Controlling Diabetes:
Successfully Using Oral Agents, Insulins, Exenatide and Pramlintide

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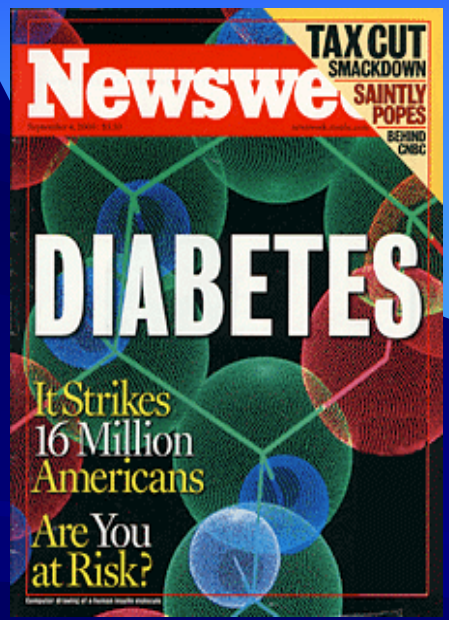
U.S. Diabetes Prevalence

18+ Million



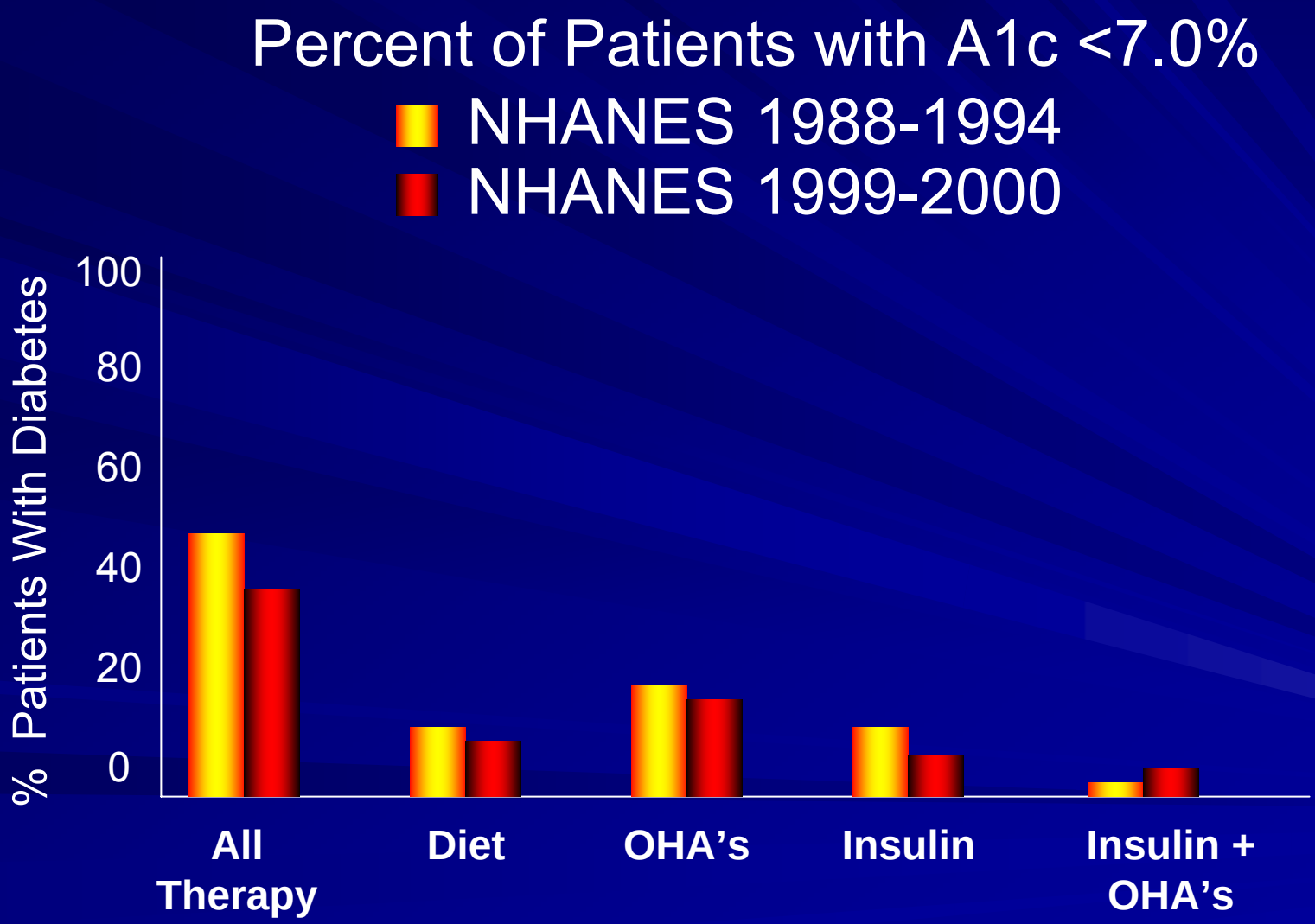
- **41+ million have Prediabetes**
- **1.3 million new cases each year**
- **#1 cause of blindness**
- **45% all new cases ESRD**
- **60% all amputations**
- **70% of people have neuropathy**
- **70% die of MI or CVA**
- **Prevalence is increasing, but control is deteriorating[2,3]**

www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.jsp

[2] ADA. *Diabetes Care*. 2003;26:917-932.

[3] Koro CE et al. *Diabetes Care*. 2004;27:17-20.

Glycemic Control Has Not Improved



Adapted from Koro CE, et al. Diabetes Care 2004;27:17

Management of T2DM Has Not Improved

Risk Factor Control

Saydah SH et al. *JAMA* 2004;291:335-342

	NHANES (1988-1994)	NHANES (1999-2000)
A1c <7%	44%	37%
BP <130/80	29%	36%
TC <200	34%	50%
All 3 at Goal	***5%***	***7%***

Therapeutic Trends In The USA For Patients With T2DM

- A single oral agent is started when the average A1c is 8.7%, *and* the A1c had been >8% for 9 months!
- A second oral agent is started when the average A1c is 8.8% *and* the patient had been a single-agent failure for 15 ~21 months!!
- Insulin is started when the average A1c is 9.6% *and* the A1c had been >8% for almost 2 years!!!

Brown JB, et al. Diabetes Care 2004;27:1535

Relationship Between Physicians' Target Fasting Glucose and Metabolic Control of T2DM
QuED Study Group Survey

- Objective:

  Investigate the relationship between physicians beliefs on tight control of T2DM versus FPS & A1c in their patients

- 456 physicians were surveyed:

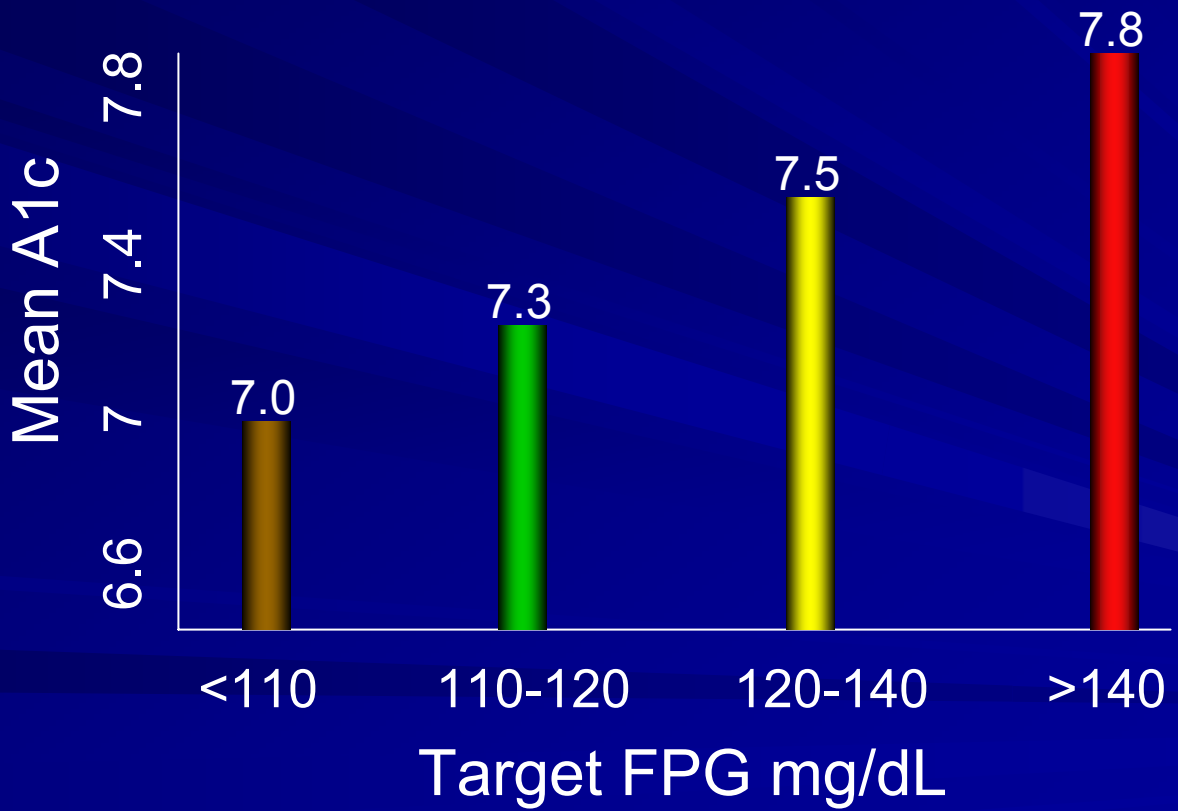
  "For your average patient with T2DM, what do *you* think the fasting glucose should be?"

