

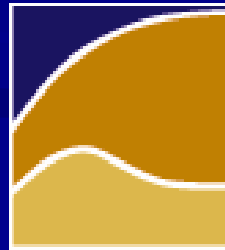
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Antidiabetic Agents: Effects on Glycemia and Potential for Cardiovascular Risk Reduction



Nutrition Therapy, Exercise, Lifestyle Changes



■ Nutrition therapy

- decrease fat content and total calories
- decrease saturated fat
- decrease salt for hypertension
- healthy diet
- weight reduction in obese patients

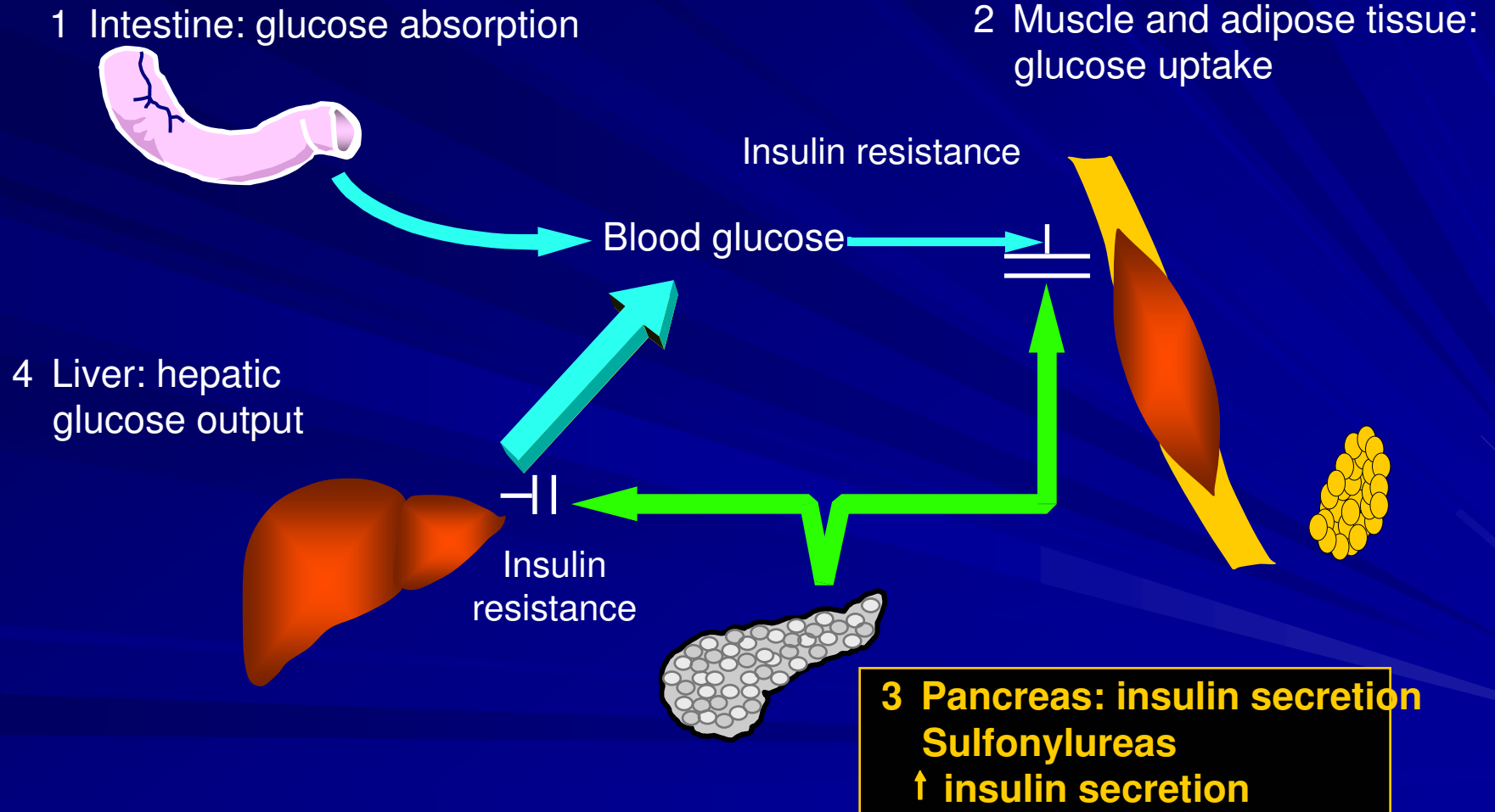
■ Exercise

- increase energy expenditure with moderate-intensity exercise

■ Lifestyle changes to reduce cardiovascular risk factors (eg, smoking cessation)

■ Training in self-management and SMBG

Sulfonylureas: Mechanism of Action



DeFronzo RA. *Diabetes*. 1988;37:667-687.
Lebovitz HE. In *Joslin's Diabetes Mellitus*. 1994:508-5



Sulfonylureas: Efficacy

- Approximately 50% of patients with newly diagnosed type 2 diabetes achieve acceptable glycemic control
- About 15%-20% of patients have little or no glycemic response

