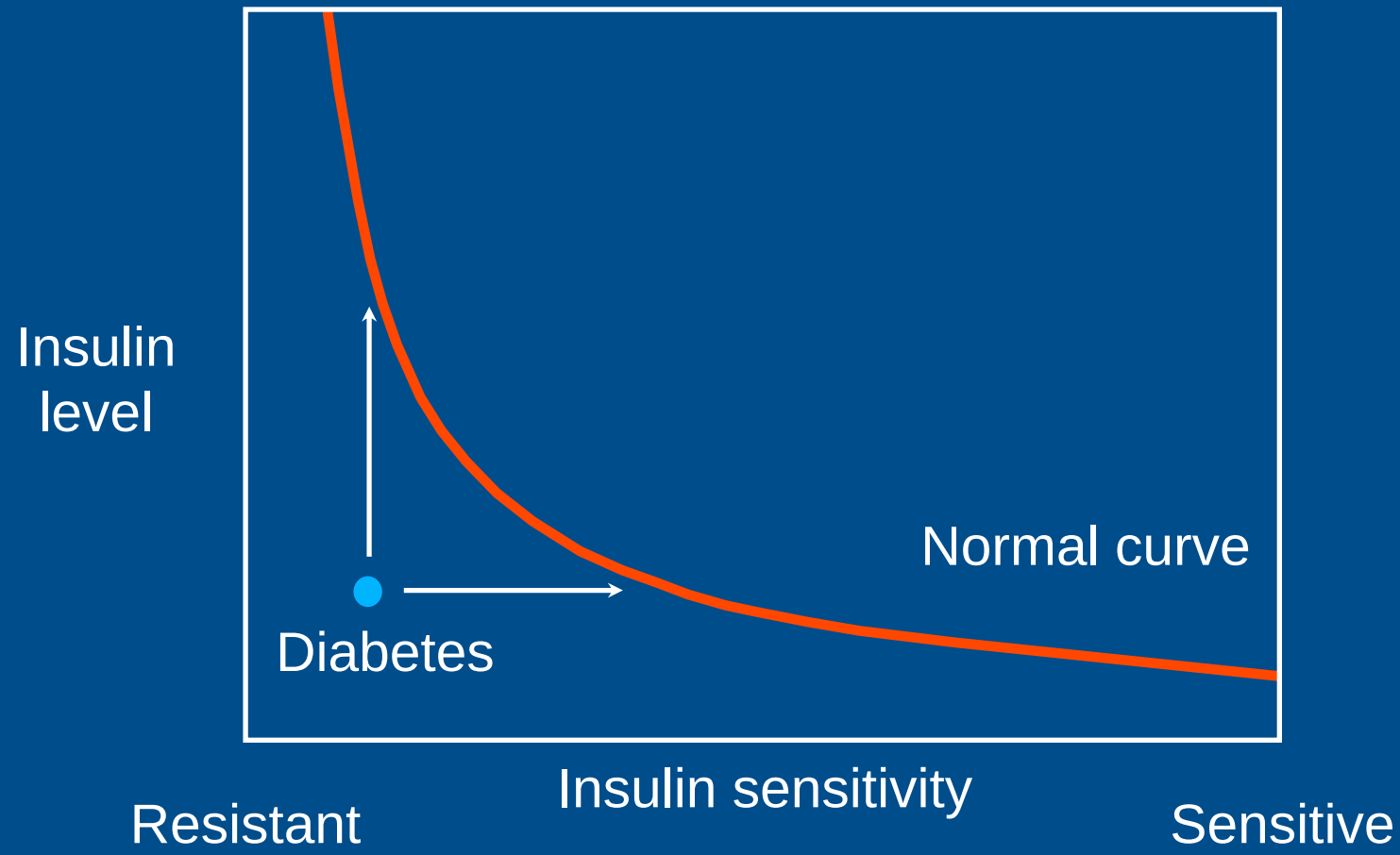
Bergman RN. *Diabetes*. 1989;38:1512-1527.

Response to Insulin Resistance: The Pancreatic β Cell

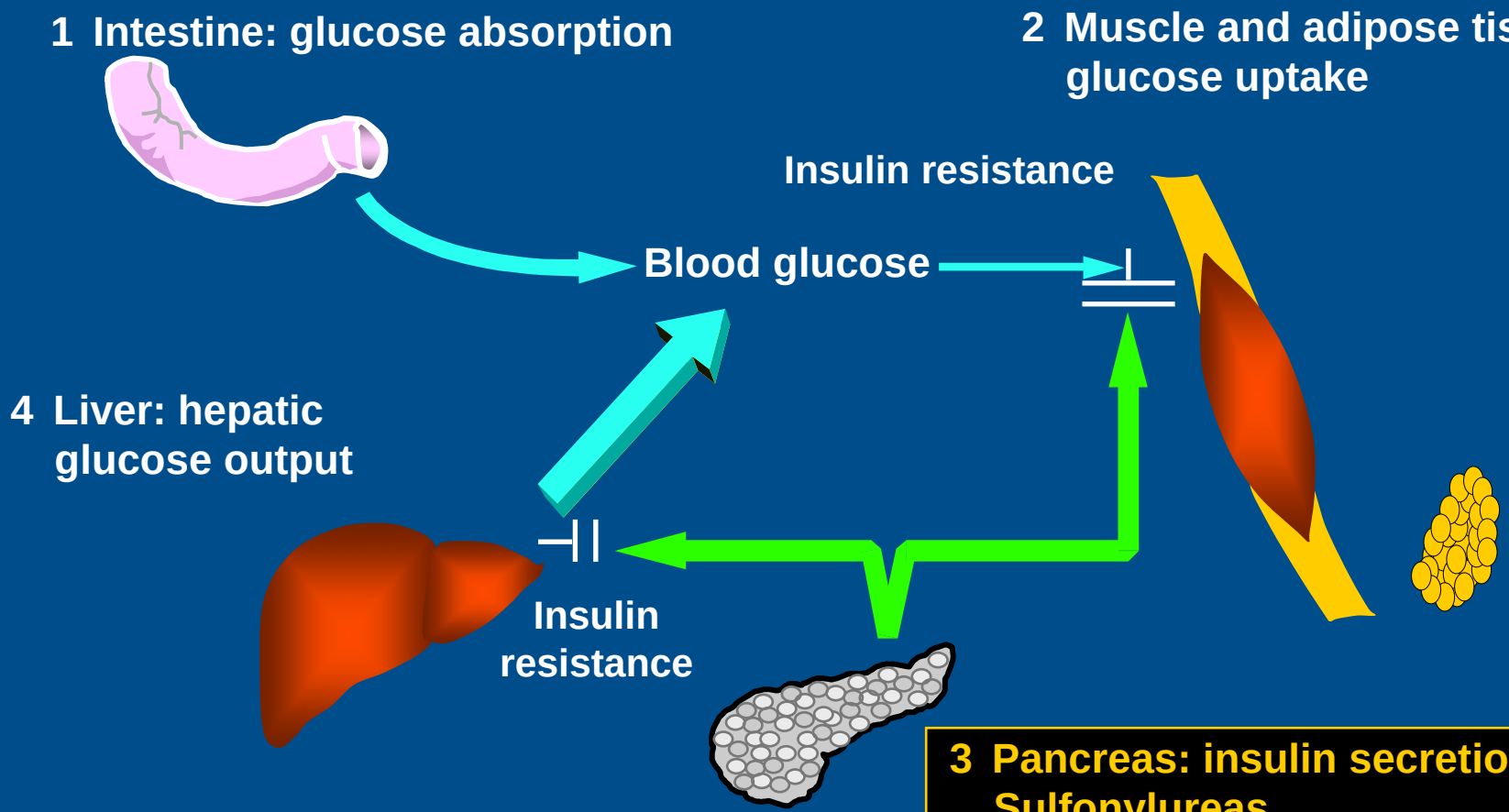


Treatment of Type 2 Diabetes

‘Getting Back on the Curve’

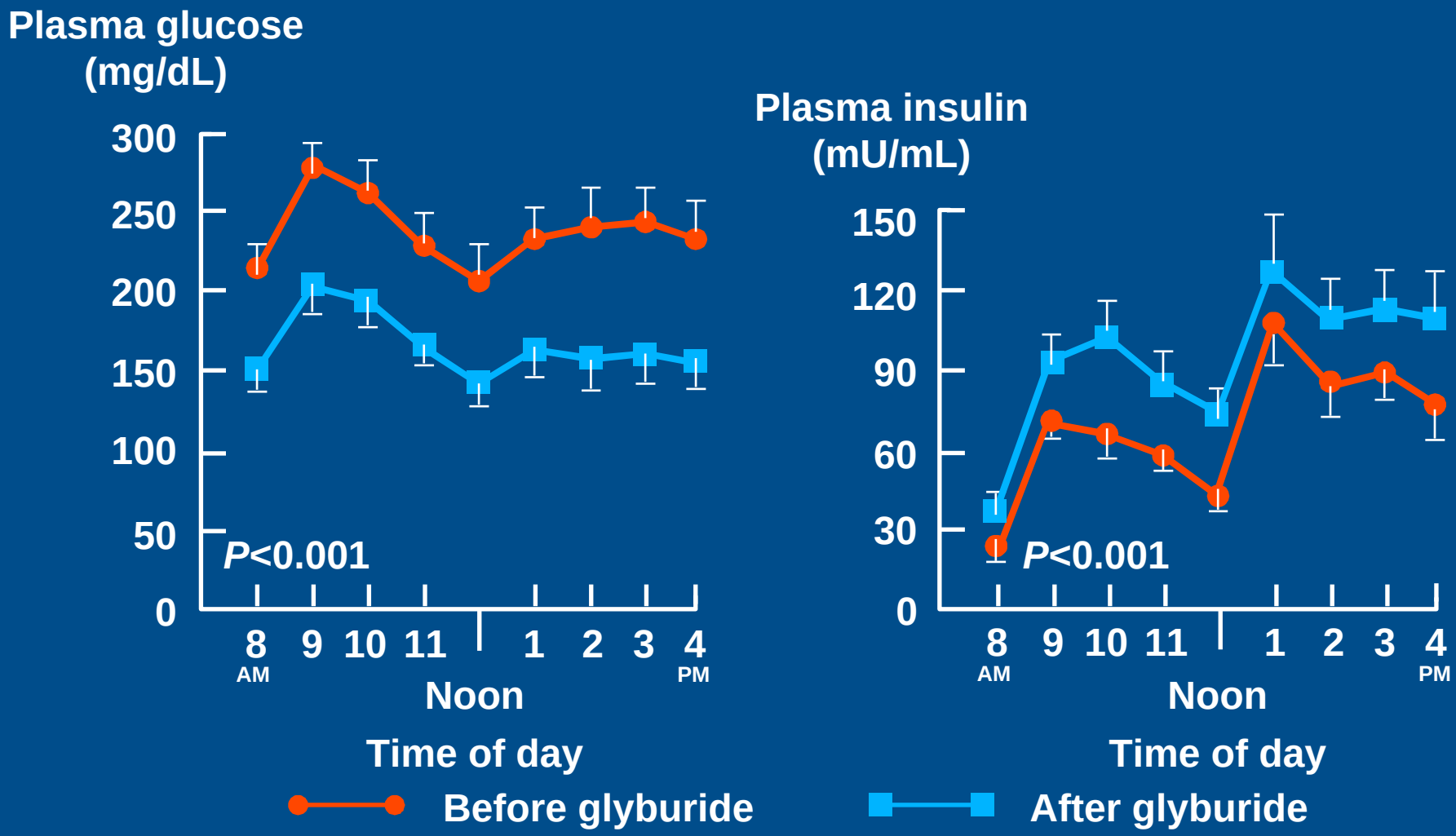


Sulfonylureas: Mechanism of Action



DeFronzo RA. *Diabetes.* 1988;37:667-687.
Lebovitz HE. In *Joslin's Diabetes Mellitus*. 1994:508-529.