- Data on glycemic control was later collected

Belfiglio M, et.al. Diabetes Care 2001;24:423-9

The QuED Study Group Results

Relationship Between Patient's A1c and Physician's Target FPG

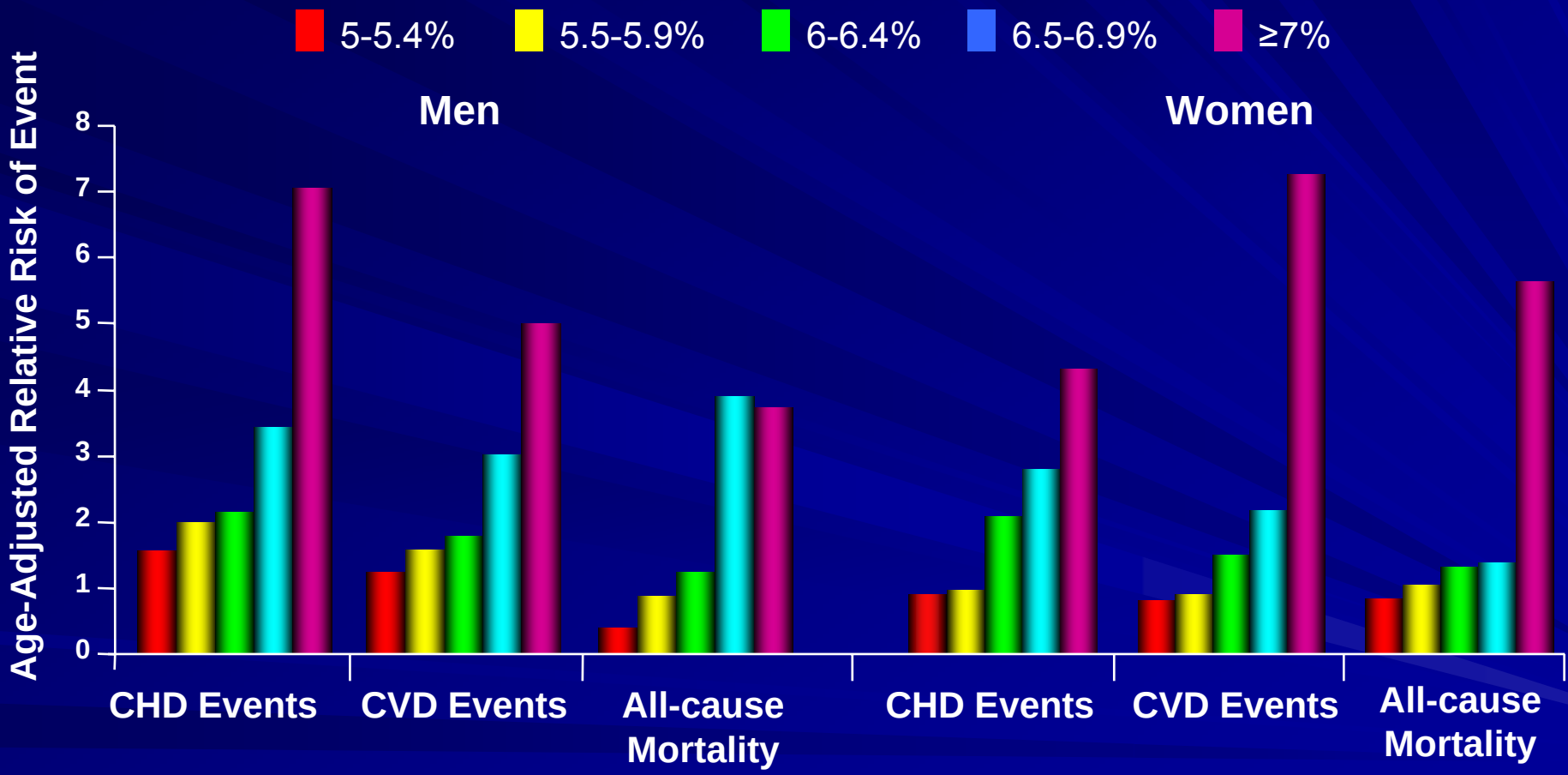


Belfiglio M, et.al. Diabetes Care 2001;24:423-9

Barriers To Achieving Control of T2DM

- Physician's attitudes
  - Hypoglycemia
  - Weight gain
  - Starting insulin
- Patient's fears
  - Hypoglycemia
  - Weight gain
  - Insulin
- Overcoming Inertia
  - Patient does not believe T2DM is a problem
  - Physician does not believe tight control is necessary

EPIC-Norfolk Study: HbA_{1c} and Risk of CV Events or Death



Khaw KT, et al. *Ann Intern Med*. 2004;141:413-420.

Therapeutic Goals

- A1c <6.5%
  Fasting glucose <110 mg/dL
  2 h postprandial <140-180 mg/dL
- Blood pressure <130/80 mmHg
- LDLc <100 mg/dL
  (<70 mg/dL if very high risk)
- Triglyceride <150 mg/dL

What Should Be The First Therapy?

- First therapy can be determined based on the A1c

  A1c ≤6.5%: Continue course

  A1c ≤8.5%: Monotherapy[1,2]
  Combination therapy

  A1c ≥8.5%: Combination therapy[3]

- Combination therapy

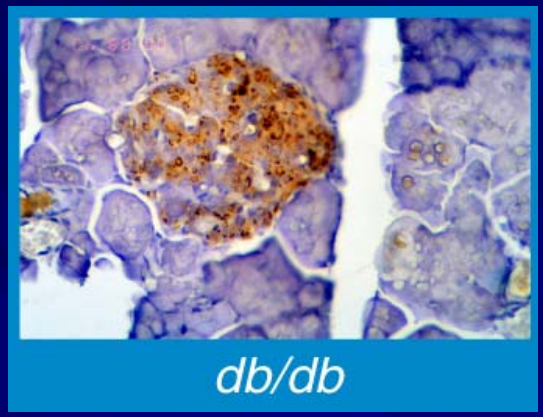
  Metformin + TZD
  Metformin + SU
  Metformin or SU + Exenatide
  Metformin + SU + Exenatide

[1] Monotherapy with SU or Metformin does not sustain A1c reductions (UKPDS)
[2] Glipizide ER and glimepiride have a lower incidence of hypoglycemia
[3] If glucose is >260 mg% and the patient is symptomatic, insulin is required

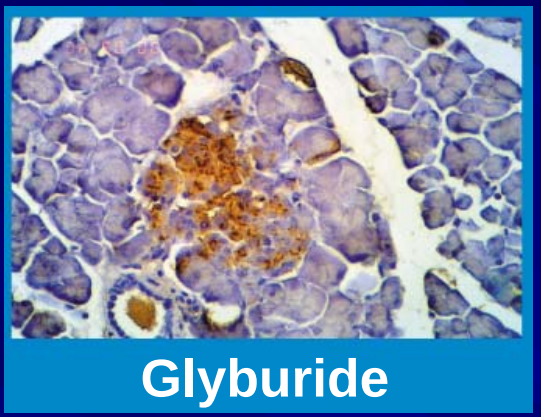
Should Combination Therapy Be The First Intervention?

- Ideal Intervention:
  - Reduce A1c to <6.5%
  - No hypoglycemia
  - No weight gain
  - Improve Beta-cell function
  - Durability
- Should metformin +TZD be the first intervention?
- Should Metformin &/or SU + Exenatide be the first intervention?