Meglitinides: Mechanism of Action



1 Intestine: glucose absorption

2 Muscle and adipose tissue: glucose uptake

Insulin resistance

Blood glucose

4 Liver: hepatic glucose output

Insulin resistance

3 Pancreas: insulin secretion
Meglitinides
↑ Insulin secretion

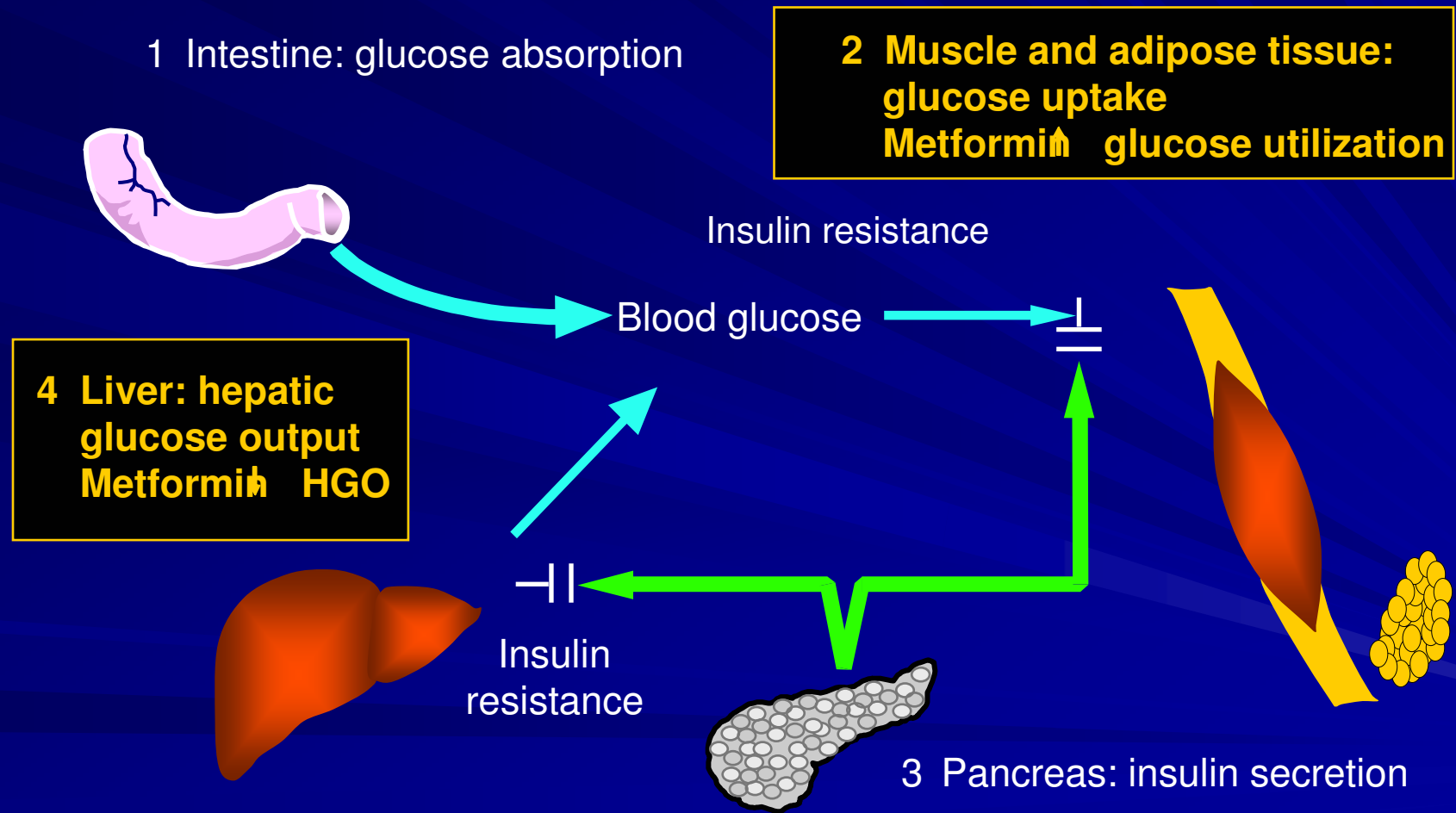


Repaglinide: Prescribing Considerations

- Contraindicated in patients with
 - diabetic ketoacidosis, with or without coma
 - type 1 diabetes
 - known hypersensitivity to the drug or its inactive ingredients
- Use cautiously in patients with impaired liver function