Glyburide Monotherapy: Effect on Plasma Glucose and Insulin Levels



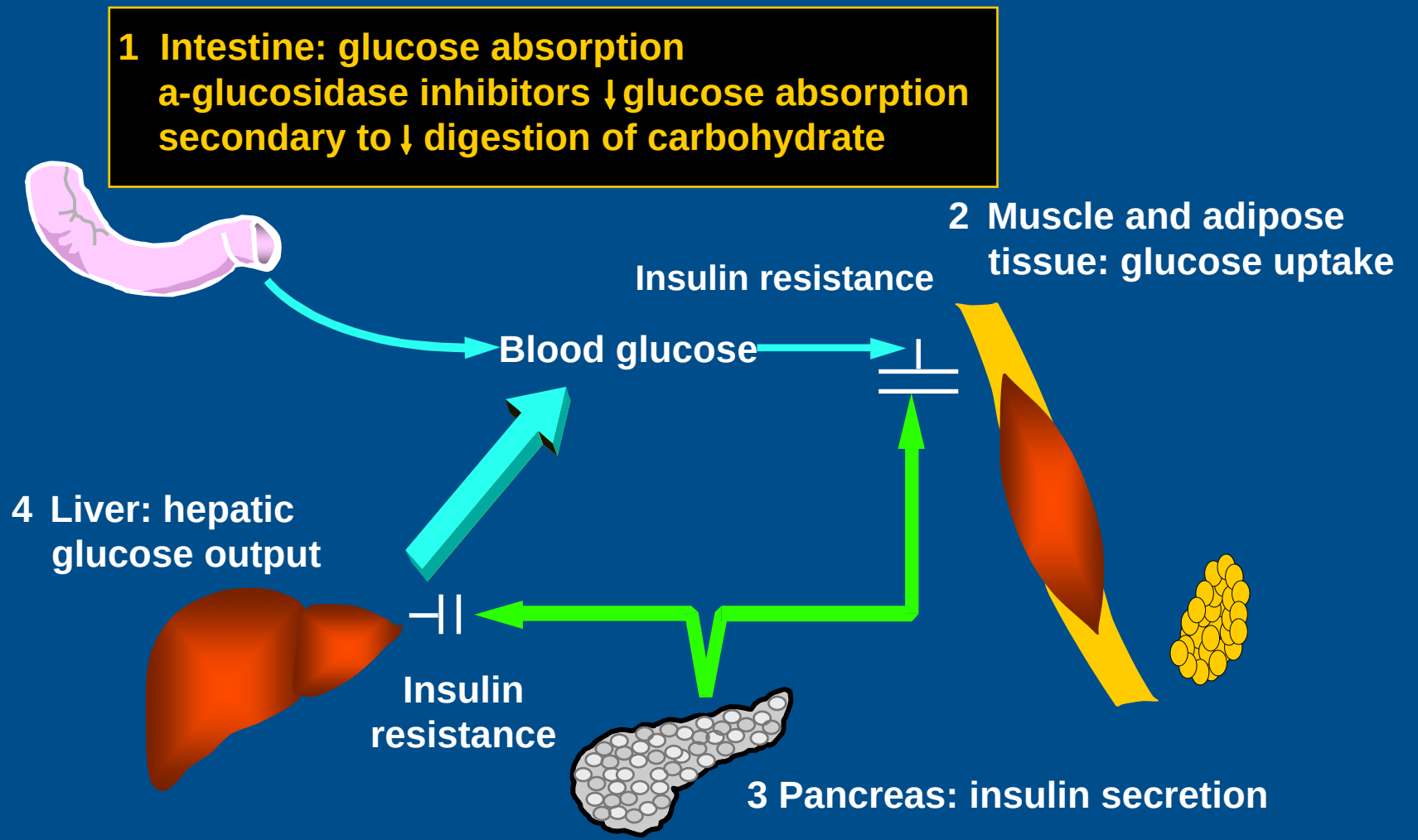
Jeng C-Y. *Diabet Med.* 1988;6:303-308.

Sulfonylureas: Prescribing Considerations

- Potential risk of hypoglycemia; predisposing factors include:
  - age
  - restricted carbohydrate intake
  - renal and hepatic dysfunction
  - potentiating effects of alcohol and drugs in common use
- Hypoglycemic action of SUs is more likely in the elderly, debilitated, or malnourished patients
- May increase hyperinsulinemia and weight gain
- Long-term failure in 30% of patients

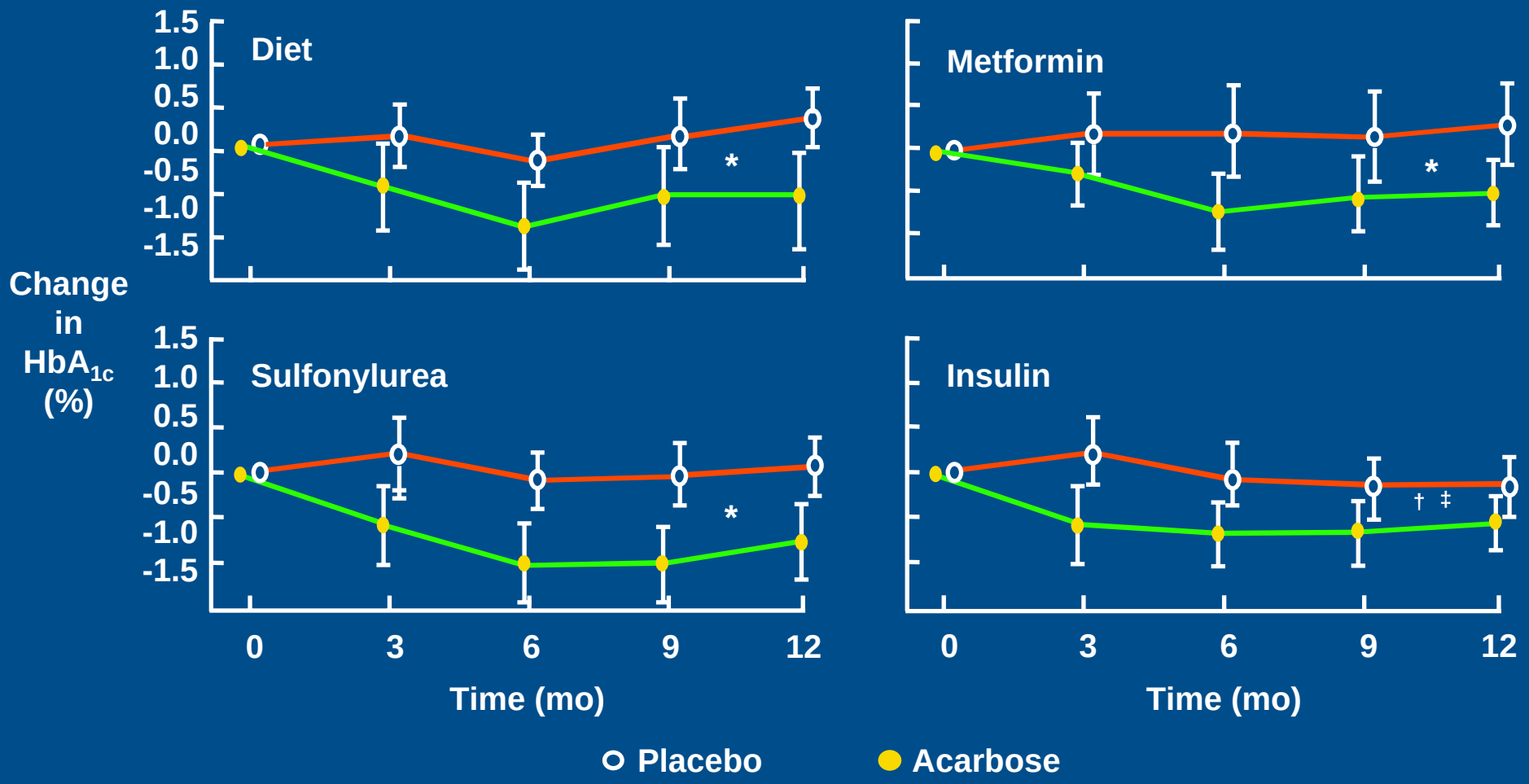
UKPDS Group. *BMJ.* 1995;310:83-88.
Physicians' Desk Reference®, 1998.

α-Glucosidase Inhibitors: Mechanism of Action



Amatruda JM. In: *Diabetes Mellitus*. 1996.

Acarbose: Effect on HbA_{1c}



*P<0.010; †P=0.007; ‡P=0.01

Chiasson J-L et al. *Ann Intern Med*. 1994;121:928-935.

Disadvantages of Acarbose

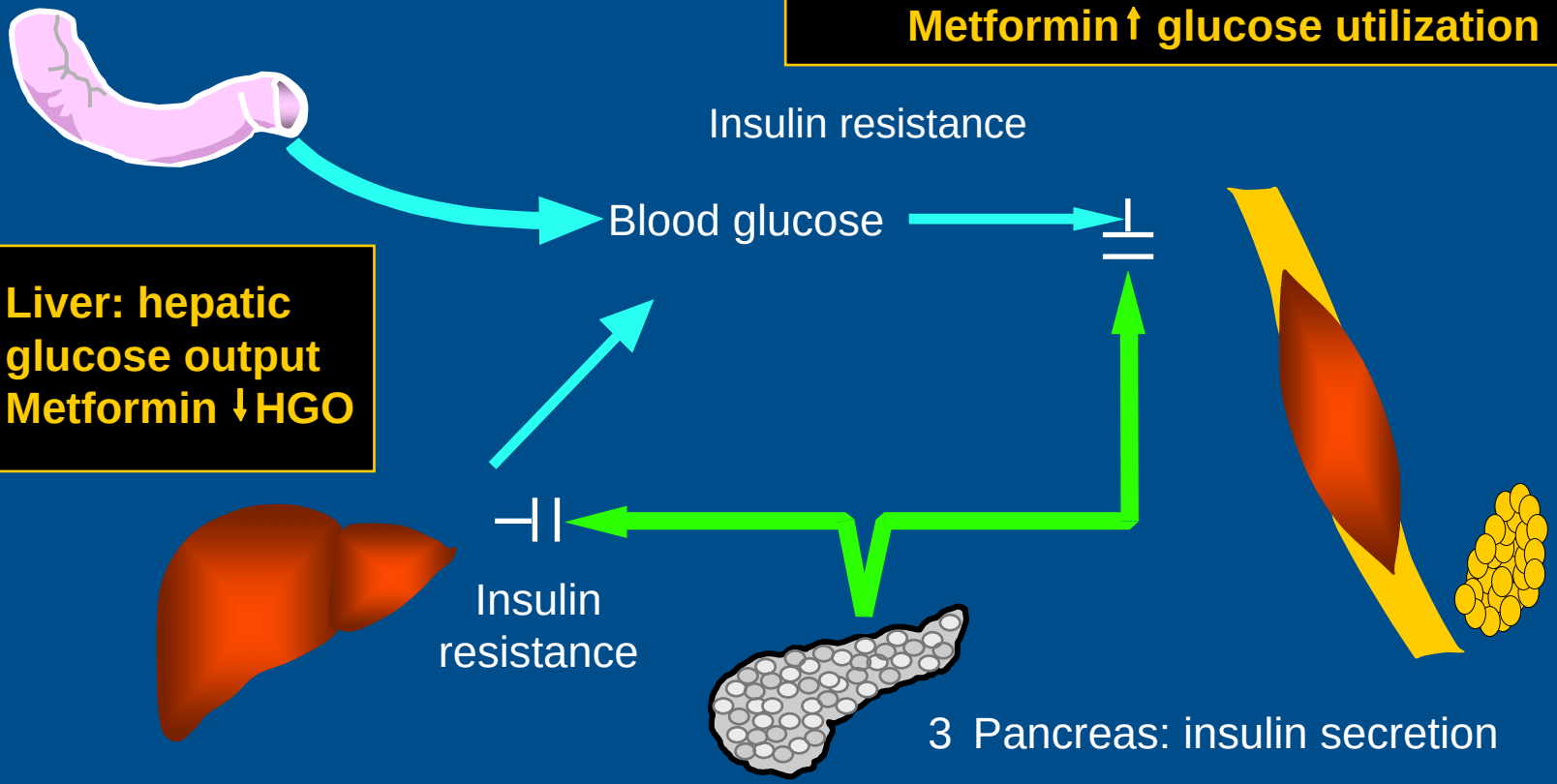
- GI side effects
  - flatulence (80%), diarrhea (27%), nausea (8%), vomiting (7%)
  - start with low doses (25 mg with each meal), titrate slowly to therapeutic range
- Elevations in serum aminotransferase may occur, particularly with doses >150 mg/day; hyperbilirubinemia rarely occurs
  - serum aminotransferase measurement every 3 months during first treatment year
  - acarbose in combination with sulfonylurea or insulin may be associated with hypoglycemia; if hypoglycemia occurs, treat with glucose PO or IV

Amatruda JM. In: *Diabetes Mellitus.* 1996.

Metformin: Mechanism of Action

1 Intestine: glucose absorption

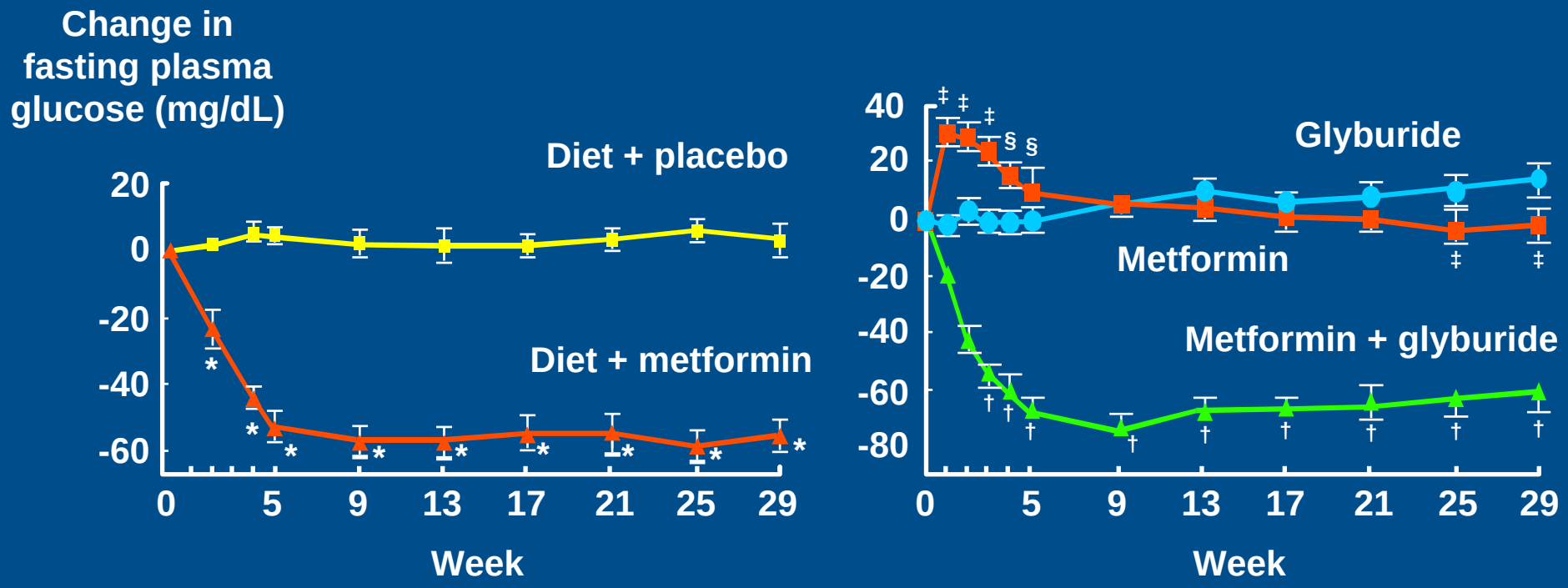
2 Muscle and adipose tissue: glucose uptake
Metformin ↑ glucose utilization



4 Liver: hepatic glucose output
Metformin ↓ HGO

DeFronzo RA et al. *J Clin Endocrinol Metab.* 1991;73:1294-1301.