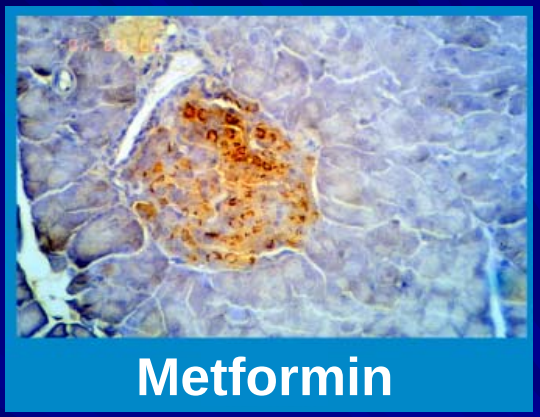
Rosiglitazone Increases Islet Insulin In db/db Mice*



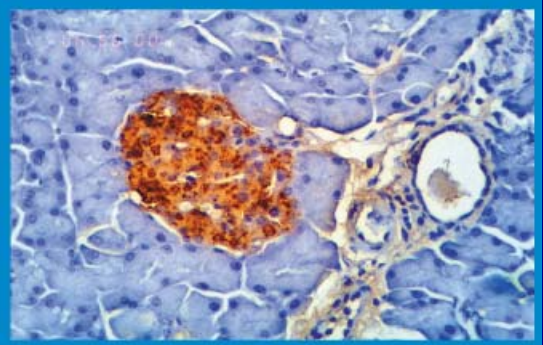
db/db



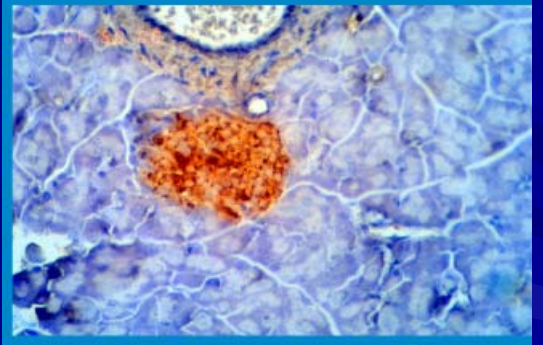
Glyburide



Metformin



Rosiglitazone



Lean Control

* Clinical significance of the preclinical findings is unknown.
28 days' treatment with rosiglitazone 1.42 mg/kg, metformin 100 mg/kg, glyburide 49.4 mg/kg.

Lister et al. *Diabetologia.* 1999;42(suppl 1):A150 (Abstract 556 and poster).

Patient F.T.N.

- 40-year-old white male had an acute onset diabetes age 34. He had always been treated with insulin and the A1c ~12% (non-adherence)
- Lab C-peptide: 3.7 ng/mL
  GAD antibody negative
- Therapeutic changes
  a. Stop insulin
     Begin sulfonylurea + metformin
     → A1c decreased to 6.9%
  b. TZD later added to SU + metformin
     → Increased C-peptide and ↓A1c

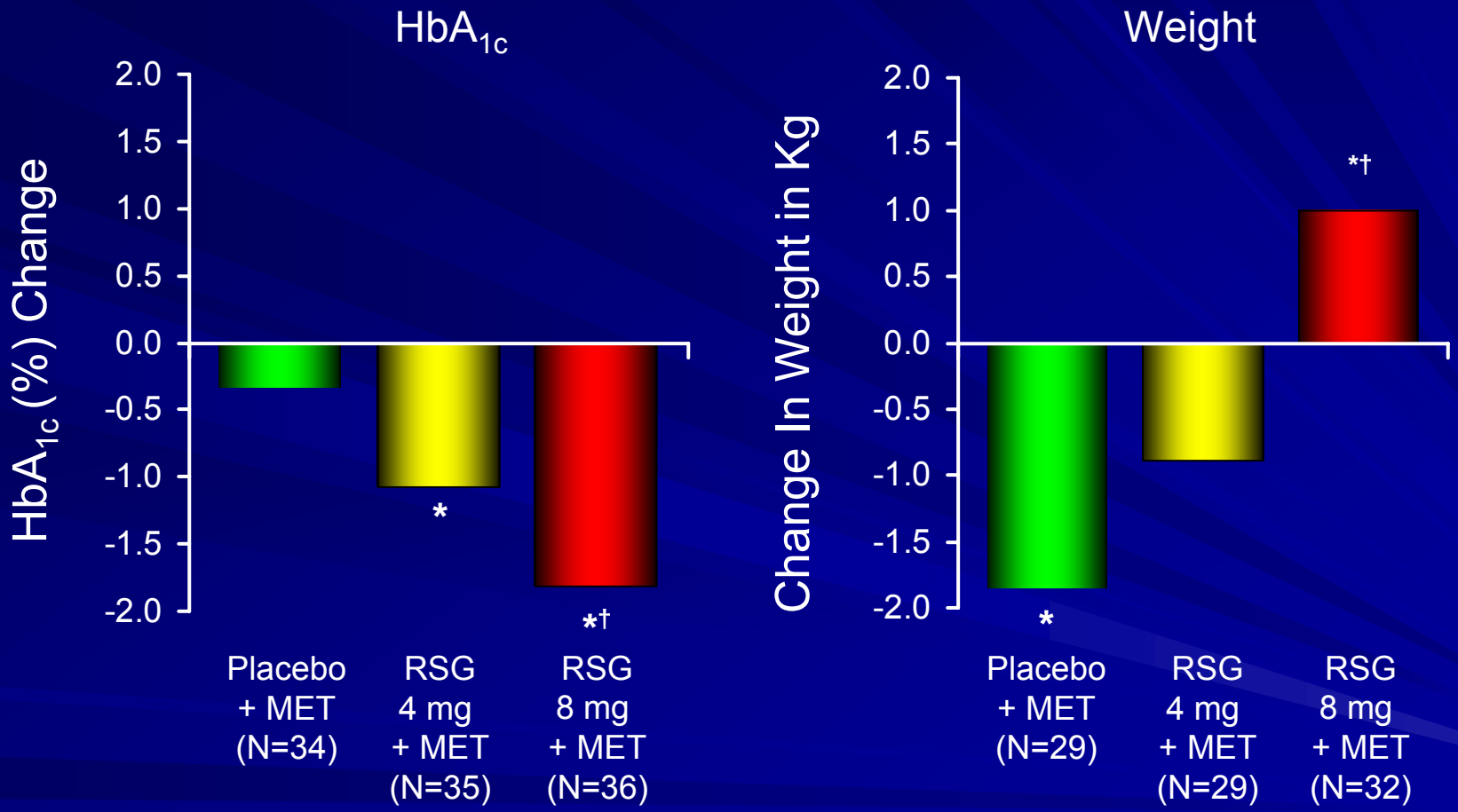
Bell DSH et al. *Am J Med*. 2003;115(8A) 20S-23S.

C-Peptide & Thiazolidinediones

Patient F.T.N.		C-Peptide	A1c
Insulin		3.7 ng/mL	12.0%
d/c insulin Begin SU + Met	6 mo	3.7	6.9
Add TZD (Rezulin)	12 mo		10.0
	18 mo	6.3	10.0
	24 mo	9.4	6.6

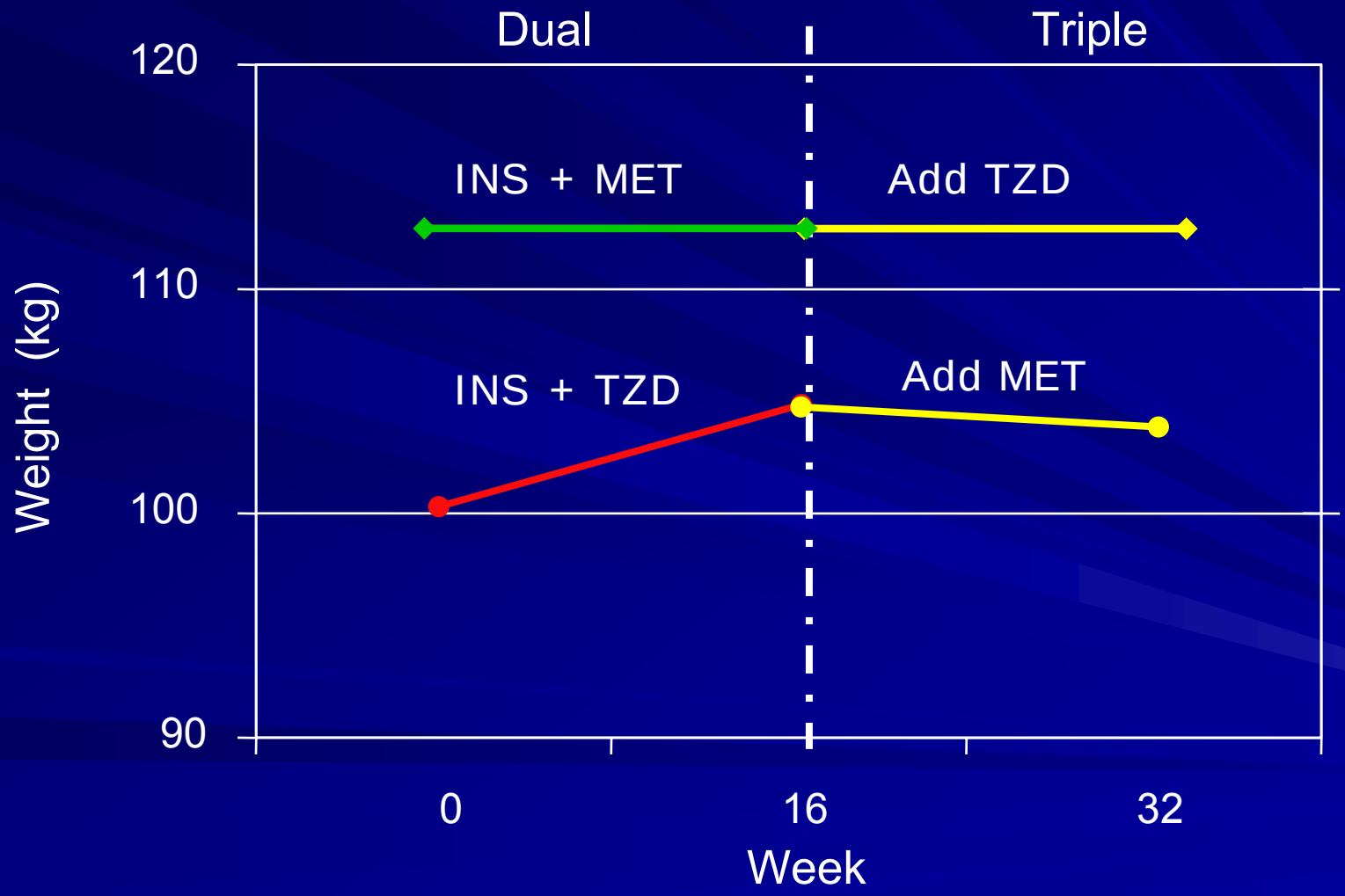
Bell DSH et al. *Am J Med.* 2003;115(8A) 20S-23S.