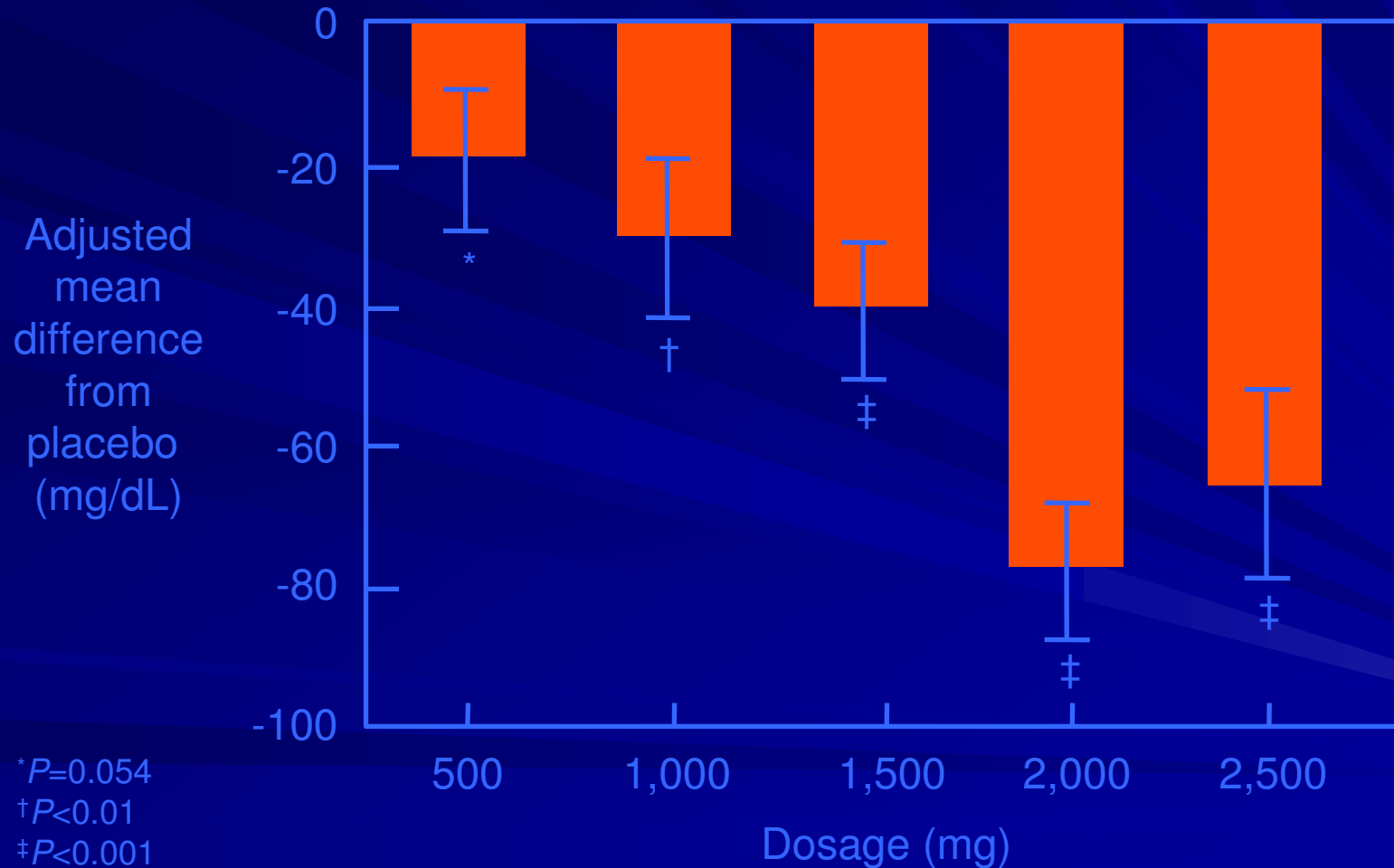


Metformin: Mechanism of Action

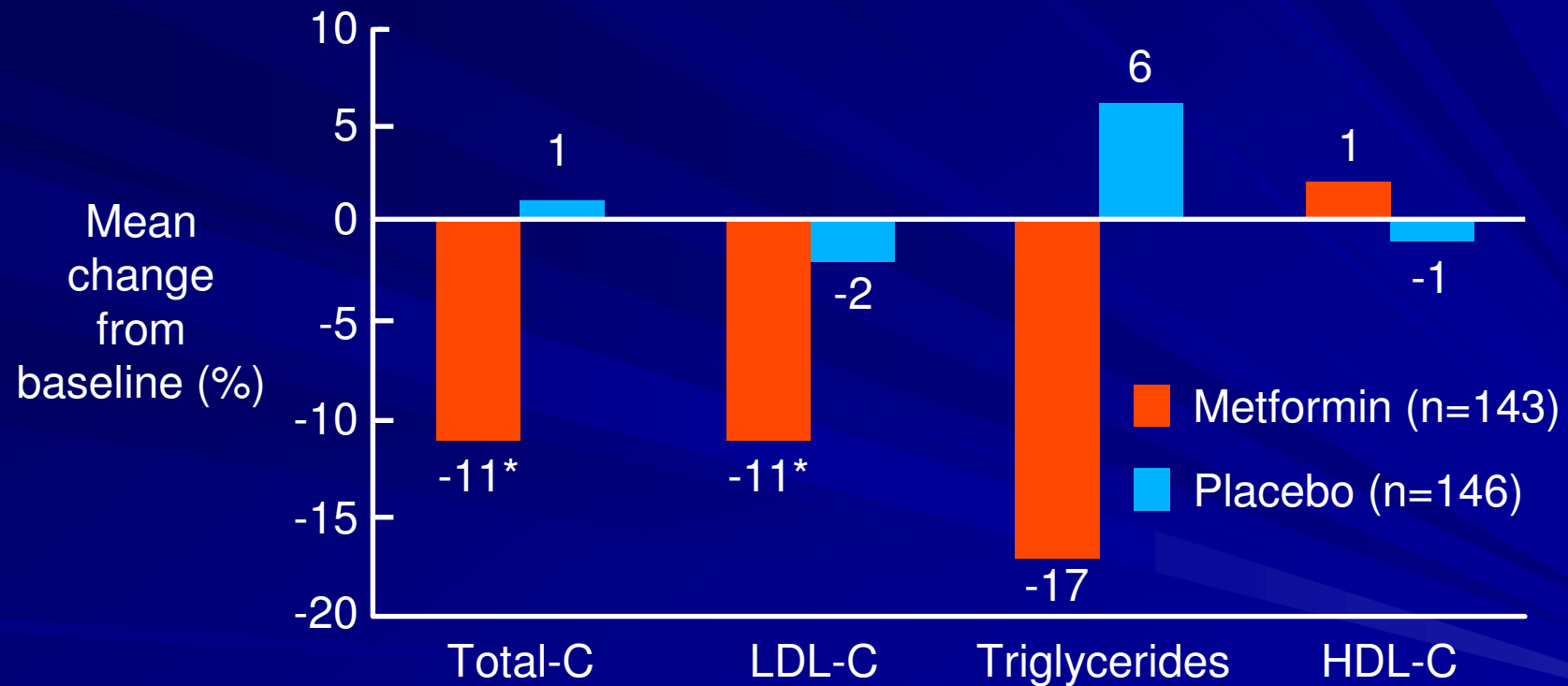




Effect of Metformin in Type 2 Diabetes: FPG

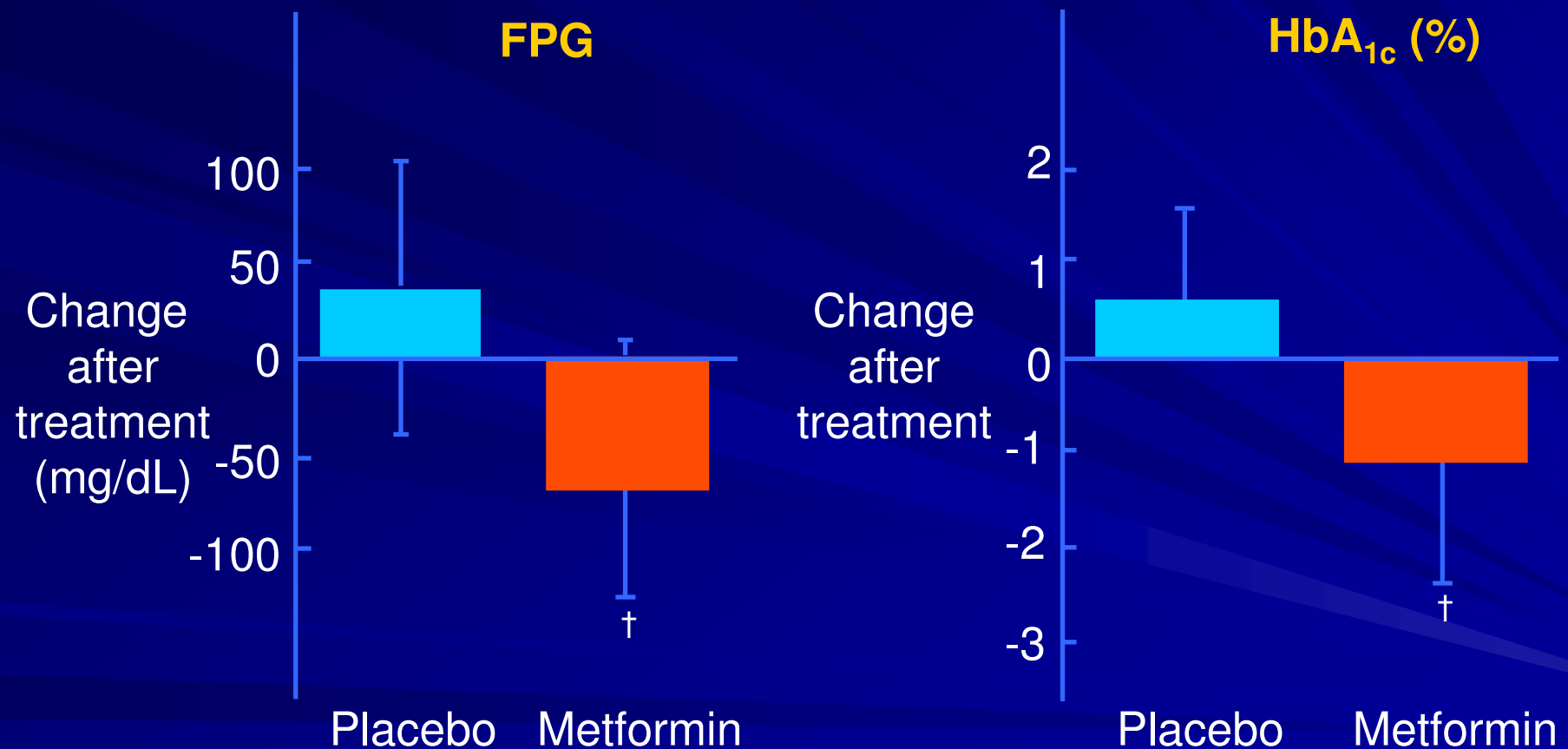


Metformin Monotherapy: Effects on Lipids



* $P < 0.05$ vs placebo

Adjunctive Metformin Therapy in Insulin-Treated Patients With Type 2 Diabetes and Suboptimal Glycemic Control