Effects of Metformin Monotherapy or Combination Therapy With Glyburide



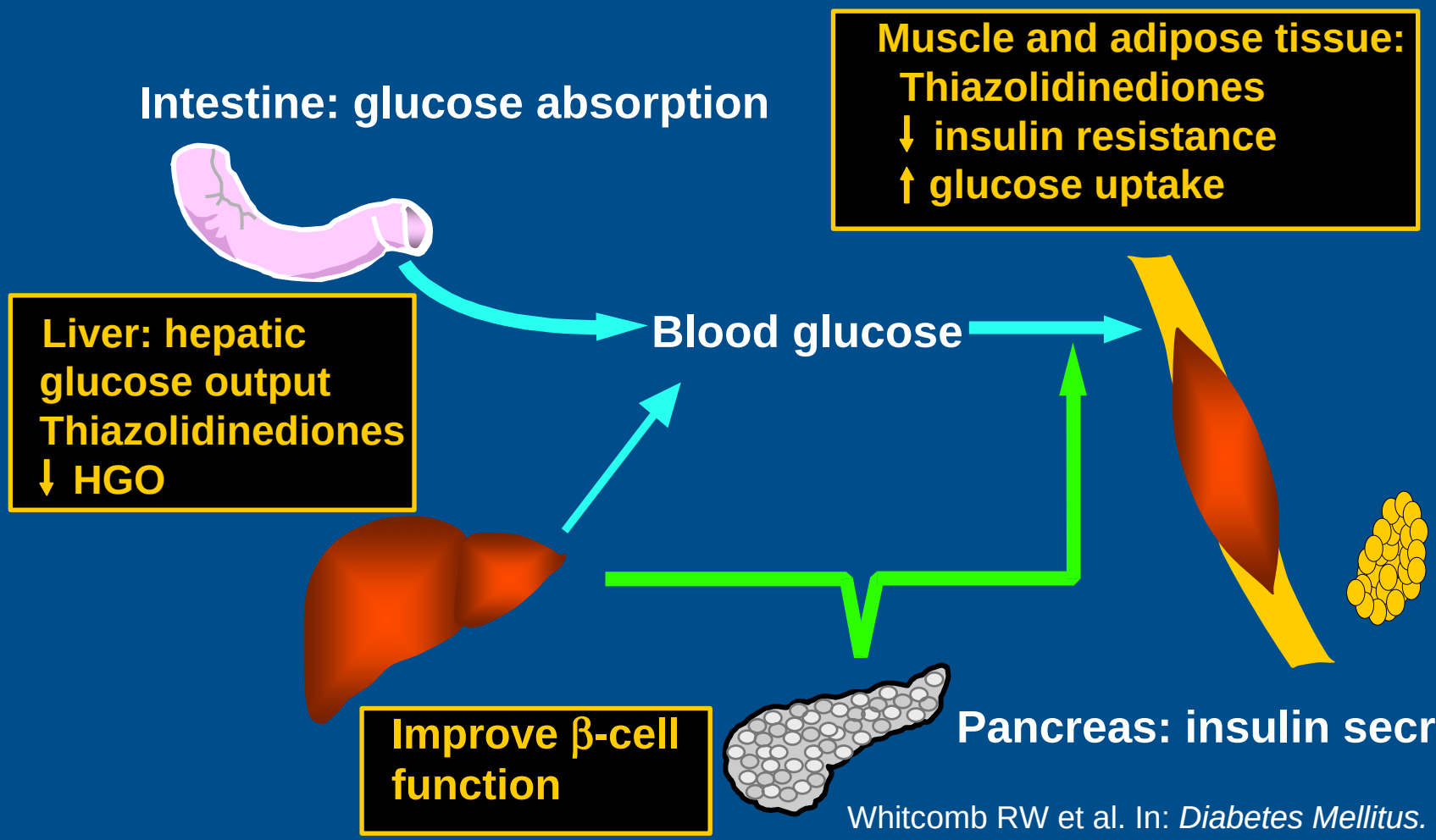
*P<0.001
†P<0.001 glyburide-metformin vs glyburide
‡P<0.001 metformin vs glyburide
§P<0.01 metformin vs glyburide

DeFronzo RA et al. *N Engl J Med.* 1995;333:541-549.

Metformin Summary

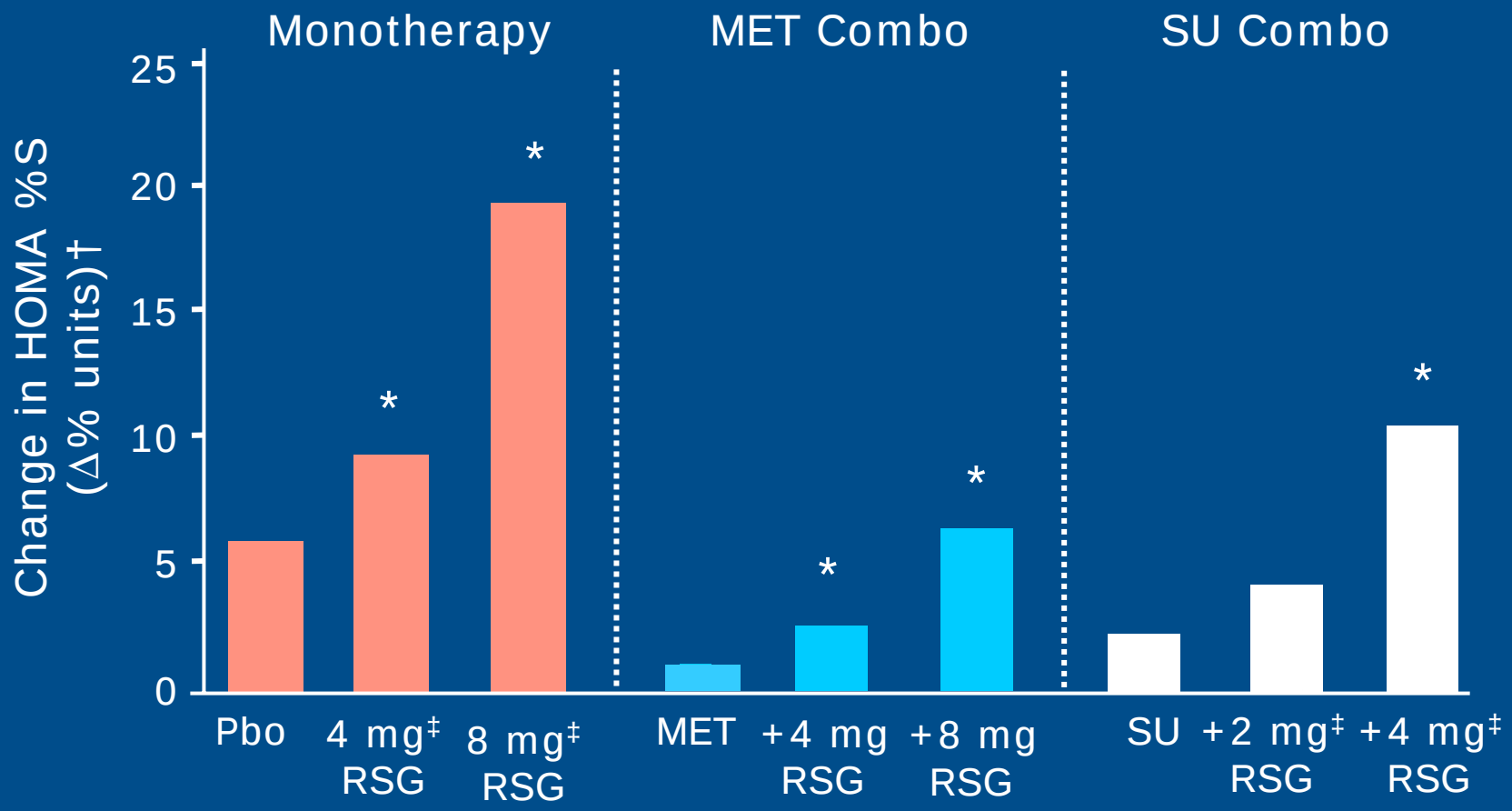
- Similar glycemic control as sulfonylureas without stimulating insulin secretion
- Does not increase weight, reduces lipid levels
- Does not produce hypoglycemia when used alone
- Most common side effects are GI, which are generally mild to moderate and self-limiting
- Adherence to prescribing guidelines is important to minimize risk of lactic acidosis
- Secondary failure rate similar to sulfonylureas

Thiazolidinediones: Mechanism of Action



Whitcomb RW et al. In: *Diabetes Mellitus.* 1996.
Cavaghan MK et al. *J Clin Invest*. 1997;100:530-537.
Ehrmann DA et al. *J Clin Endocrinol Metab*. 1997;82:2108-2116.

HOMA %S: Insulin Sensitivity Index



*Significant vs baseline; †median change from baseline at week 26; ‡given in divided doses.

Studies 011, 094, 015. Data on file. GlaxoSmithKline.

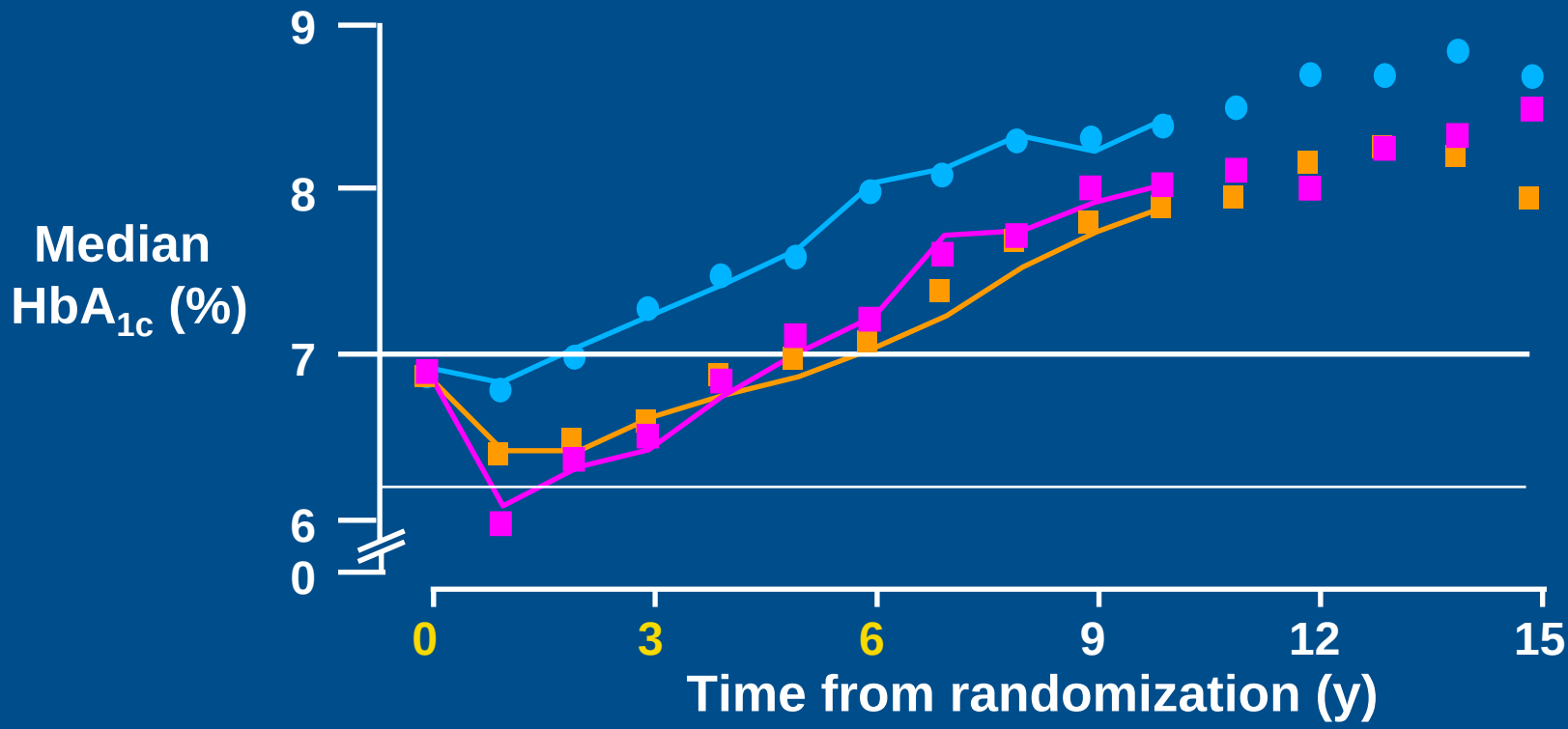
Rosiglitazone Efficacy Data

	Mean Change From Baseline	
	HbA_{1c} (%)	FPG (mg/dL)
Monotherapy[1]		
Rosiglitazone (4 mg bid)	-0.7	-55
Rosiglitazone (8 mg qd)	-0.3	-42
Combination therapy		
Rosiglitazone (4 mg bid) + sulfonylurea[2]	-0.9	-38
Rosiglitazone (4 mg bid) + insulin[3*]	-1.2	-44
Rosiglitazone (8 mg qd) + metformin[4]	-0.8	-48

*Not an FDA-approved use.