Effects Of Rosiglitazone Plus Metformin On A1c and Weight



*Significant difference from screening. †Significant difference from metformin.
Study 044. Data on File. GlaxoSmithKline.

Change in Mean Weight With Dual and Triple Therapy

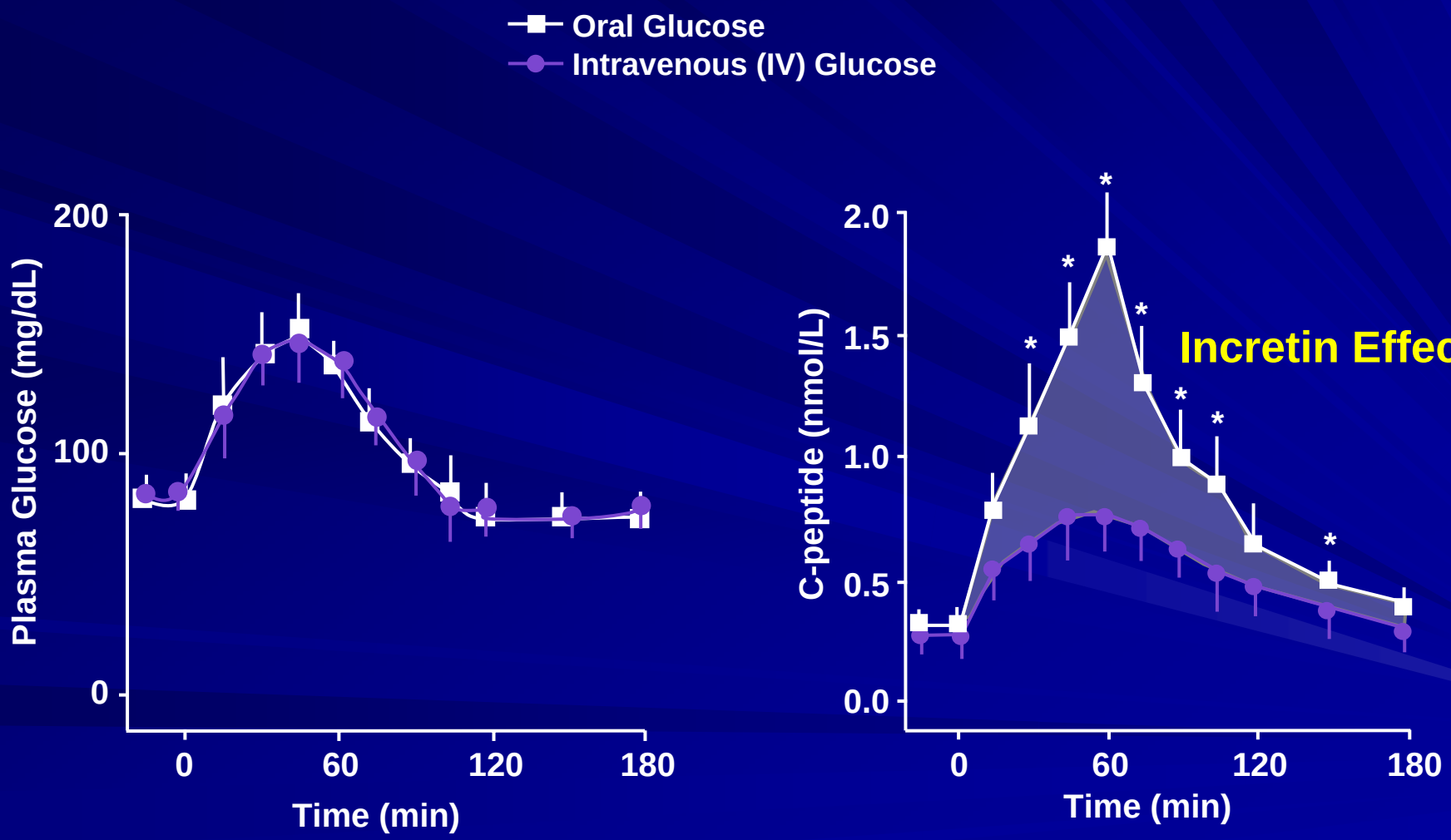


Strowig SM et al. *Diabetes Care*. 2004;27:1577-1583.

Options For Combination Therapy In Patients Who Cannot Use Metformin or a TZD: Incretins

- Use Exenatide (GLP-1 analog incretin mimetic)
- Options include
  - SU + Exenatide
  - Metformin + Exenatide
  - SU + Metformin + Exenatide
- Exenatide is not yet approved for use with TZD's