† $P < 0.001$; mean \pm SD

Metformin Prescribing Considerations

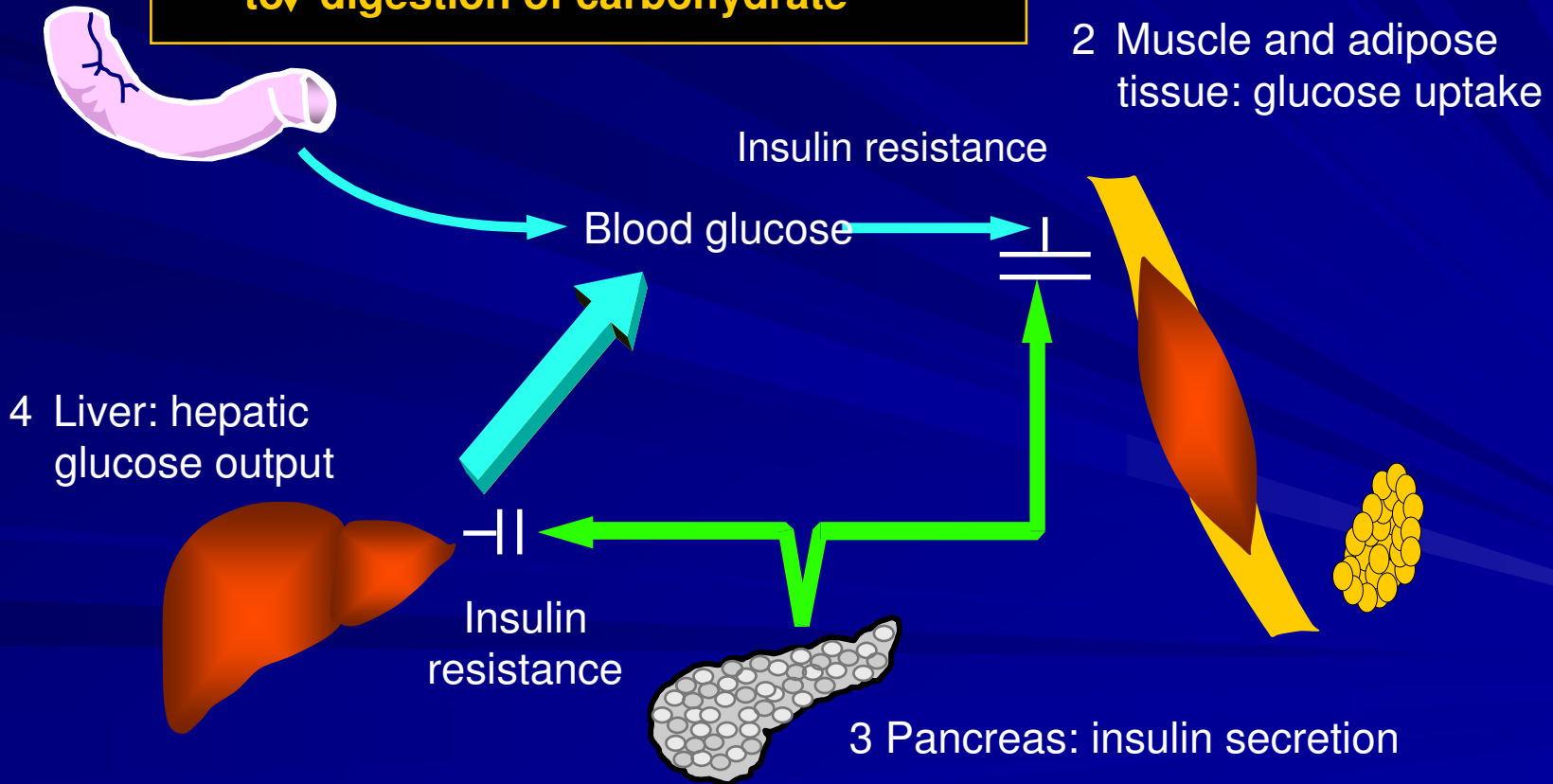


- Metformin is contraindicated in
 - renal dysfunction: serum creatinine ≥ 1.5 mg/dL (men) or ≥ 1.4 (women), or abnormal creatinine clearance
 - CHF requiring pharmacologic treatment
 - use of iodinated contrast materials for radiologic studies
 - known hypersensitivity to metformin
 - acute or chronic metabolic acidosis, including diabetic ketoacidosis
- Special warning on increased risk of cardiovascular mortality