1. Rosiglitazone Package Insert.
2. Gomis R et al. *Diabetes*. 1999;48(suppl 1):A63. Abstract 0266.
3. Raskin P et al. *Diabetes*. 1999;48(suppl 1):A94. Abstract 0404.
4. Fonseca VA et al. *JAMA*. 2000;283:1695-1702.

UKPDS Results: Treatment With SU or Insulin vs Conventional Therapy

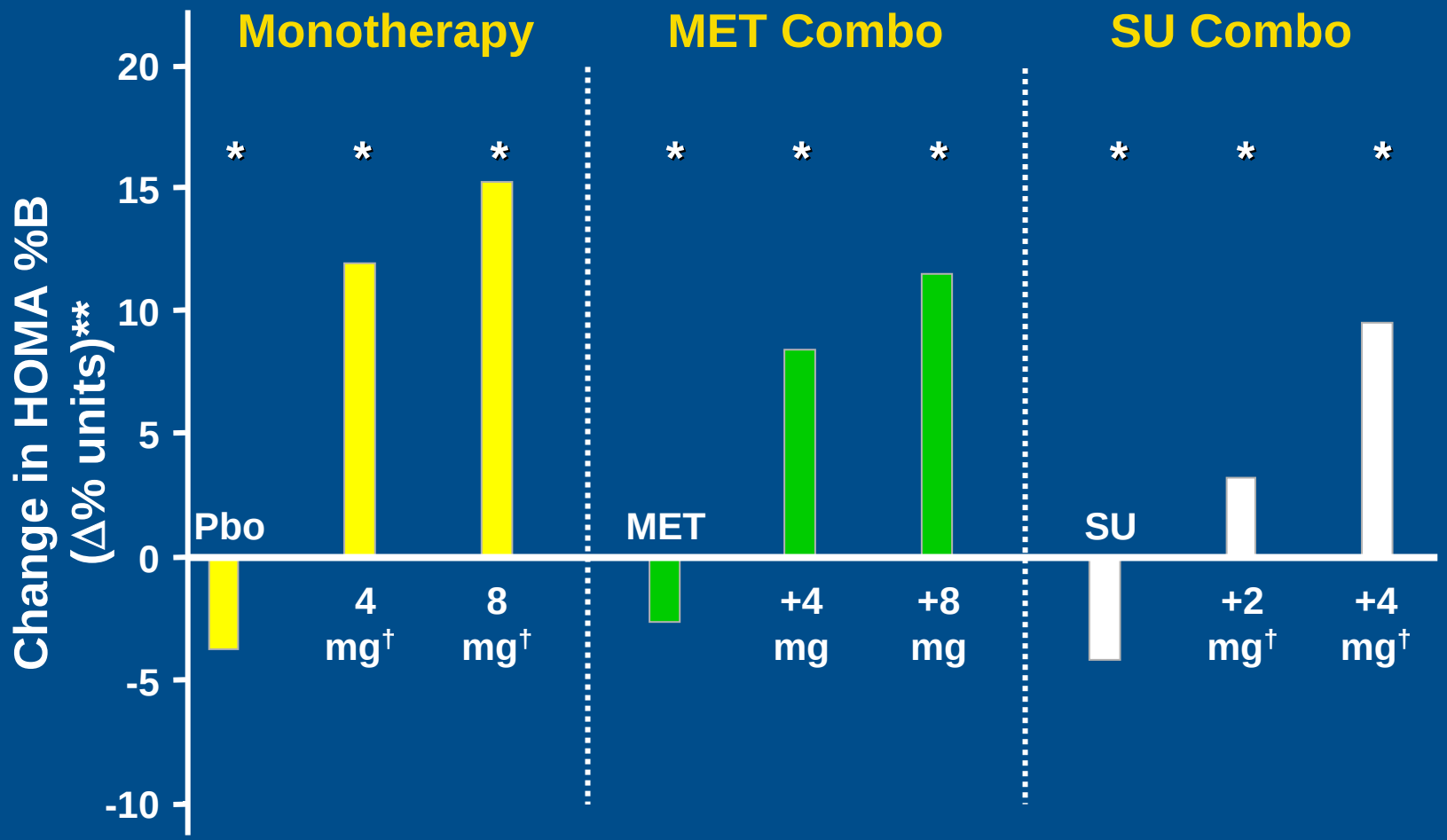


Patients followed for 10 years
- Conventional
- Insulin
- Glibenclamide (glyburide)

All patients assigned to regimen
- Conventional
- Insulin
- Glibenclamide (glyburide)

UKPDS Group. *Lancet.* 1998;352:837-853.

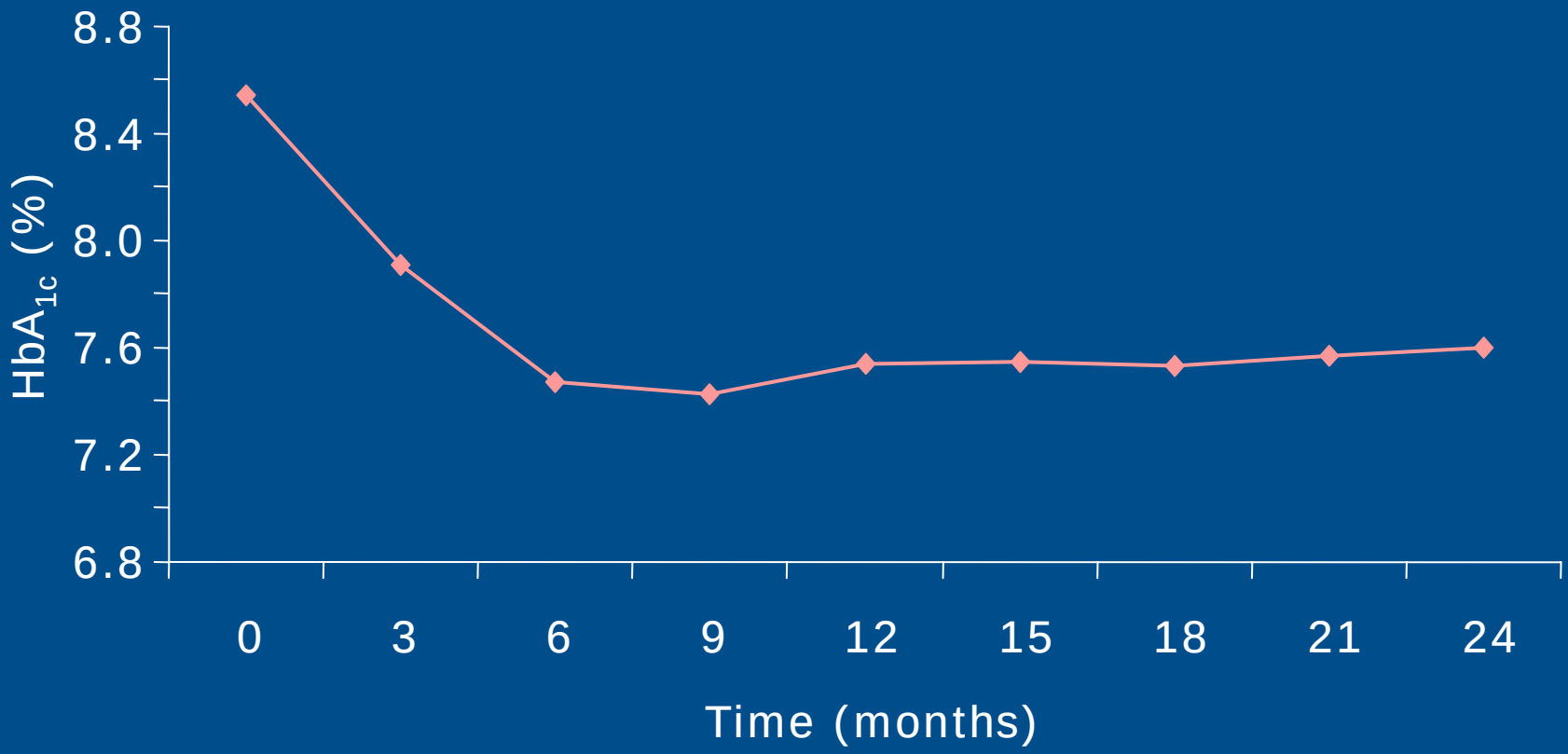
HOMA %B: Index β-cell Function



*Significant vs baseline; **Median change from baseline at week 26; †Given in divided doses; Data on file.

Long-term Rosiglitazone Monotherapy (HbA_{1c})

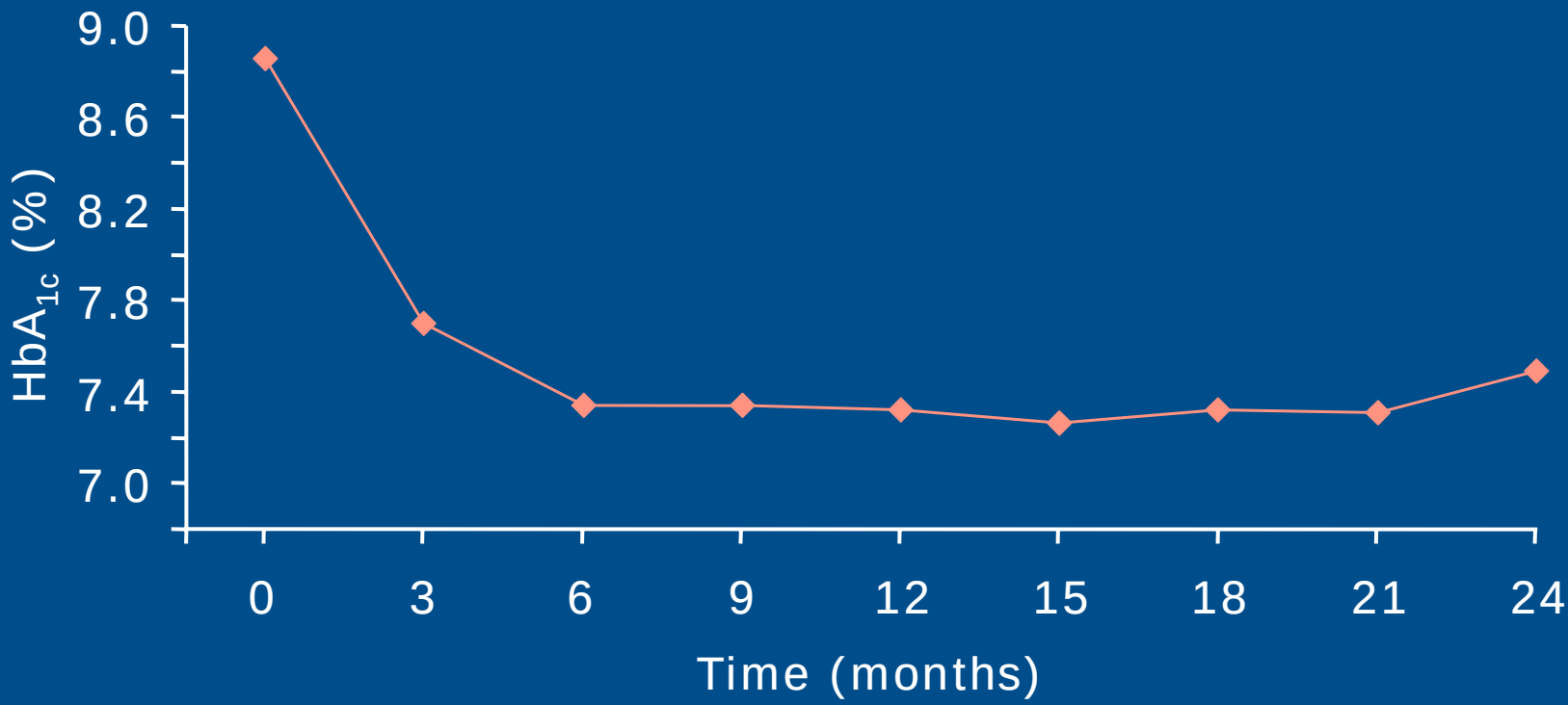
Rosiglitazone 8 mg/day (n=266)



Studies 011, 024, 084, 105. Data on file. GlaxoSmithKline.