The Incretin Effect in Healthy Subjects

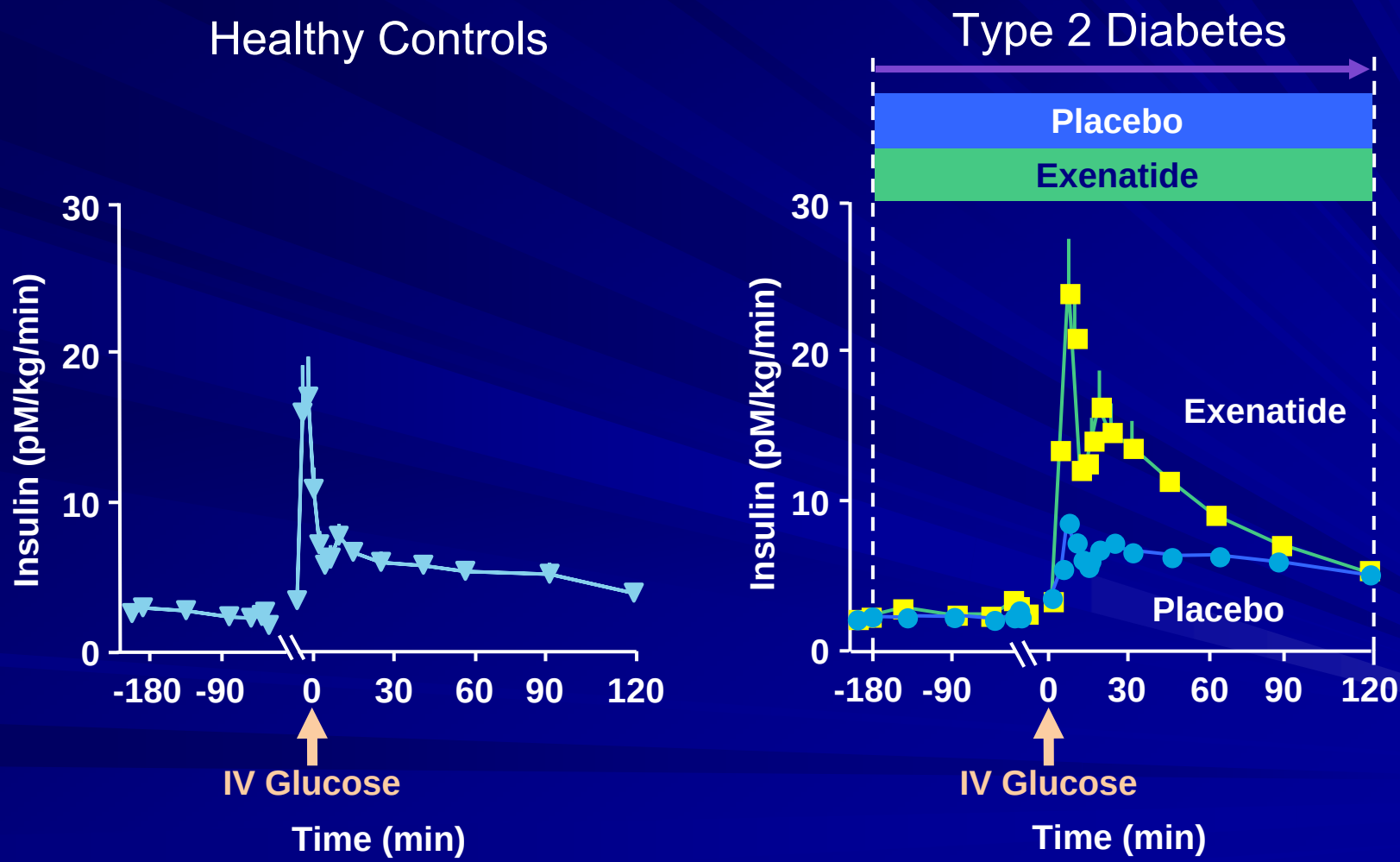


Data from Nauck MA, et al. *J Clin Endocrinol Metab*. 1986;63:492-498

Exenatide: The Synthetic Analog of GLP-1

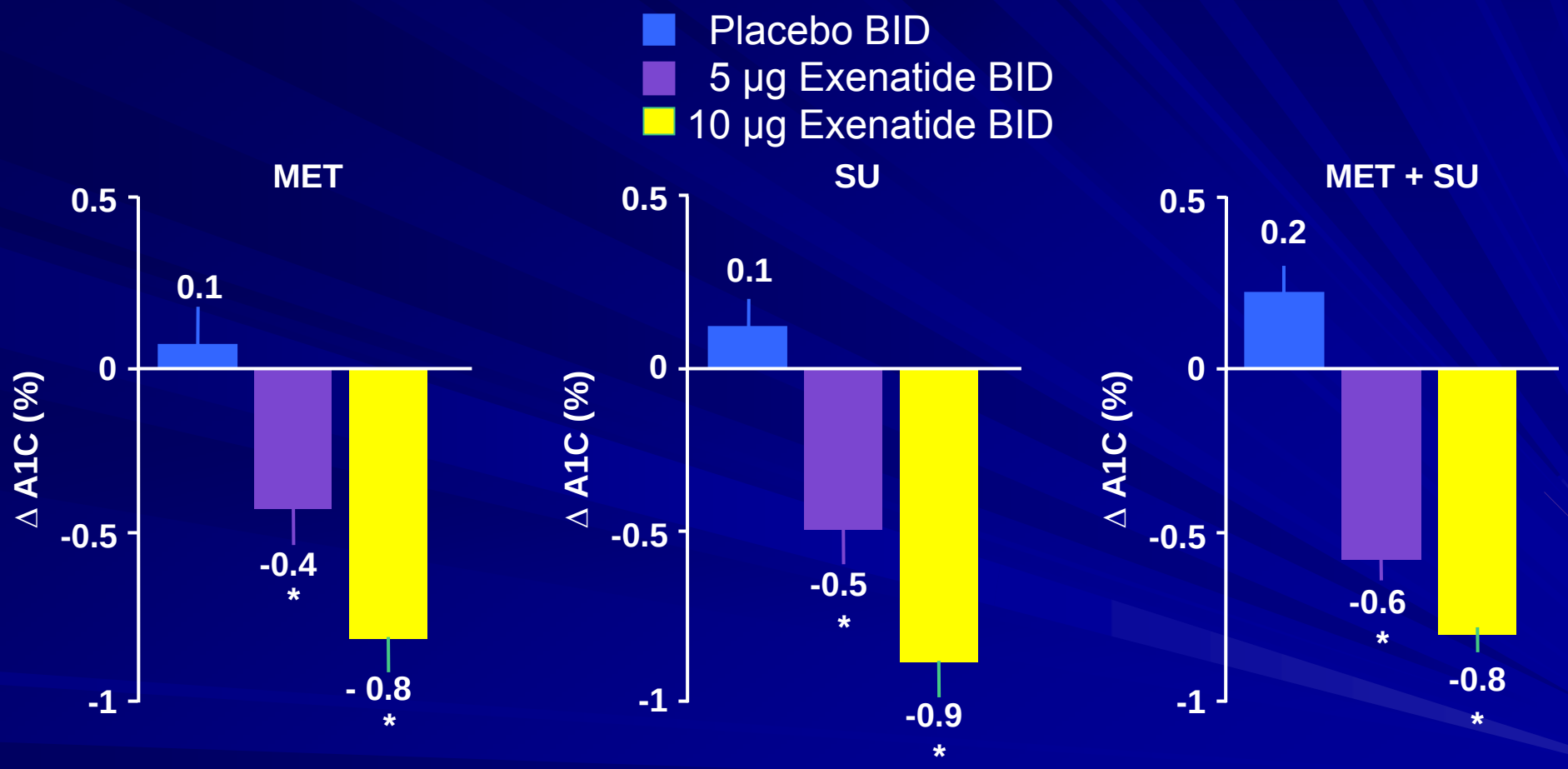
	GLP-1	Exenatide
↑ Glucose-dependent insulin secretion	✓	✓
↓ Glucagon secretion ↓Hepatic glucose output	✓	✓
↓ Gastric emptying ↓ Glucose absorption	✓	✓
↓ Food intake (induces satiety)	✓	✓
↓ Postprandial glucose to near-normal	✓	✓
Weight loss	No	Yes
Resistant to DPP-IV degradation	No	Yes
Half-life after SQ injection	Short	Long

Exenatide Restores the 1st Phase Insulin Response



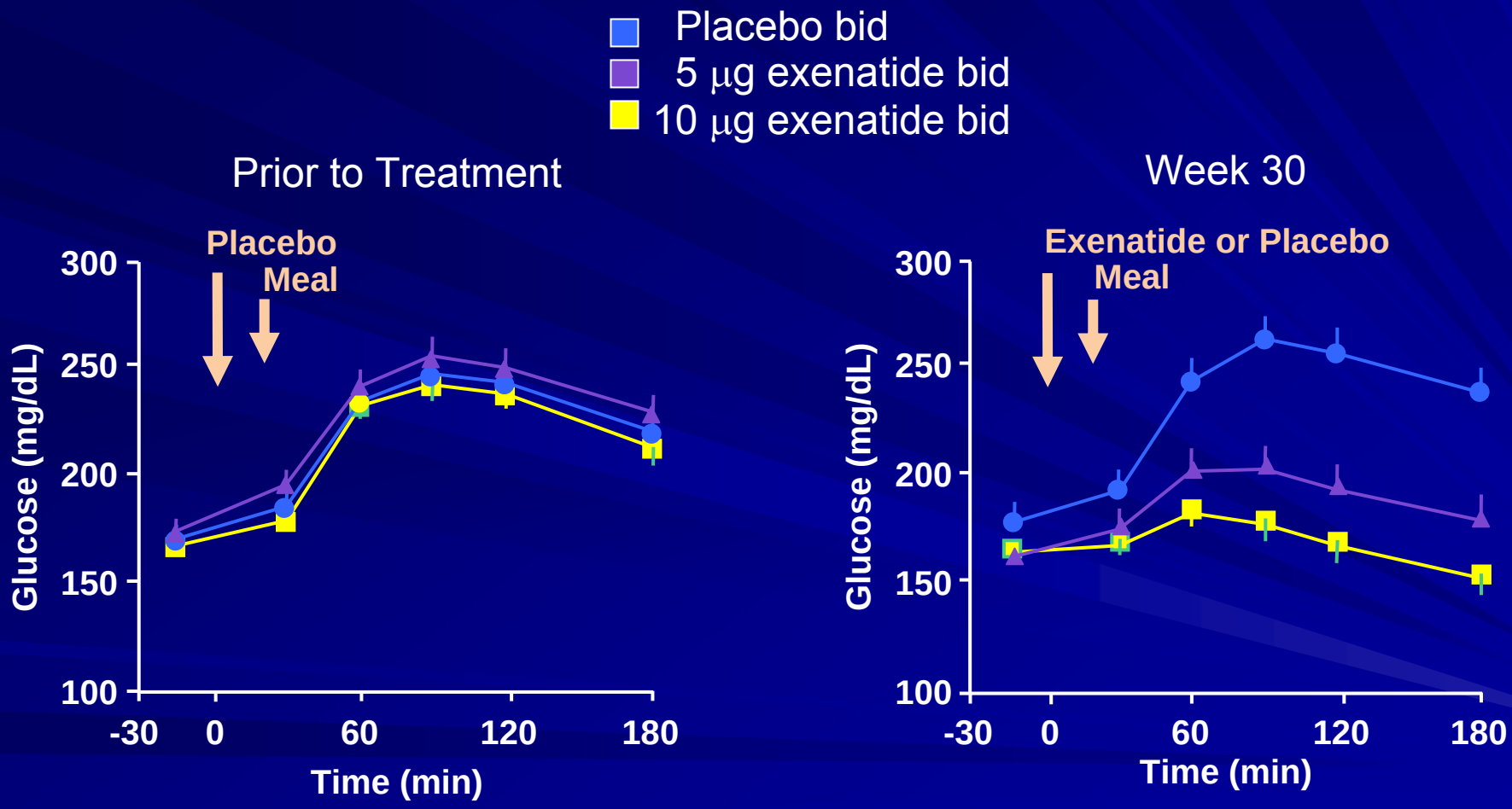
Data from Fehse F, et al. *Diabetologia*. 2004;47(suppl 1):A279