α -Glucosidase Inhibitors: Mechanism of Action

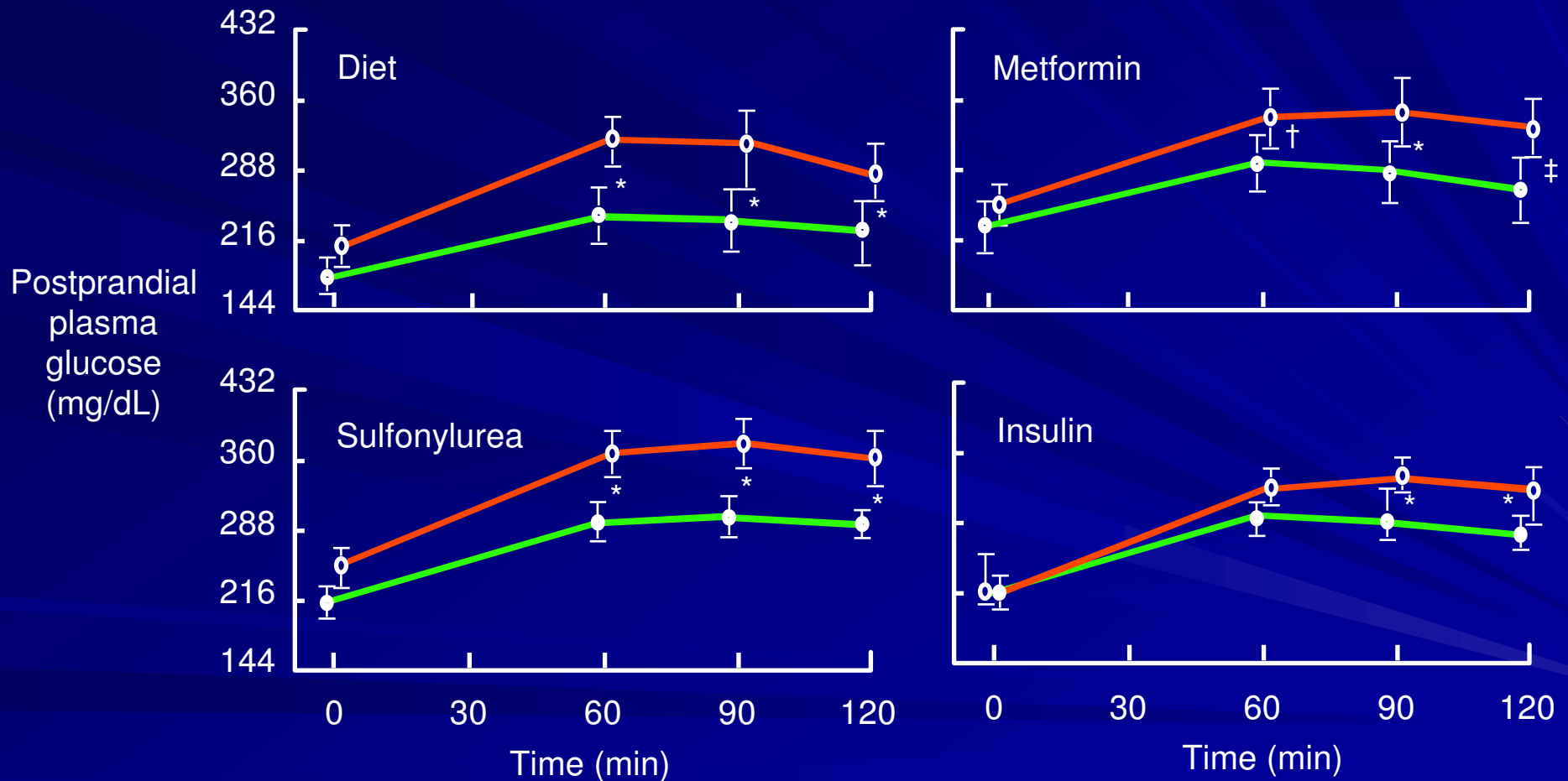


1 Intestine: glucose absorption
Acarbose ↓ glucose absorption secondary
to ↓ digestion of carbohydrate





Acarbose: Effect on Postprandial Glucose



* $P < 0.01$; † $P < 0.019$; ‡ $P < 0.026$

○ Placebo ● Acarbose



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

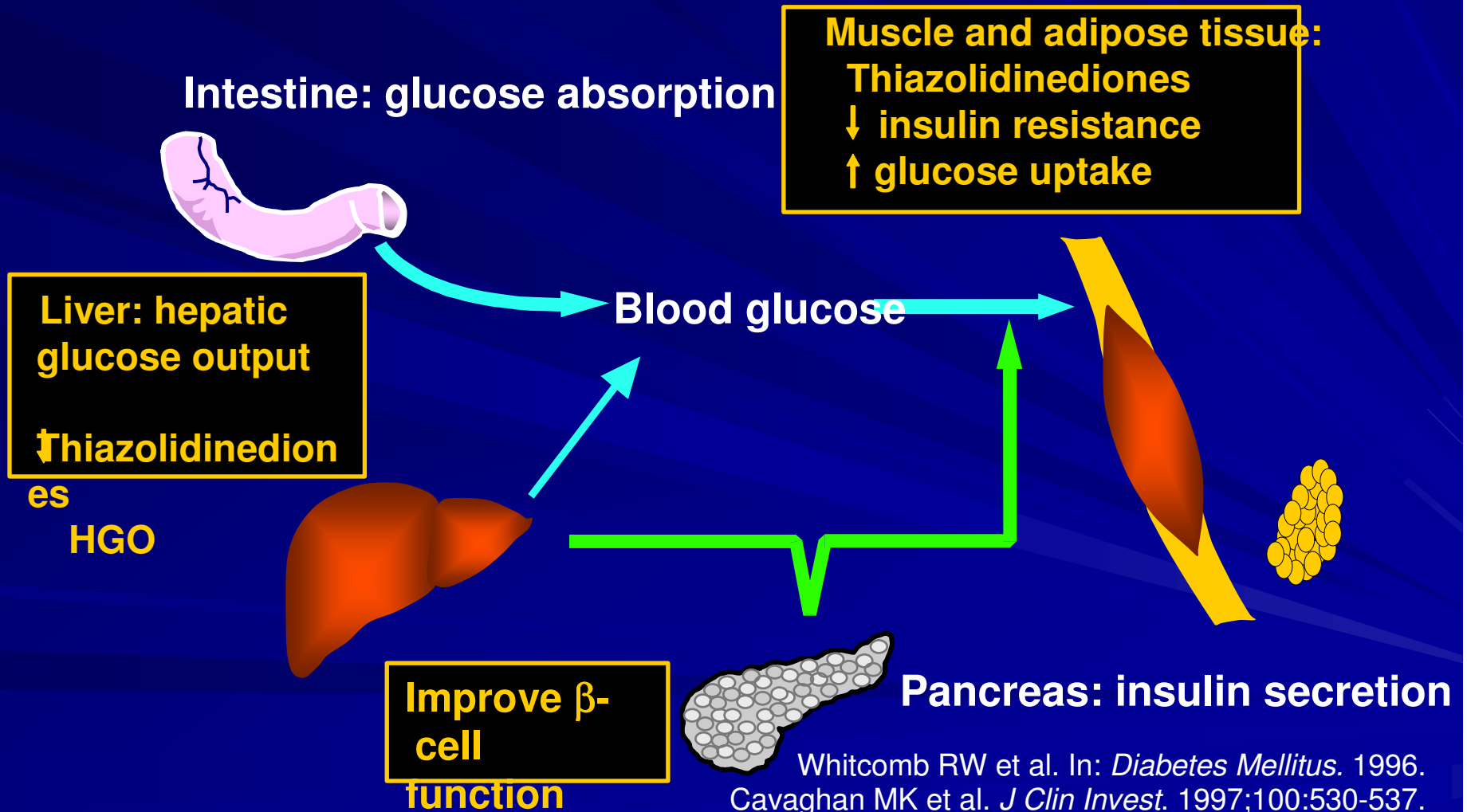


Acarbose Summary

- Reduced postprandial plasma glucose and insulin responses
- Effective in patients with type 2 diabetes treated with diet, sulfonylureas, metformin, or insulin
- No increase in hypoglycemia when used alone
- No effect on lipid profiles



Thiazolidinediones: Mechanism of Action



Muscle and adipose tissue:
Thiazolidinediones
↓ insulin resistance
↑ glucose uptake

Liver: hepatic glucose output
↓ Thiazolidinediones

HGO

Improve β -cell function

Pancreas: insulin secretion

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.