Long-term Rosiglitazone + Metformin (HbA_{1c})

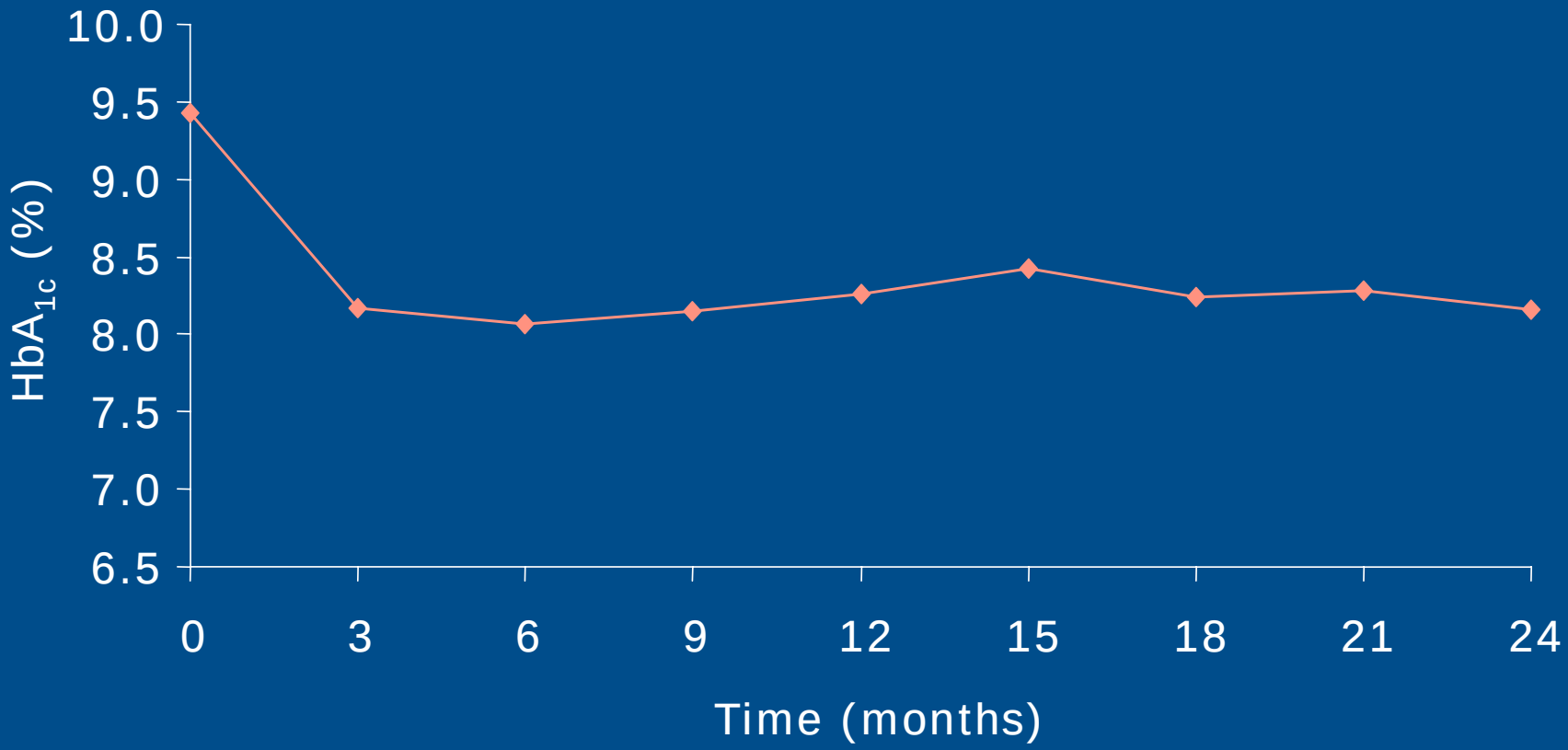
Rosiglitazone 8 mg/day + Metformin (n=100)



Study 093 and open-label extension (113). Data on file. GlaxoSmithKline.

Long-term Rosiglitazone + SU (HbA_{1c})

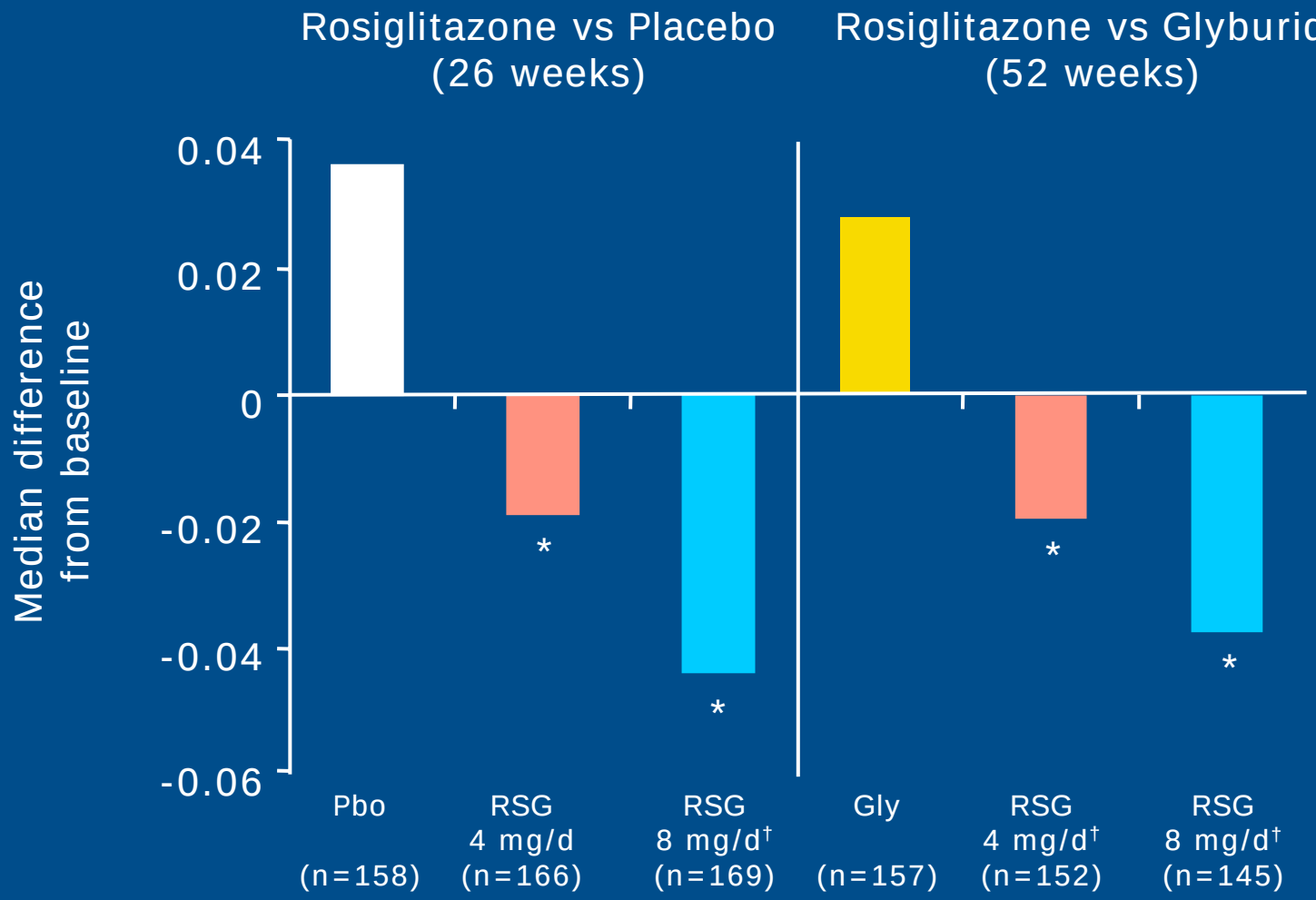
Rosiglitazone 4 mg* + SU (n=76)



*Given in divided doses.

Study 079 and open label extension (112). Data on file. GlaxoSmithKline.

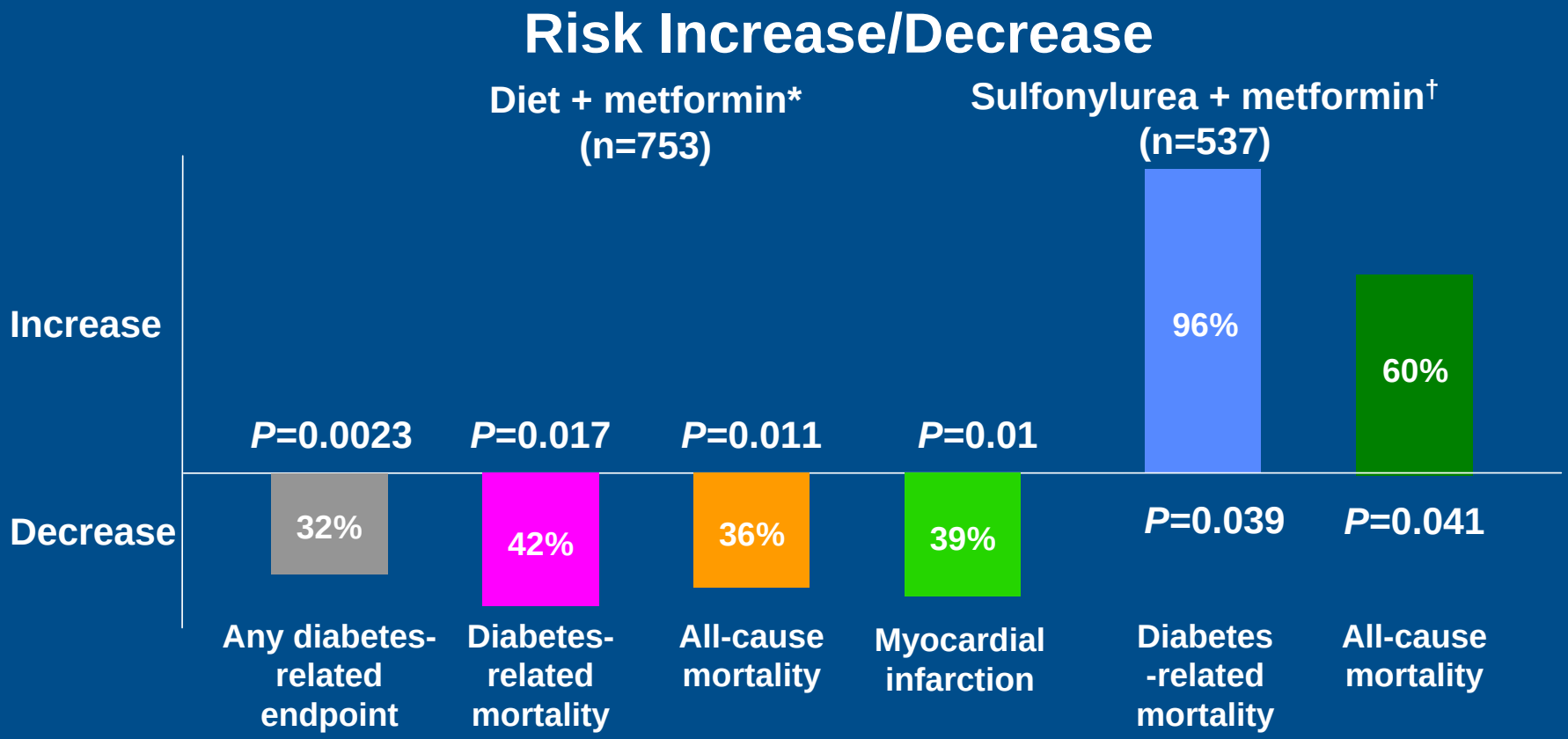
Rosiglitazone Improves Proinsulin:Insulin Ratios



*Significant difference from placebo or glyburide.
†Given in divided doses.

Porter LE et al. *Diabetes* 2000;49(suppl 1):A122 (Abstract 495).