Exenatide Lowers A1c



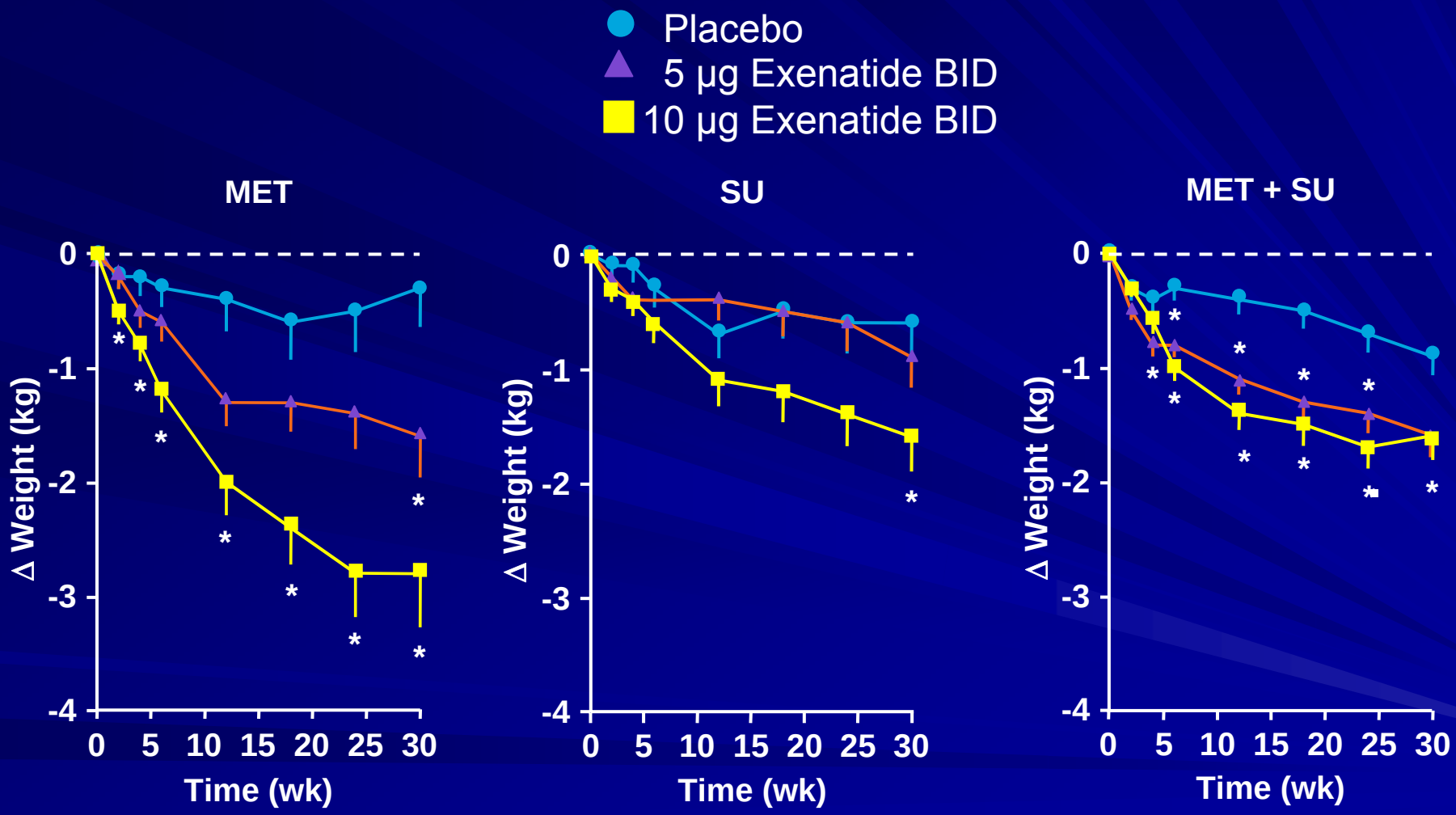
DeFronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100; Buse JB, et al. *Diabetes Care.* 2004;27:2628-2635
Kendall DM, et al. *Diabetes Care.* 2005;28:1083-1091

Exenatide Lowers Postprandial Glucose



Data on file, Amylin Pharmaceuticals, Inc.

Exenatide: Effect on Weight



DeFronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100; Buse JB, et al. *Diabetes Care.* 2004;27:2628-2635
Kendall DM, et al. *Diabetes Care.* 2005;28:1083-1091

What Is The Next Step For The Patient Who Has Failed Dual Therapy?

- If Glycemic goals have not been met after 3 months on dual therapy:

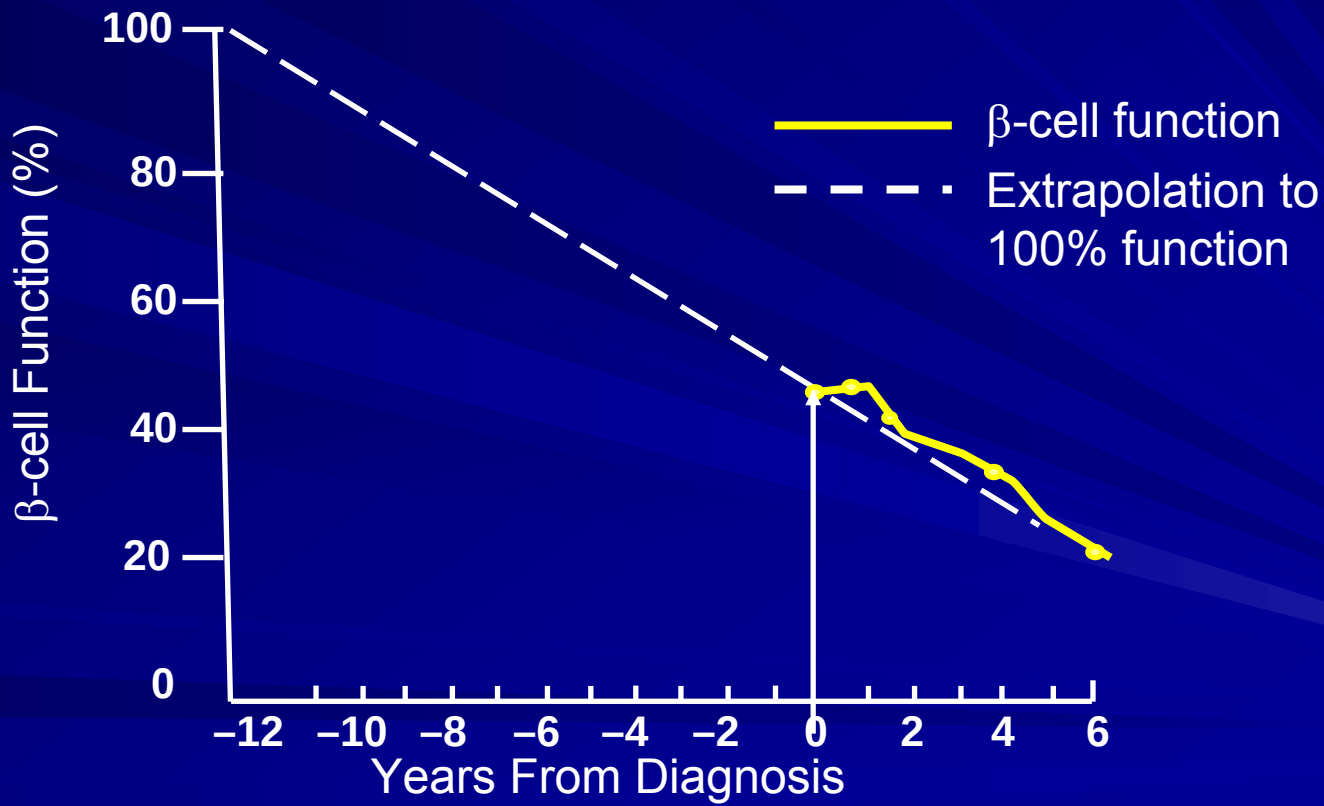
  Add a 3 oral agent or Exenatide if A1c is < 8.5%