The PPAR Family

Ligand

Fibrates

Thiazolidinediones

Fatty acids

Receptor

PPAR- α

PPAR- γ

PPAR- δ

Effect on: Lipoprotein
expression

Peroxisome
proliferation

Lipid
synthesis

Carbohydrate
metabolism

Thiazolidinedione Dosage/Potency



Agent

Dosage Range

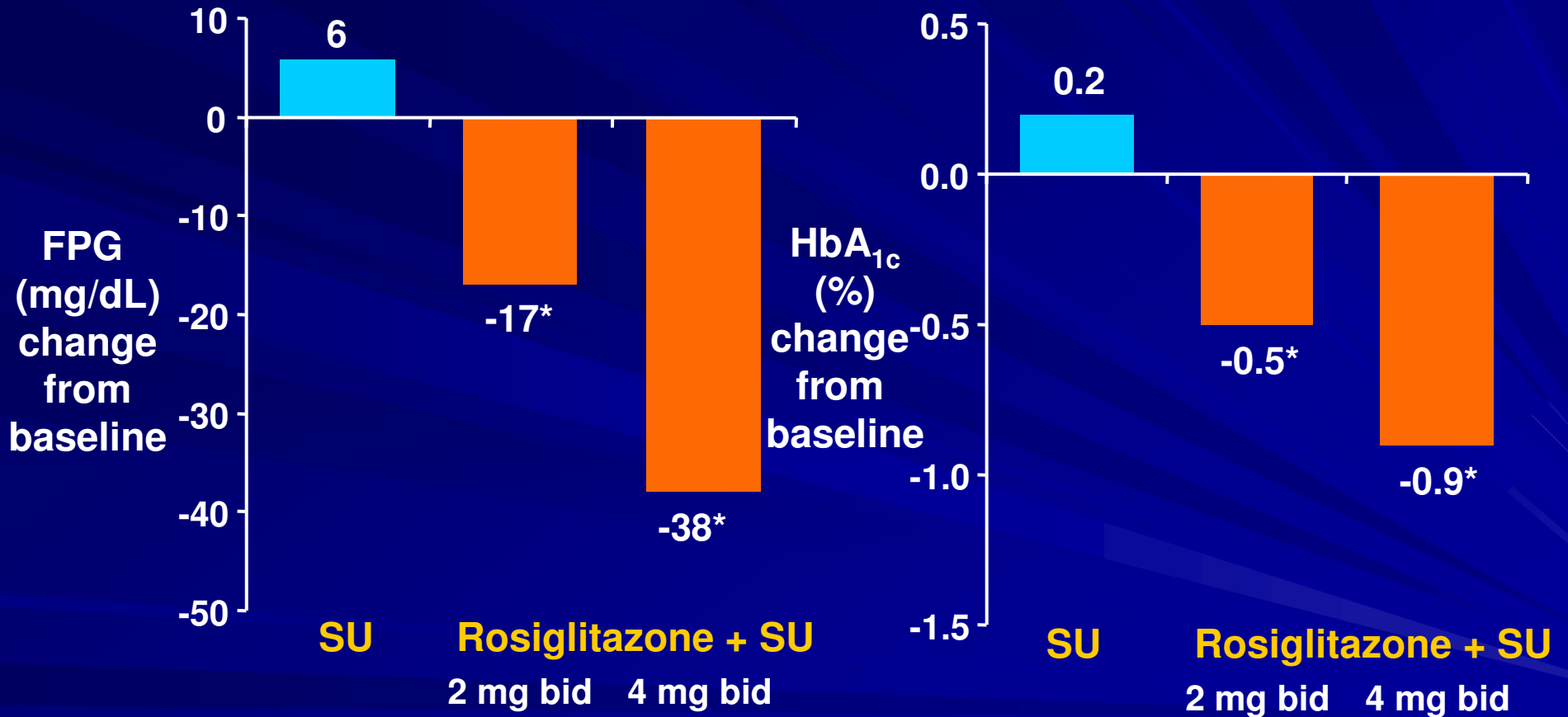
Rosiglitazone
doses)

4–8 mg daily (in 1 or 2

~~Pioglitazone~~

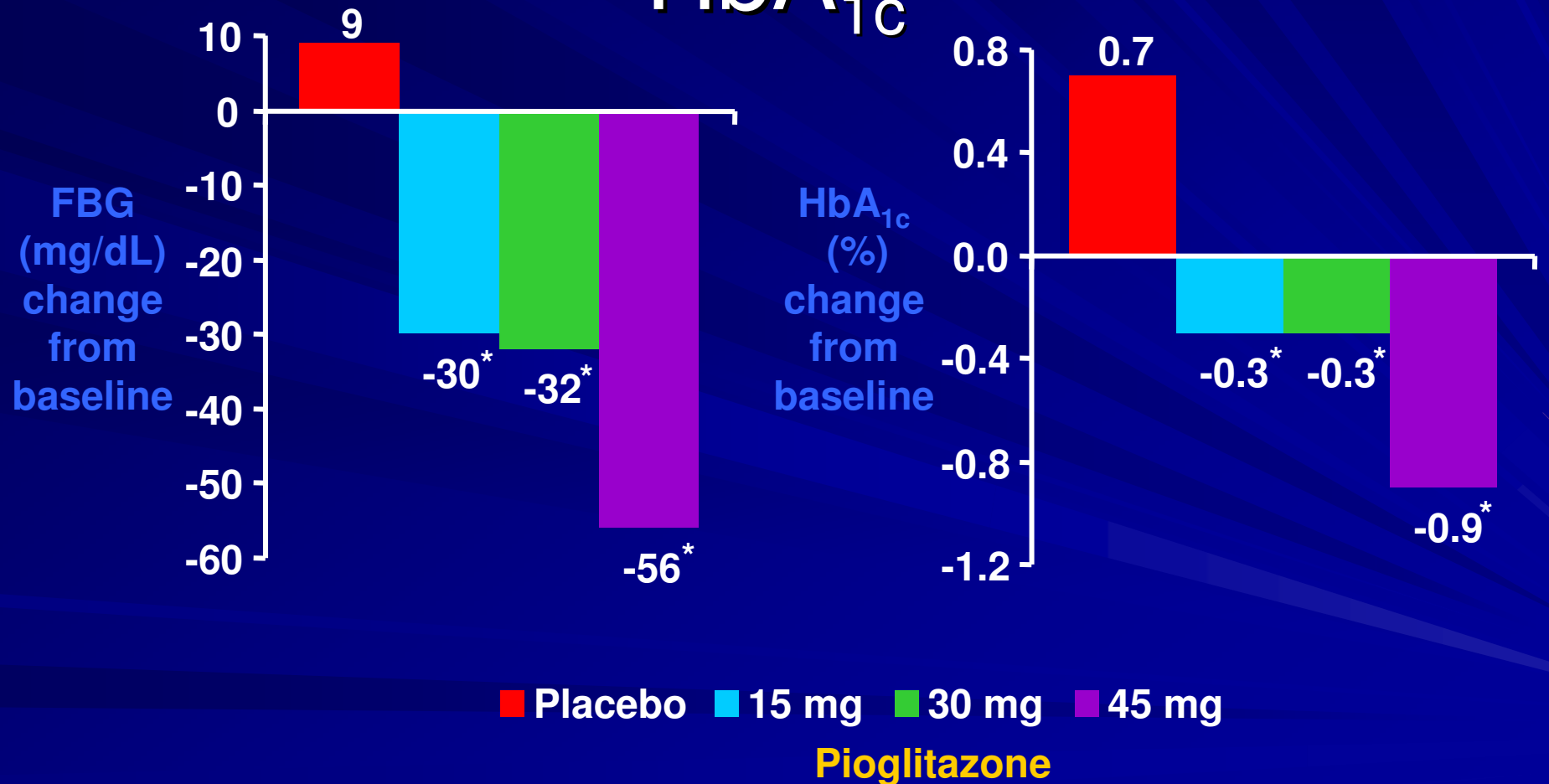
~~15–45 mg once daily~~

Effects of Rosiglitazone and Sulfonylurea on FPG and HbA_{1c}



* $P < 0.0001$ for comparison with SU alone

Effects of Pioglitazone Monotherapy on FBG and HbA_{1c}



* $P \leq 0.05$ for comparison with placebo

Monitoring Recommendations:

Pioglitazone and Rosiglitazone

- LFT before initiation of therapy
 - Do not start pioglitazone or rosiglitazone treatment if ALT $>2.5X$ ULN
- LFT once every 2 months for first year, periodically thereafter, or more often if ALTs $>2.5X$ ULN
- If ALT is $>3X$ ULN, repeat test as soon as possible; discontinue pioglitazone or rosiglitazone if ALT remains $>3X$ ULN or jaundice occurs

Insulin Therapy in Type 2 Diabetes: Indications



- Significant hyperglycemia at presentation
- Hyperglycemia despite maximal doses of oral agents
- Decompensation
 - acute injury, stress, infection
 - severe hyperglycemia with ketonemia and/or ketonuria
 - uncontrolled weight loss
- Surgery
- Pregnancy
- Renal disease
- Allergy or serious reaction to oral agents

American Diabetes Association. *Medical Management of Non-Insulin-Dependent (Type II) Diabetes*. 3rd ed. 1994:44-

48.