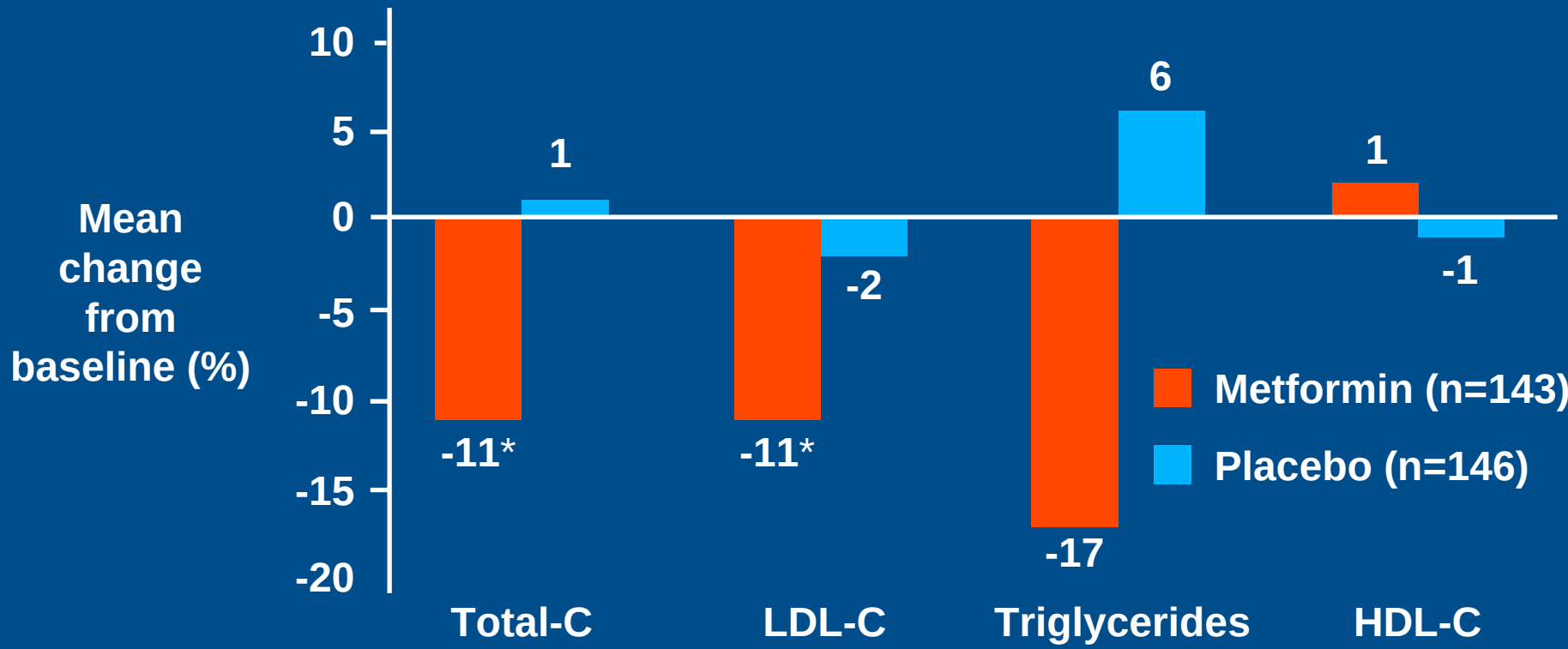
UKPDS Results of Intensive Therapy: Metformin



***Risk reduction compared with conventional therapy.**
† Risk increase compared with sulfonylurea alone.

American Diabetes Association. *Diabetes Care*. 1999;22(suppl 1):S27-S31.
UKPDS Group. *Lancet*. 1998;352:854-865.

Metformin Monotherapy: Effects on Lipids



*P<0.05 vs placebo

DeFronzo RA et al. *N Engl J Med.* 1995;333:541-549.

Lipid Effects: Rosiglitazone

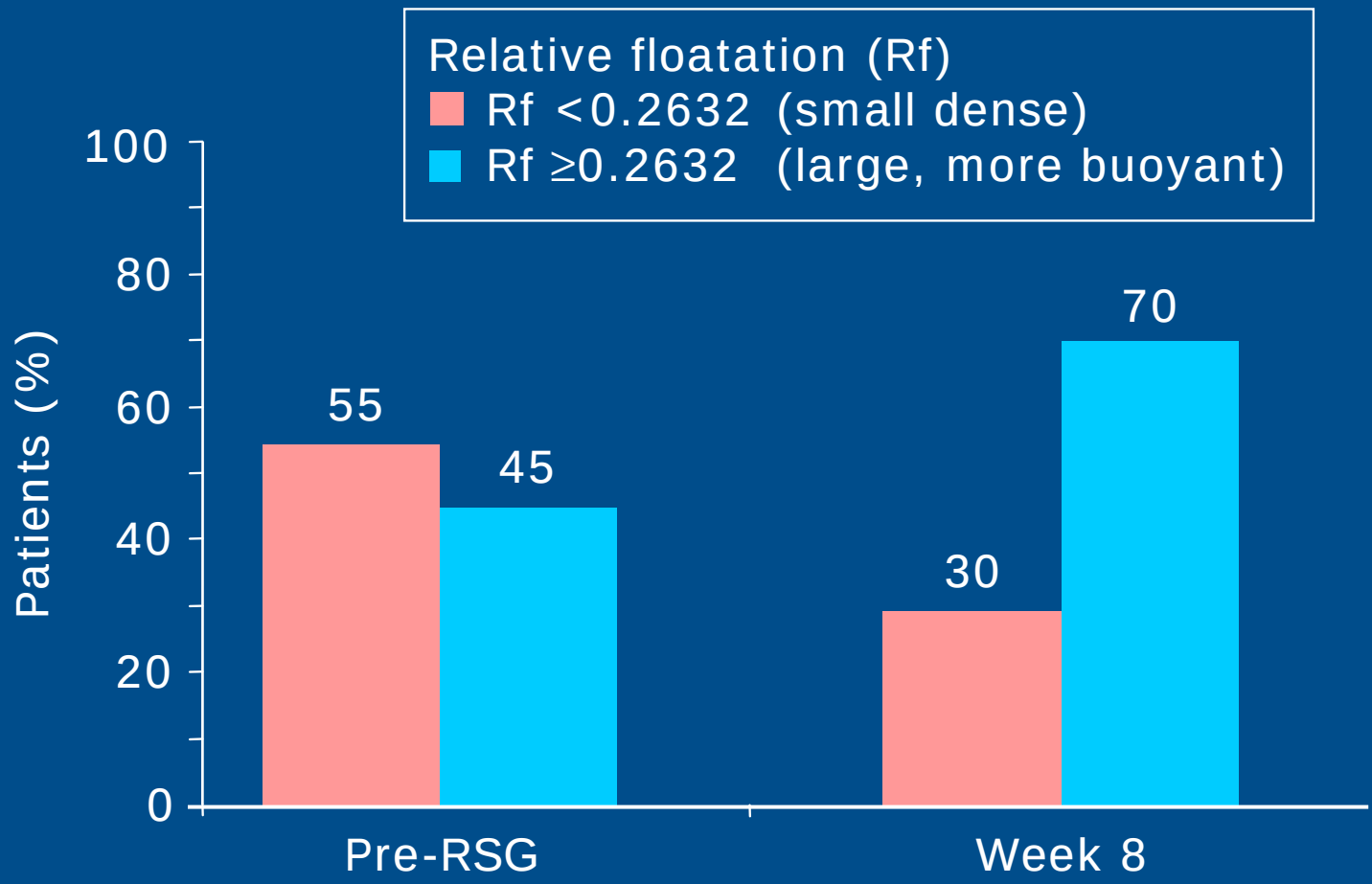
	% Change in Lipid Levels From Baseline		
	TG	LDL-C	HDL-C
Rosiglitazone 8 mg/d monotherapy[1]			
Placebo-controlled (26 weeks) —	Variable*	↑19%†‡	↑12%†‡
Glyburide-controlled (52 weeks) —	Variable*	↑12%†‡	↑19%†‡
Rosiglitazone 8 mg/d + metformin[2]	↓0.1%	↑18%§	↑13%§
Rosiglitazone + sulfonylurea[1]	↑16%		

* Generally not statistically significant from placebo or glyburide controls.
† Statistically significant; *P* value not provided.
‡ Mean percent change.
§ Median percent change; *P*<0.0001.

Pattern of LDL-C and HDL-C changes generally similar to those seen with monotherapy and rosiglitazone + metformin

1. Rosiglitazone package insert.
2. Fonseca VA et al. *JAMA*. 2000;283:1695-1702.

Rosiglitazone Treatment Improves LDL Particle Density Phenotype



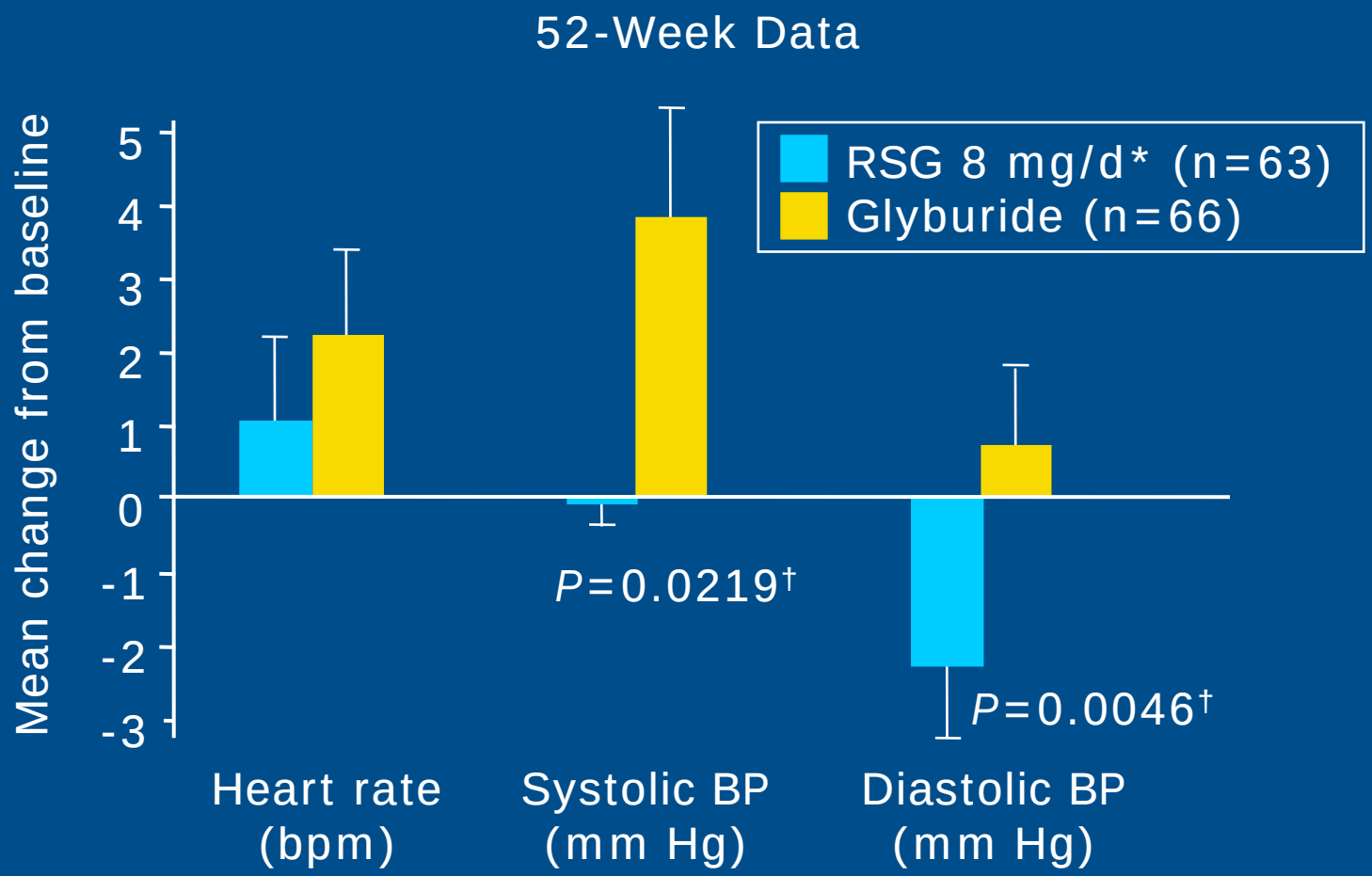
Study 108. Data on file. GlaxoSmithKline.

60.4% reduction

in lesion area

Collins A., et al. Diabetes 2001, 50(Suppl 2): 292

Effect of Rosiglitazone on 24-Hour Ambulatory Blood Pressure

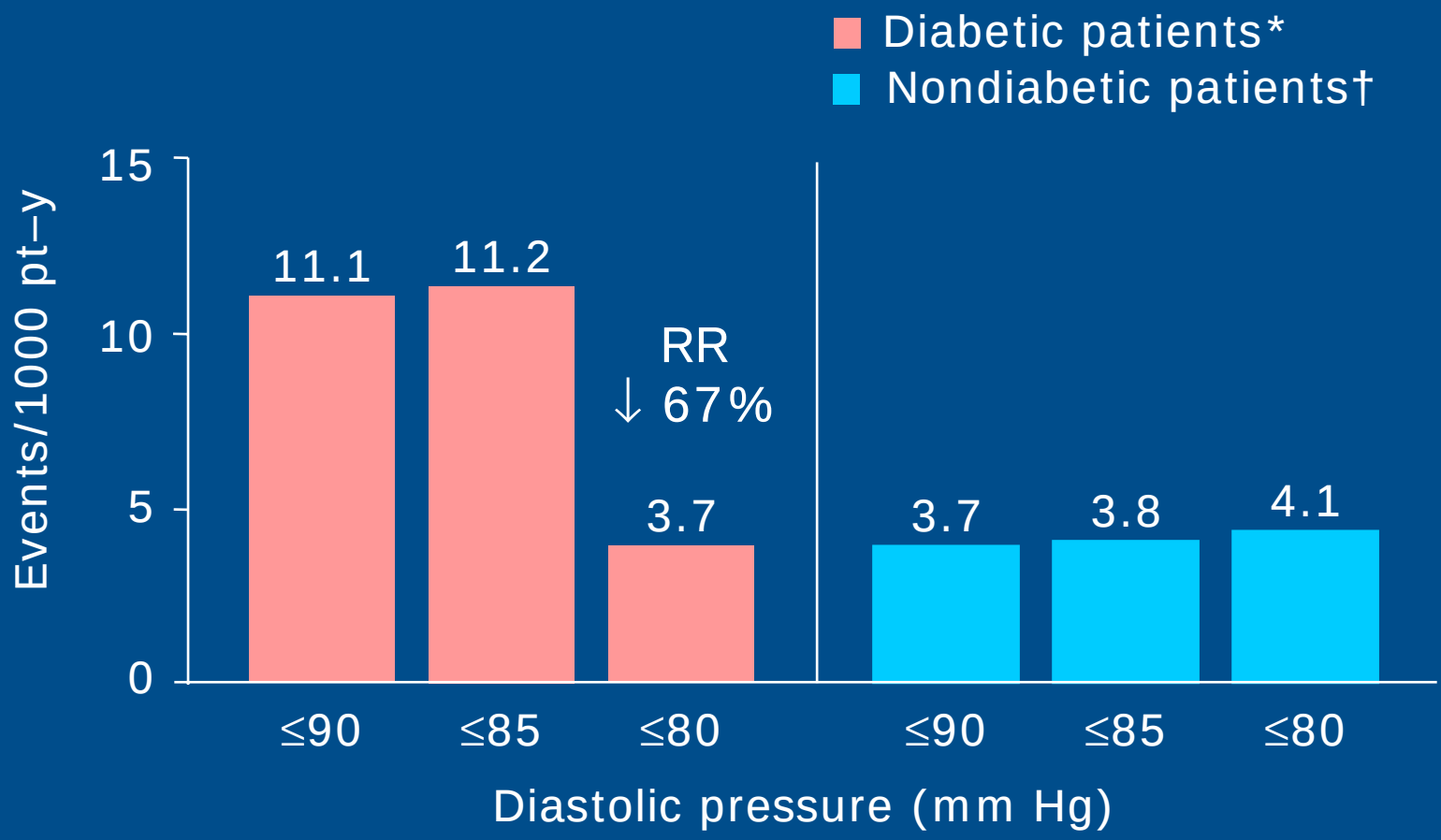


*Given in divided doses; †Comparison with glyburide; 080/all randomized [OC] population.