  OR

  Add insulin for any A1c above goal

TYPE 2 DIABETES..... A PROGRESSIVE DISEASE

Over Time, Most Patients Will Need Insulin To Control Glucose



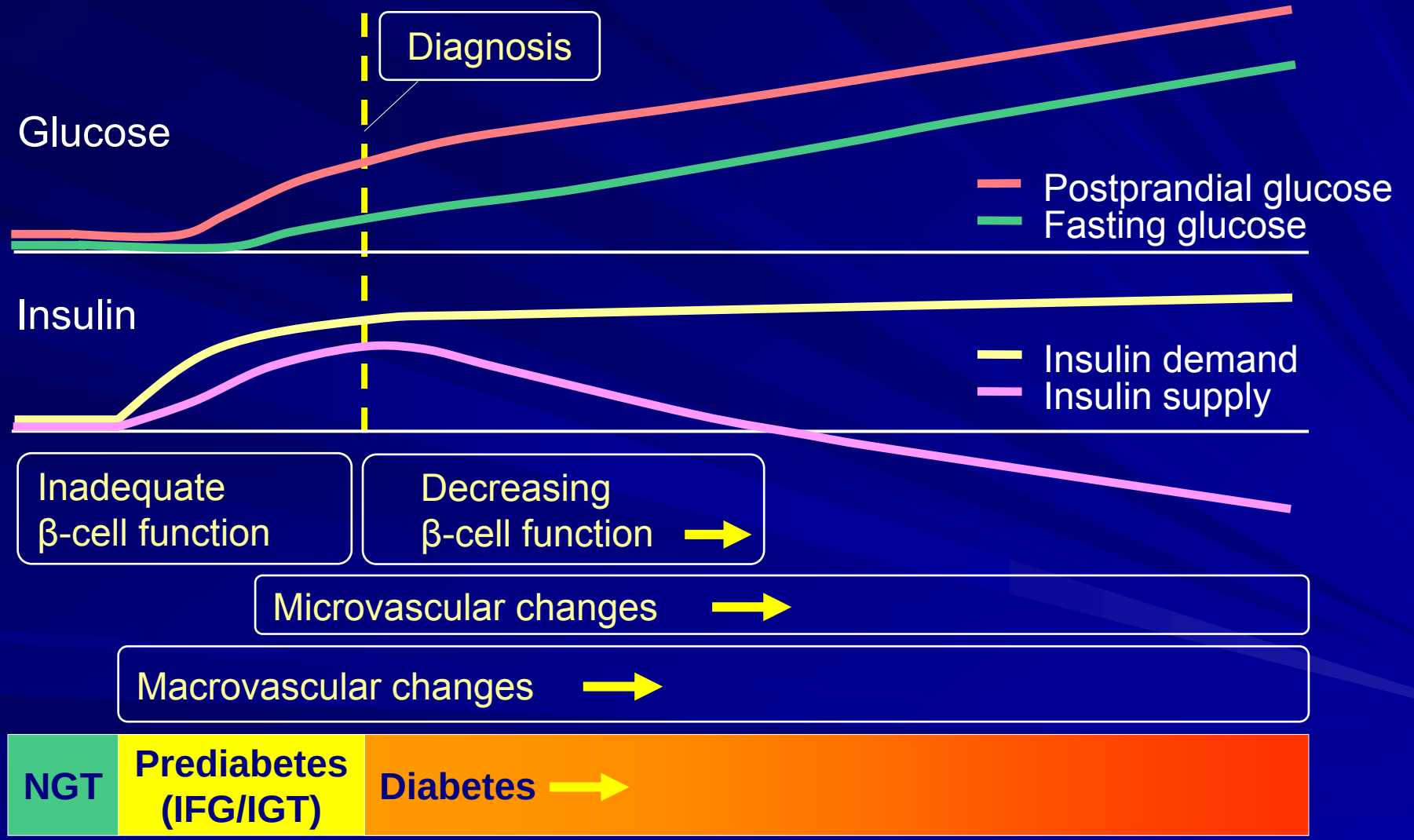
Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl)S21, modified from UKPDS Group. *Diabetes* 1995;44:1249

ACE Position Statement*

Early use of insulin therapy is frequently needed for timely achievement of glycemic goals. In type 2 diabetes, targets may be achieved by basal insulin plus oral agents or basal-bolus insulin regimens; pre-mixed insulin preparations can be used in special situations

*Implementation Conference for ACE Outpatient Diabetes Mellitus Consensus Conference Recommendations, February 2, 2005

Progression of T2DM Reflects an Increasing Imbalance Between Insulin Supply and Demand



Adapted from *Type 2 Diabetes BASICS.* International Diabetes Center; 2000.

Why Is Basal-Bolus Insulin Therapy Recommended?

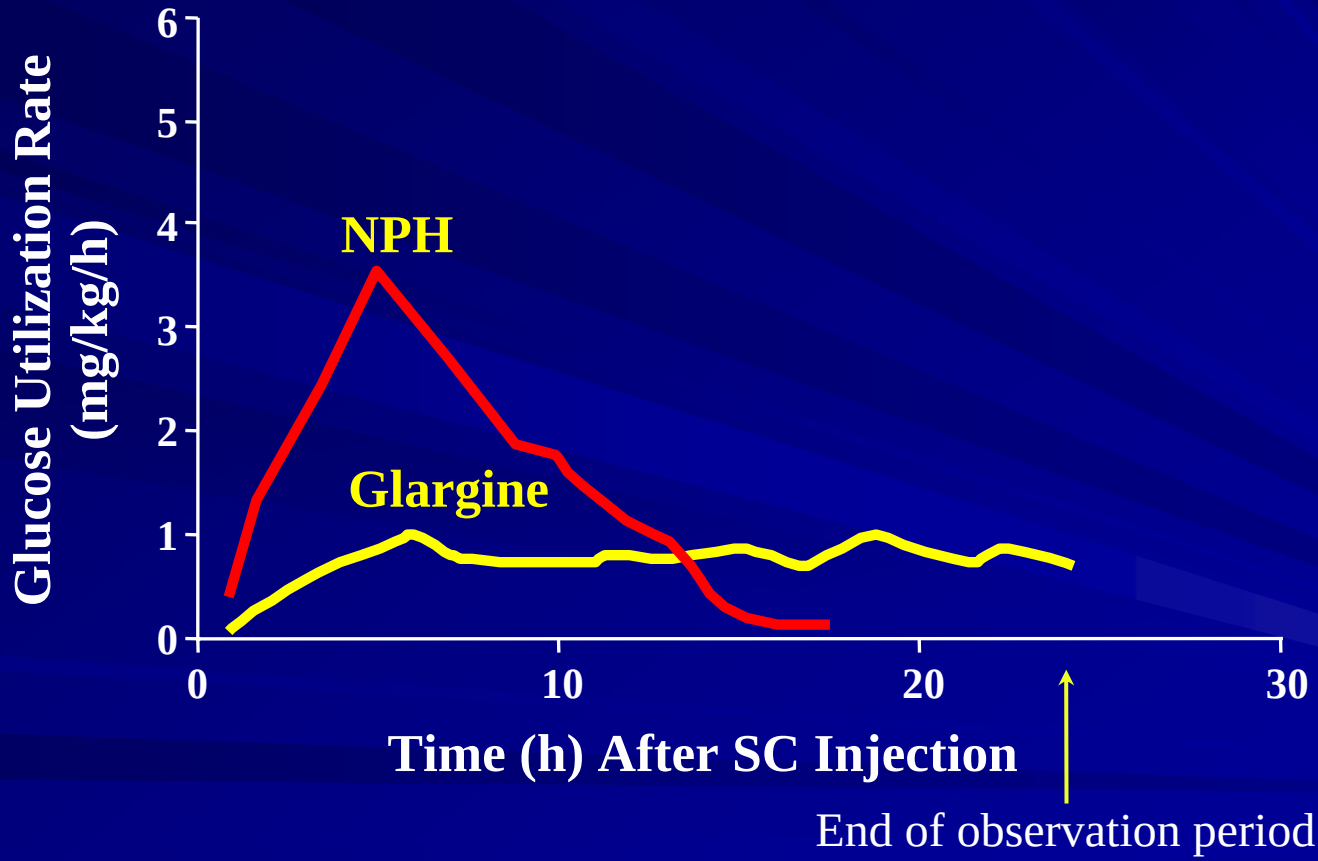
- Safety: There are now more than 30 studies demonstrating that glucose can be managed to goal with about 50% less hypoglycemic events using glargine rather than NPH