Exenatide: Clinical Pharmacology

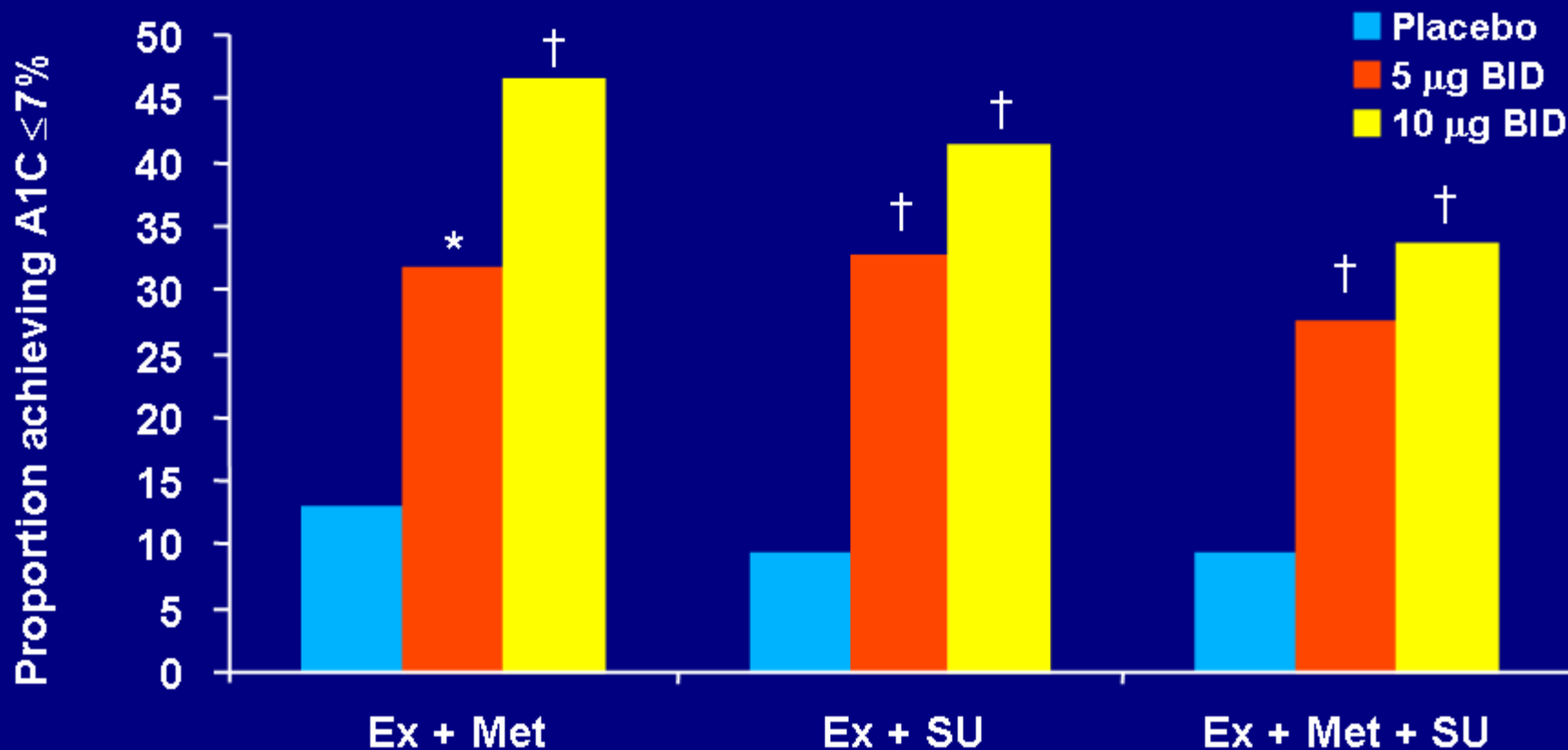
- First agent in a new class called incretin mimetics
 - enhances glucose-dependent insulin secretion
 - suppresses inappropriately elevated glucagon secretion
 - slows gastric emptying
 - available in 2 prefilled pens that deliver 5- or 10- μ g doses
 - each pen delivers 60 doses (30-day BID dosing)
- Metabolism
 - predominantly excreted by glomerular filtration
- Drug interactions
 - digoxin – lisinopril
 - lovastatin – acetaminophen
- Contraindications and cautions
 - hypersensitivity, type 1 diabetes, end-stage renal disease or severe renal impairment, severe GI disease
- Pharmacology not affected by age, gender, race, or obesity

Exenatide [prescribing information].

Available at: <http://www.fda.gov/cder/foi/label/2005/021773lbl.pdf>.



Exenatide: Proportion of Patients Achieving A1C $\leq 7\%$



* $P < 0.01$ vs placebo;

† $P < 0.0001$ vs placebo.

Ex=exenatide; Met=metformin;

SU=sulfonylurea.