Data on file. GlaxoSmithKline. Bakris et al. *Diabetes* 2000;49(suppl 1):A96 (Poster 388P).

HOT (Hypertension Optimal Treatment) Trial

Effect of Diastolic BP Control on Cardiovascular Mortality at 4 Years

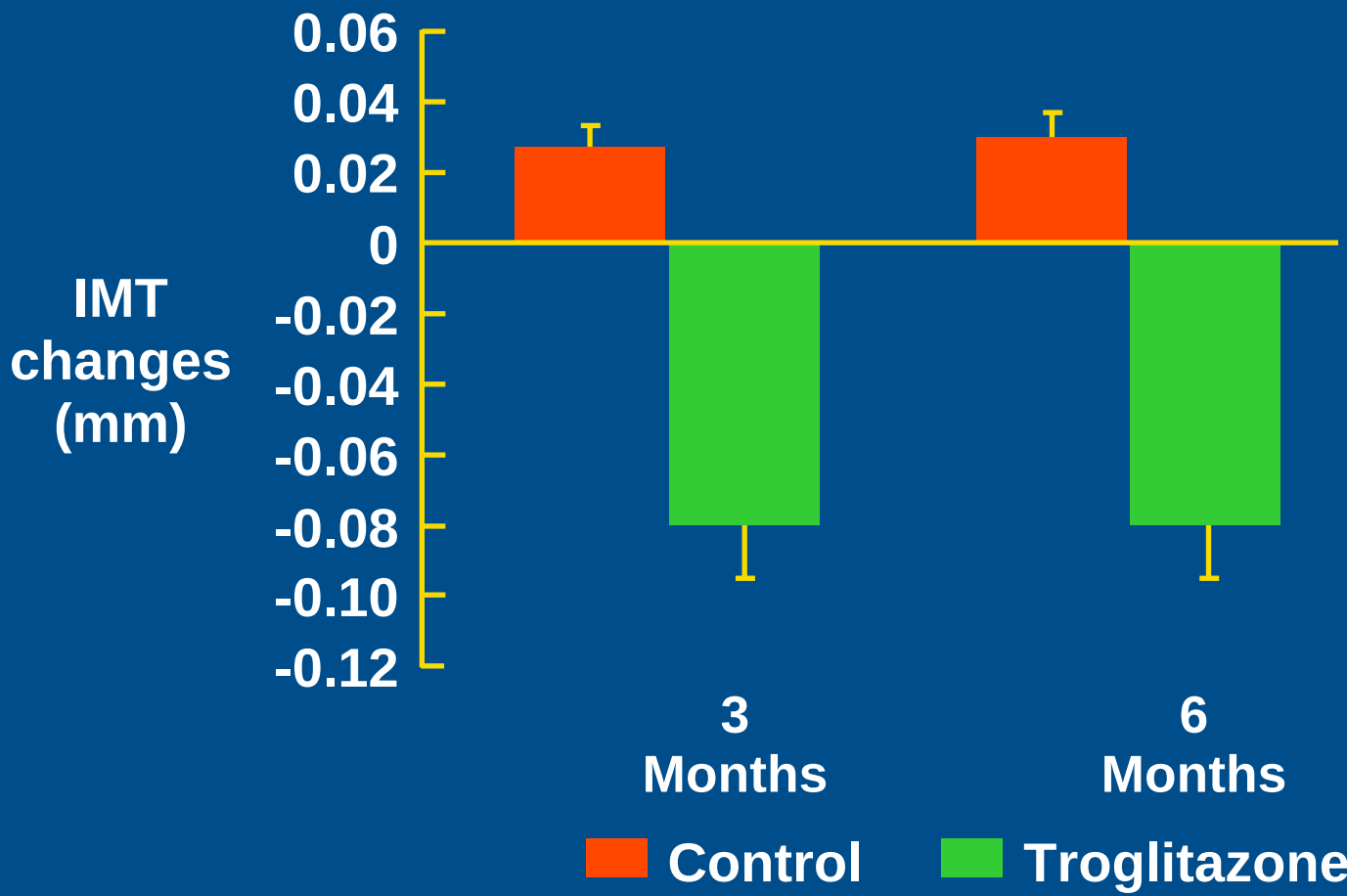


*n=1501, *P*=0.016.

†n=18,790, *P*=NS.

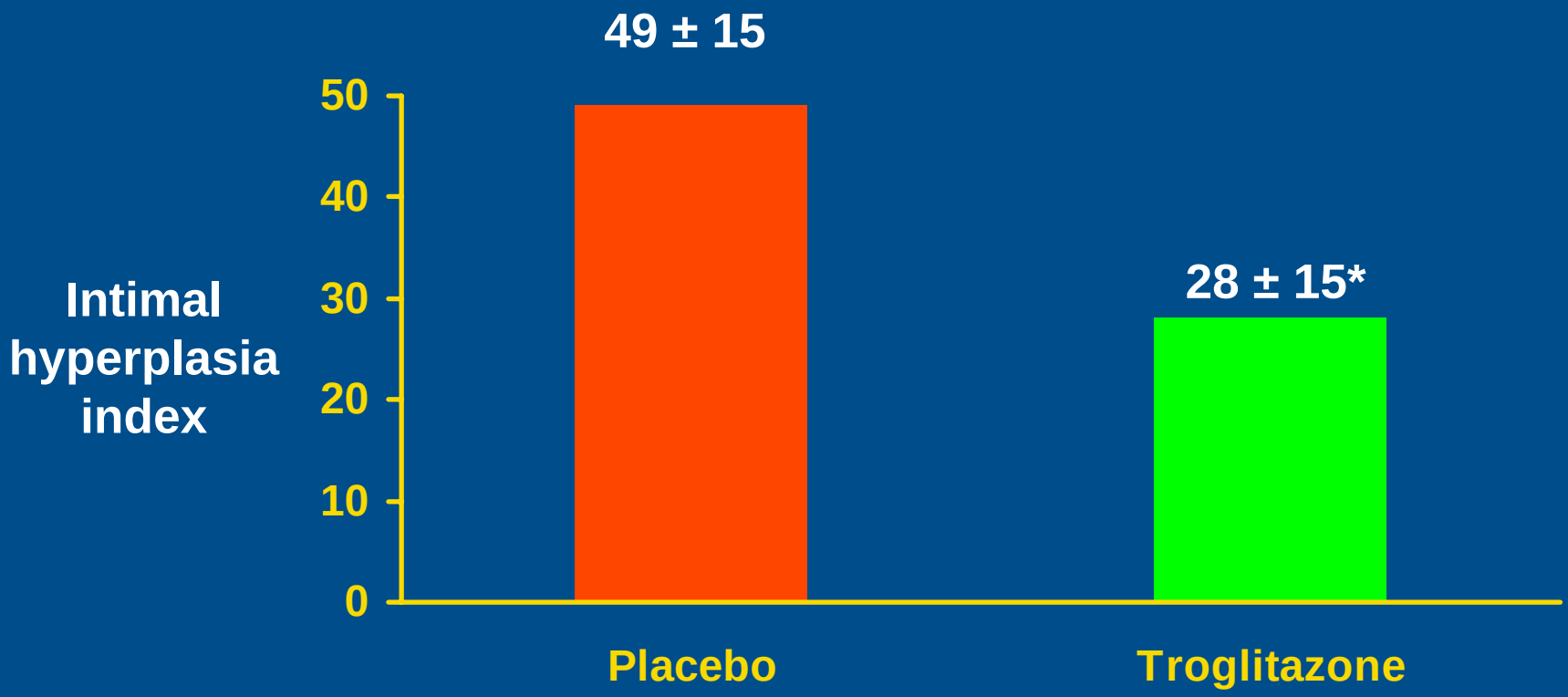
Adapted from Hansson L et al. *Lancet* 1998;351:1755–1762.

Effect of Troglitazone on Carotid Artery IMT Ratio



Minamikawa J et al. *J Clin Endocrinol Metab.* 1998;83:1818-1820.

Effect of Troglitazone on Intimal Hyperplasia After Coronary Stent Implantation



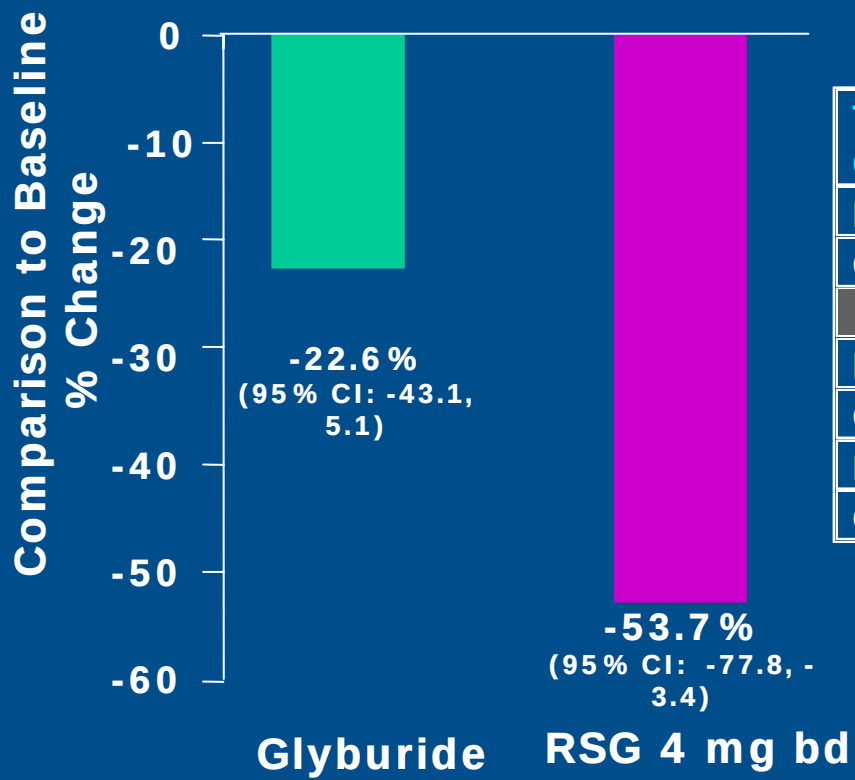
*P=0.009

Takagi T et al. *J Am Coll Cardiol*. 1999;(suppl 1):Abstract 886-2.

Rosiglitazone Reduces Urinary Albumin Excretion (ACR)

Baseline Microalbuminuria

n:	16	14
PreRx ACR:	87.3	82.7



Bakris et al. Diabetalogia,1999

Correlates of Reduced Microalbuminuria

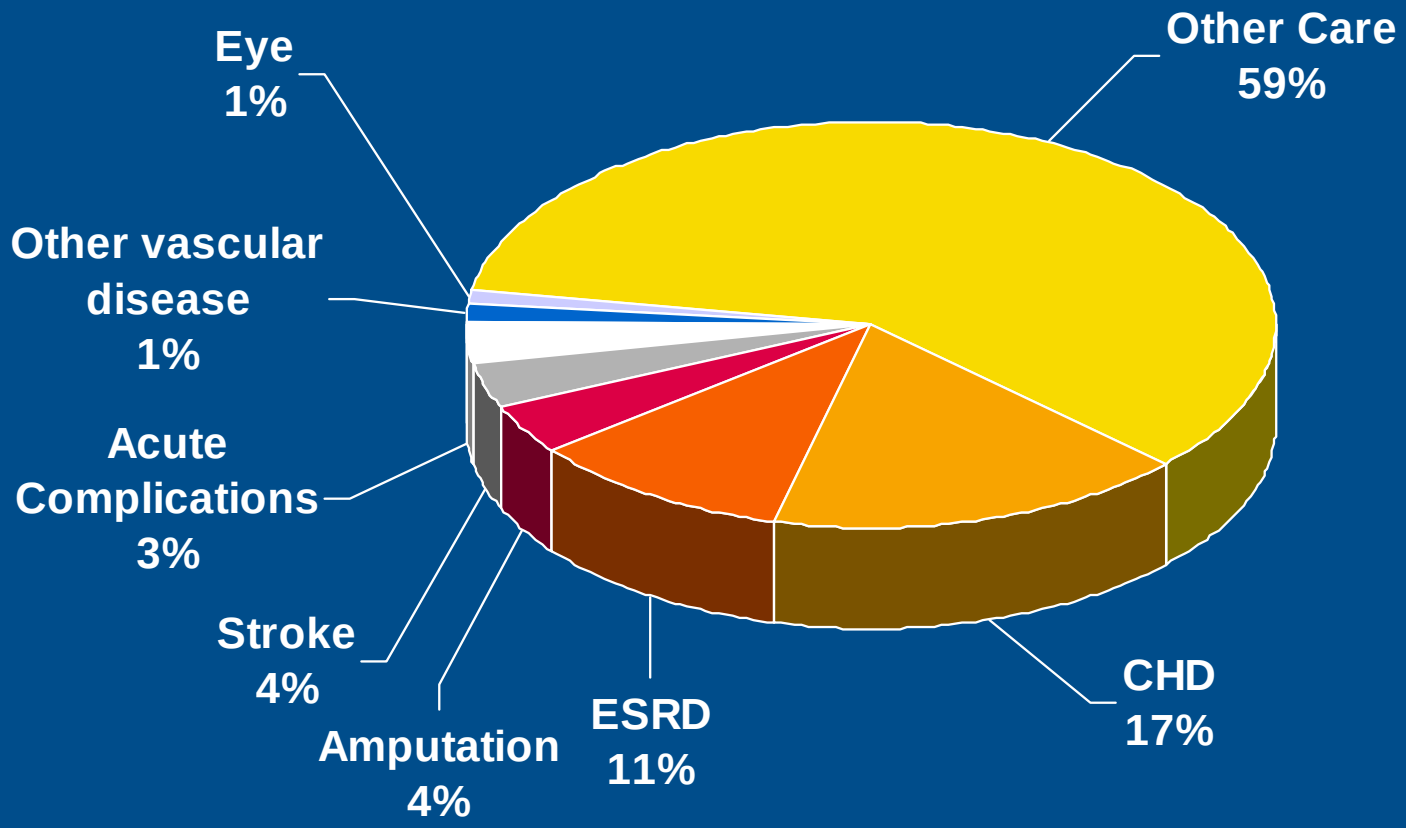
Treatment Group	n	Parameter vs ΔACR	r-coefficient
RSG	14	FPG	0.344
Glb	15	FPG	0.291
RSG	12	MASBP	0.875
Glb	15	MASBP	0.083
RSG	12	MADBP	0.755
Glb	15	MADBP	0.248

Costs of Diabetes (United States)

- 1 in every 7 healthcare dollars spent in the care of people with diabetes
- 25% of Medicare budget is spent on diabetes despite the fact that only 10-15% of the Medicare population has diabetes
- Total costs attributable to diabetes (direct and indirect) estimated at $98 billion in 1997

Songer TJ. Euaro L. *Studies on the cost of diabetes.* Centers for Disease Control, Atlanta, GA, 1998.
Centers for Disease Control and Prevention. *Chronic diseases and conditions.* Online editor, Atlanta, GA, 2000.
American Heart Association. *Heart and stroke statistical update.* Dallas, TX, 1999.
American Diabetes Association. *Diabetes Facts and Figures.* March 2000. Online edition.

Complications of Diabetes: Contribution to Excess Healthcare Costs in a Managed Care Population

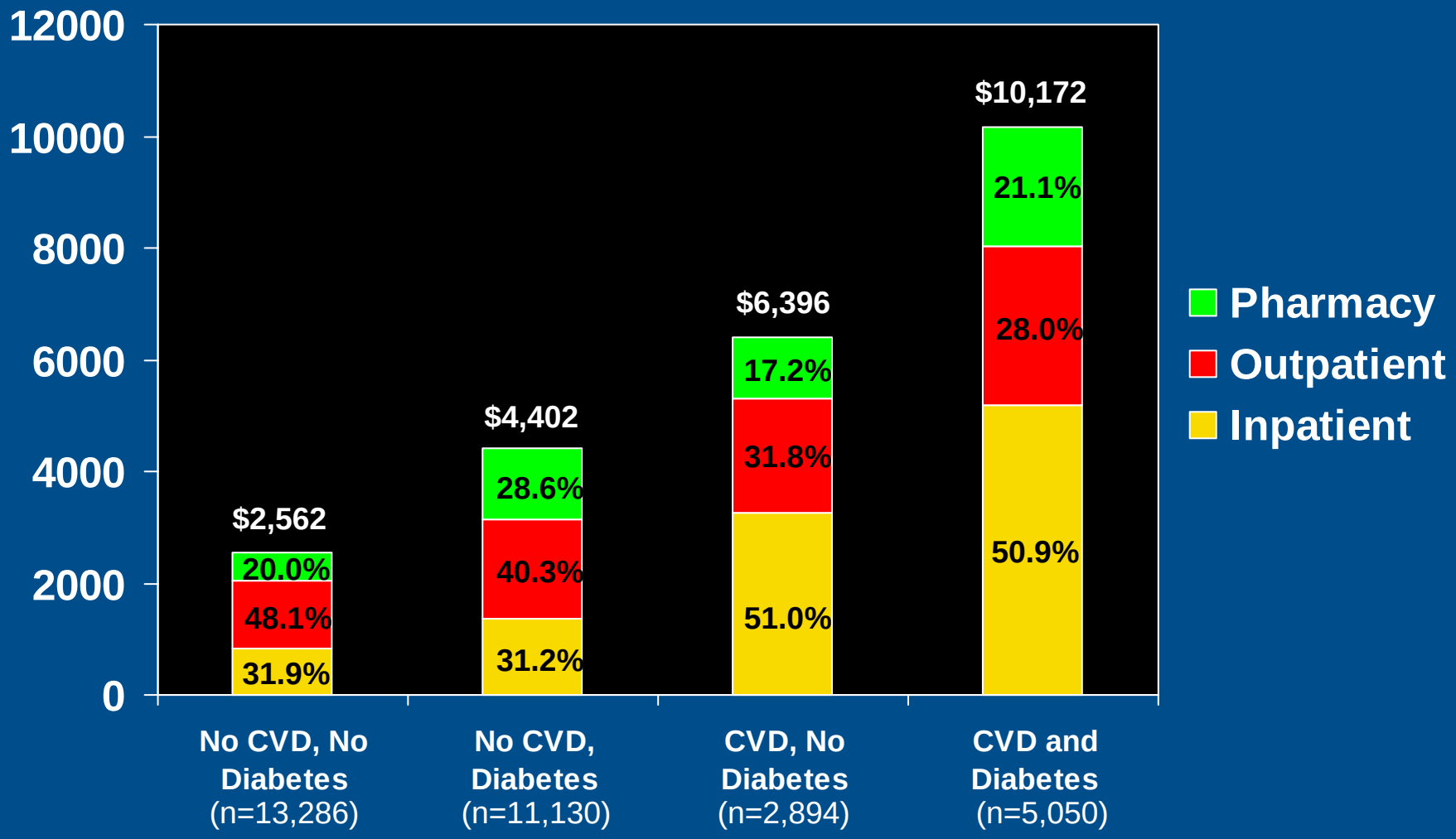


Total excess: $282.7 million
Contribution of macrovascular complications: 22.1% ($62.5 million)

Adapted from Salby JV, et al. *Diabetes Care* 1997;20:1396-1402.

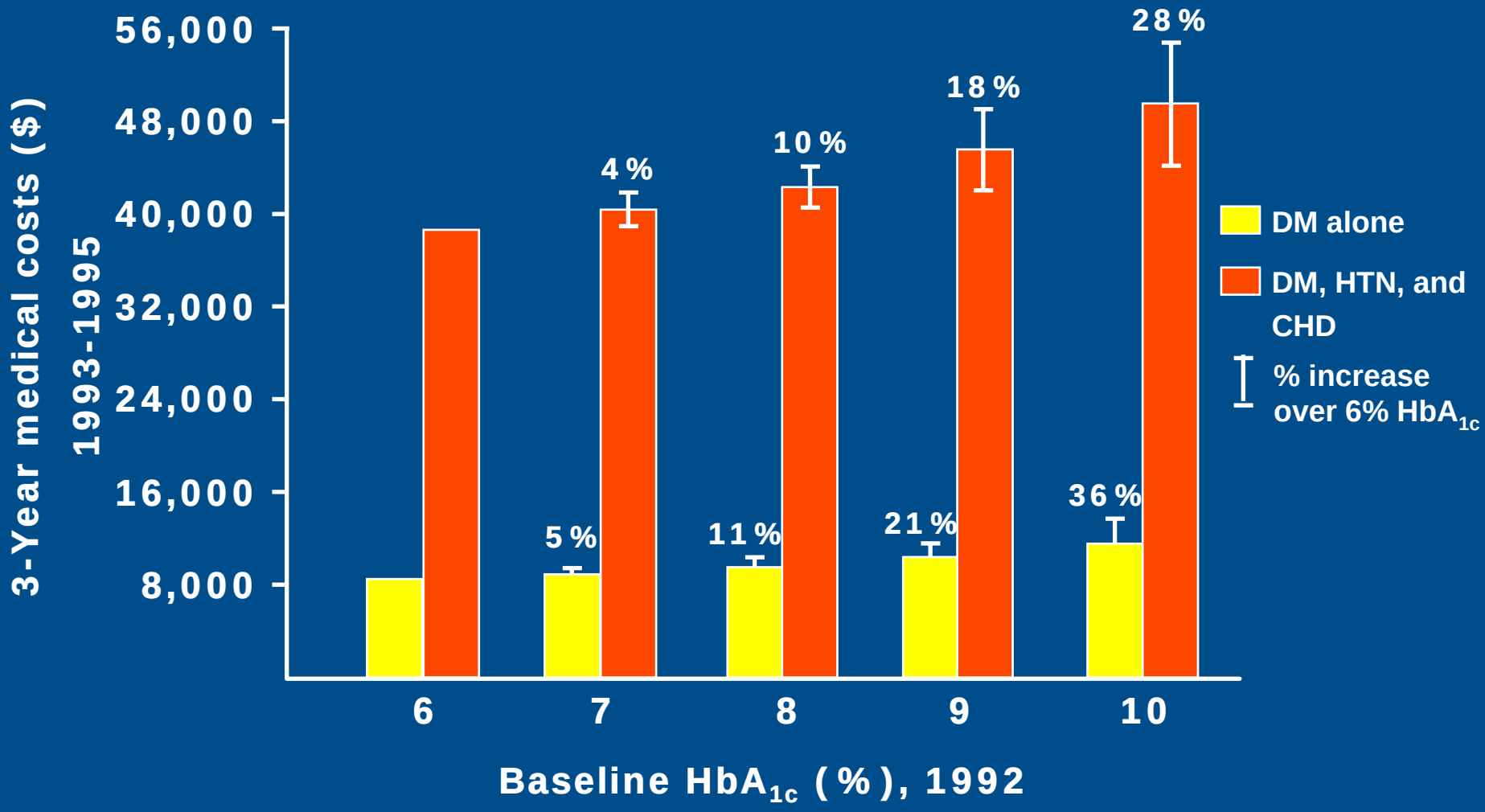
Cardiovascular Disease and Medical Care Costs in Patients With and Without Diabetes

Average annual medical care costs by component of cost, adjusted for age and sex



Adapted from Nichols GA. Brown JB. *Diabetes Care* 2002;25:482-486.

Complications of Diabetes: Greater Glycemic Control Reduces Healthcare Costs



Gilmer TP, et al. *Diabetes Care*. 1997;20:1847-1853.

Control of Glycemia = Control of Health Care Cost

- 732 patients “improved” whose A1c fell at least 1% during first year of observation and was maintained for at least 1 year, compared to 4,012 patients “unimproved” whose A1c declined < 1%
- Lower total healthcare cost in “improved” group -- observed within first year after A1c improvement, and sustained thereafter
- During the 4 years after improved A1c, avg. cost savings to HMO was $685-$950/patient/year
- Global reduction in utilization accompanied cost reduction
- 67% of “improved” succeeded without adding new drug(s) to the treatment regimen

Adapted from Wagner EH, et al. *JAMA* 2001;285:182-189.

Diabetes Disease Management Produces Short-term Savings and Quality Improvement

	Program (n=3,118)	Non-Program (n=3,681)
Avg # of visits to program nurse	3.63	----
Mean # PCP ov's/patient/year	8.36	7.78*
Mean in-patient days/patient/year	0.56	0.98*
Mean patient/month paid charges+	$394.62	$502.48*
Total estimated cost of program/yr.	$1.81M	-----
Total reduced claims paid/year	$4.04M	-----
A1c uncontrolled	6.7%	14.4%*
Eye examination	79.1%	64.9%*
Microalbuminuria testing	68.5%	39.3%*

*statistically significant difference vs. program; + excludes pharmacy costs

Adapted from Sidorov J, et al. *Diabetes Care.* 2002;25:684-689.

Insulin-Sensitizing Drugs: Opportunity for Disease Prevention