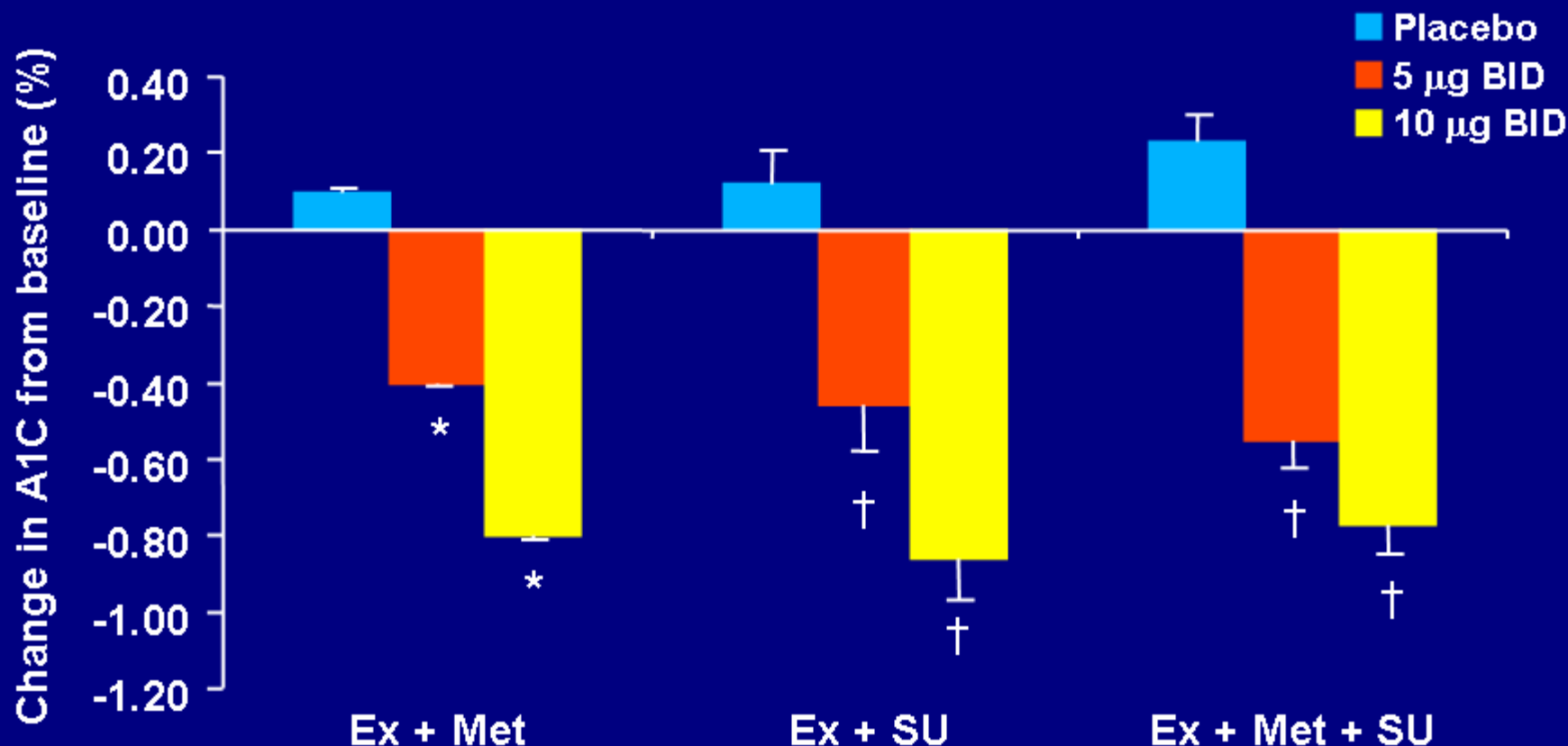
Buse JB et al. *Diabetes Care*. 2004;27:2628-2635.

DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100.

Kendall DM et al. *Diabetes Care*. 2005;28:1083-1091.



Exenatide: Effects on Glycemic Control in Combination With Current Oral Therapies



* $P < 0.001$ vs placebo;

† $P < 0.0001$ vs placebo.

Ex=exenatide; Met=metformin;
SU=sulfonylurea.

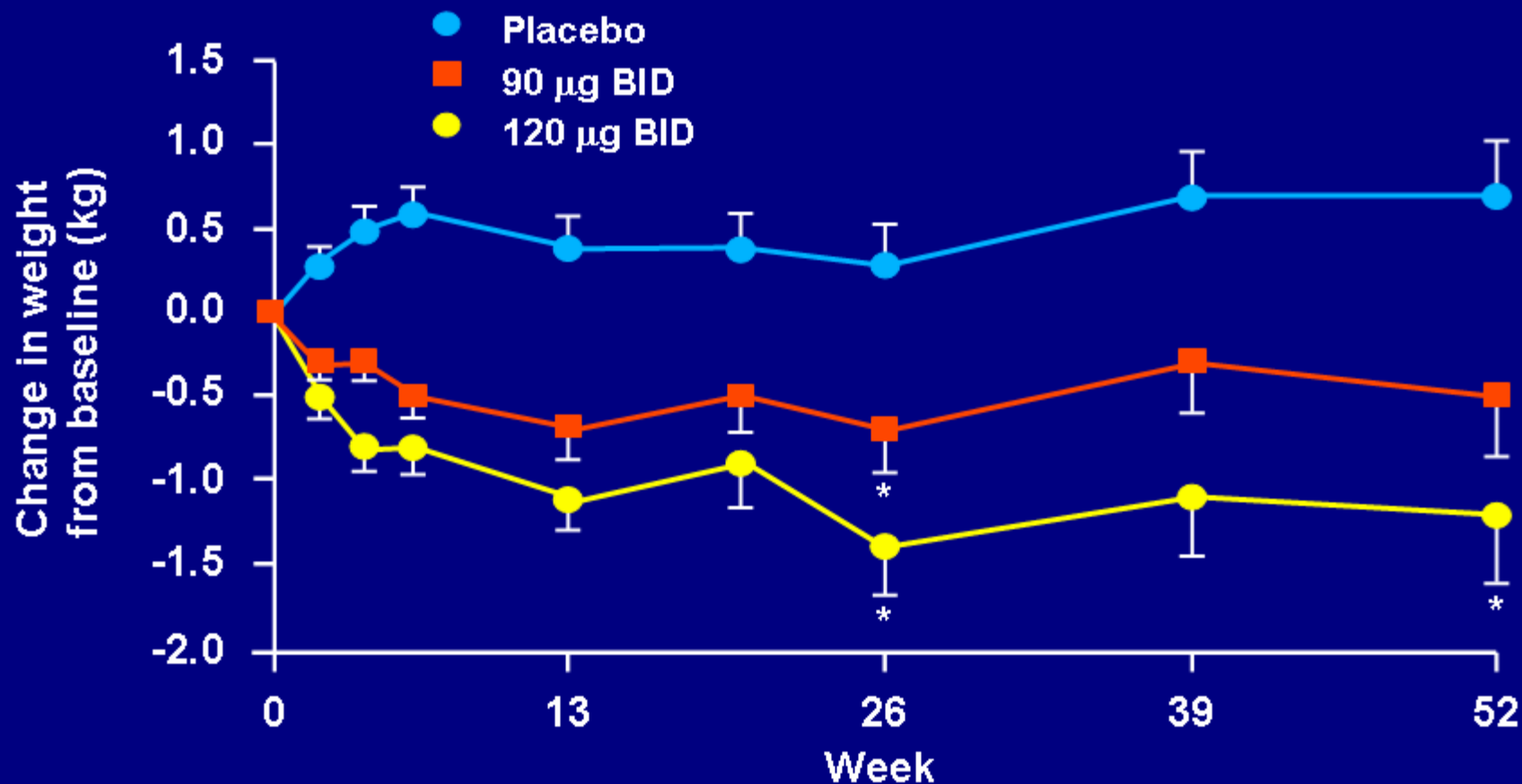
Buse JB et al. *Diabetes Care*. 2004;27:2628-2635.

DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100.

Kendall DM et al. *Diabetes Care*. 2005;28:1083-1091.



Effect of Pramlintide Adjunctive Therapy on Weight in Patients With Type 2 Diabetes



* $P < 0.05$ vs placebo.

Hollander PA et al. *Diabetes Care*. 2003;26:784-790.
Pramlintide [prescribing information]. Available at:
<http://www.fda.gov/cder/foi/label/2005/021332lbl.pdf>.



Effect of Antidiabetic Agents on Weight



Weight Neutral or Slight Weight Loss

- Meglitinides (repaglinide, nateglinide)
- α -Glucosidase inhibitors (acarbose, miglitol)
- Metformin

Weight Gain

- Insulin
- Sulfonylureas
- Thiazolidinediones

Aronne LJ et al. *Practical Guide to Drug-Induced Weight Gain*.
Minneapolis, Minn: McGraw-Hill Companies; 2002.