Spellman, CW 2005. Overcoming barriers to tight glycemic control. JAOA, *In Press*

The Basal - Bolus Concept

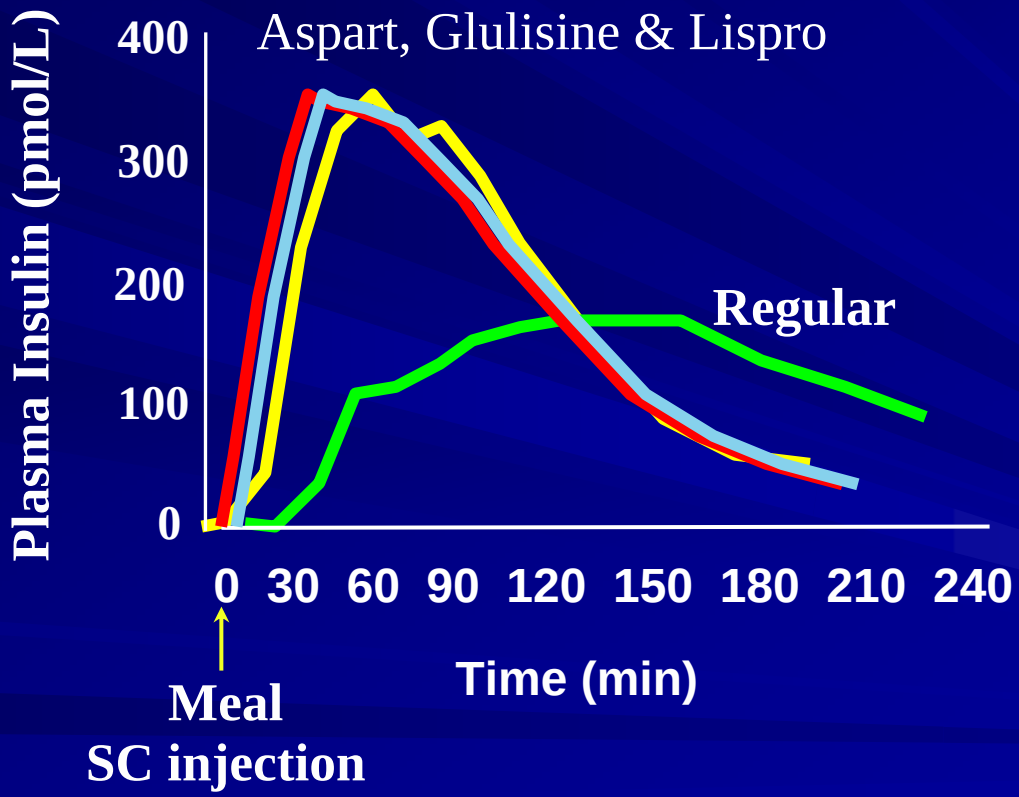
- Basal Insulin
  - Suppresses glucose production between meals and overnight fasting
  - Produced at nearly constant levels
  - Supplies about 50% of daily needs
- Bolus Insulin (Mealtime or Prandial)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of total daily insulin requirement at each meal

Glargine vs NPH Insulin: Action Profiles by Glucose Clamp



Lepore, et al. *Diabetes*. 1999;48(suppl 1):A97.

Fast Analogues Aspart, Glulisine & Lispro: Plasma Insulin Profiles



Heinemann, et al. *Diabet Med*. 1996;13:625-629; Mudaliar, et al. *Diabetes Care*. 1999;22:1501-1506.

What Is The Role of Oral Therapy, ±Exenatide, When A Patient Starts Insulin?

- When starting insulin after oral therapy failure:
  a. Continue ALL oral agent!
  b. Stop exenatide (not approved with insulin)
  c. After glycemic control is achieved, determine if the SU may be weaned

Initiating Once-Daily Insulin Therapy

- Begin 10 units glargine q a.m. (or NPH, 10 units h.s.)
- Alternative:

  0.1-0.25 units per Kg per day (weight-based dose)
- Titrate every 2 days until fasting glucose is <110

>180 mg/dL	+ 6 units		
141-180	+ 4		Add 2 units
121-140	+ 2	OR	every 2 days
100-120	+ 1		until FPG <110
<80	- 2		

Advancing Insulin Therapy

- Bolus insulin may be started several ways
  a. Arbitrarily give 5 units a.c.
  b. Give bolus based on carbohydrate counting
     i. 1 unit/15 grams carbohydrate
     ii. "Rule 500"
     500/TDD = Number grams of carbohydrate 1 unit of insulin will cover
  c. Give correction dose to cover hyperglycemia
     "Rule of 1800"
     1800/TDD =How much 1 unit of insulin will decrease the blood glucose

Advancing Insulin Therapy

- A patient using 35 units basal insulin glargine reports

a.m.	2h pp brkfst	2 h pp lunch	2 h pp dinner
95	140	140	230

- Options:
  - a. Arbitrarily add 5 units bolus insulin before dinner
  - b. Add bolus insulin based on "Carb Counting"
    - i. Give 1 unit per 15 grams carb *or*
    - ii. 500/35 = 1 unit per 14 grams carbohydrate

Advancing Insulin Therapy

- A patient uses 35 units basal insulin glargine reports

a.m.	2h pp brkfst	2 h pp lunch	2 h pp dinner
95	140	140	240

- Titrate the bolus insulin
  a. Monitor 2 h postprandial glucose
  b. Increase the dinner time insulin by 2 units every 1-2 days until the 2 h postprandial glucose that is <140-180
- Correct hyperglycemia (Rule 1800): 1800/35 = ~50
  Add 1 extra unit bolus insulin for every 50 mg% glucose >150

Advancing Insulin Therapy

- A patient using 50 units basal insulin glargine reports

a.m.	2h pp brkfst	2 h pp lunch	2 h pp dinner
95	140	190	240

- Options:

  a. Arbitrarily add 5 units bolus insulin before lunch and before dinner

  b. "Carb Count" bolus before lunch and dinner
     i. Give 1 unit per 15 grams carb *or*
     ii. 500/50 = 1 unit per 10 grams carbohydrate

Advancing Insulin Therapy

- A patient using 50 units basal insulin glargine reports

a.m.	2h pp brkfst	2 h pp lunch	2 h pp dinner
95	140	190	240

- Titrate the bolus insulins
  a. Monitor 2 h postprandial glucose
  b. Independently increase each bolus dose of insulin by 2 units every 1-2 days to reach the 2 h postprandial goals of<140-180
- Correct hyperglycemia: 1800/50 = ~35
  Add 1 extra unit bolus insulin for every 35 mg% glucose >135

Advancing Insulin Therapy

- An 80 Kg patient using 30 units glargine reports

a.m.	2h pp brkfst	2 h pp lunch	2 h pp dinner
95	190	240	240

- Options: Add bolus *or* begin Physiologic Insulin
- Physiologic Insulin: Give 0.5 units insulin per Kg
  50% = basal glargine
  50% = bolus fast analog ÷ t.i.d.
- Example: 80 Kg x 0.5 units/Kg = 40 U insulin
  Give 20 units glargine each morning
  Give ~7 units bolus before each meal
- Titrate and add correction doses. Recalculate the Rule 500 and Rule 1800 values as TDD increases

Advancing Insulin Therapy

- A patient is using 40 units of NPH insulin at bedtime. The morning glucose is 110 mg/dL, but hypoglycemia occurs frequently in the early a.m.

- How you convert once daily NPH to glargine?

  → Conversion is "unit-for-unit"

  Give 40 units glargine each morning

Advancing Insulin Therapy

- A patient is using NPH twice-daily: 40 units each a.m. and 25 units each p.m.

  Fasting and evening glucose are controlled, but hypoglycemia occurs ~0200 and when the patient is active.

- How do you convert a patient from multi-dose intermediate to basal insulin?

  → Glargine dose is 80% of the *total* NPH dose, *or* 80% (40 +25) = 52

  Give 52 units glargine each morning

Advancing Insulin Therapy

- A patient is using 70/30 premix twice-daily: 30 units q a.m. + 20 units q p.m. Glycemic excursions occur.
- How do you convert from twice-daily premix to basal:bolus insulin?

→ Glargine is 80% of the *total* intermediate insulin

Total intermediate = 70% (30 + 20) = 35 units

Glargine = 80% x 35 units = 28 units

Give 28 units glargine each morning

→ Bolus is "unit-for-unit" of the fast-acting insulin

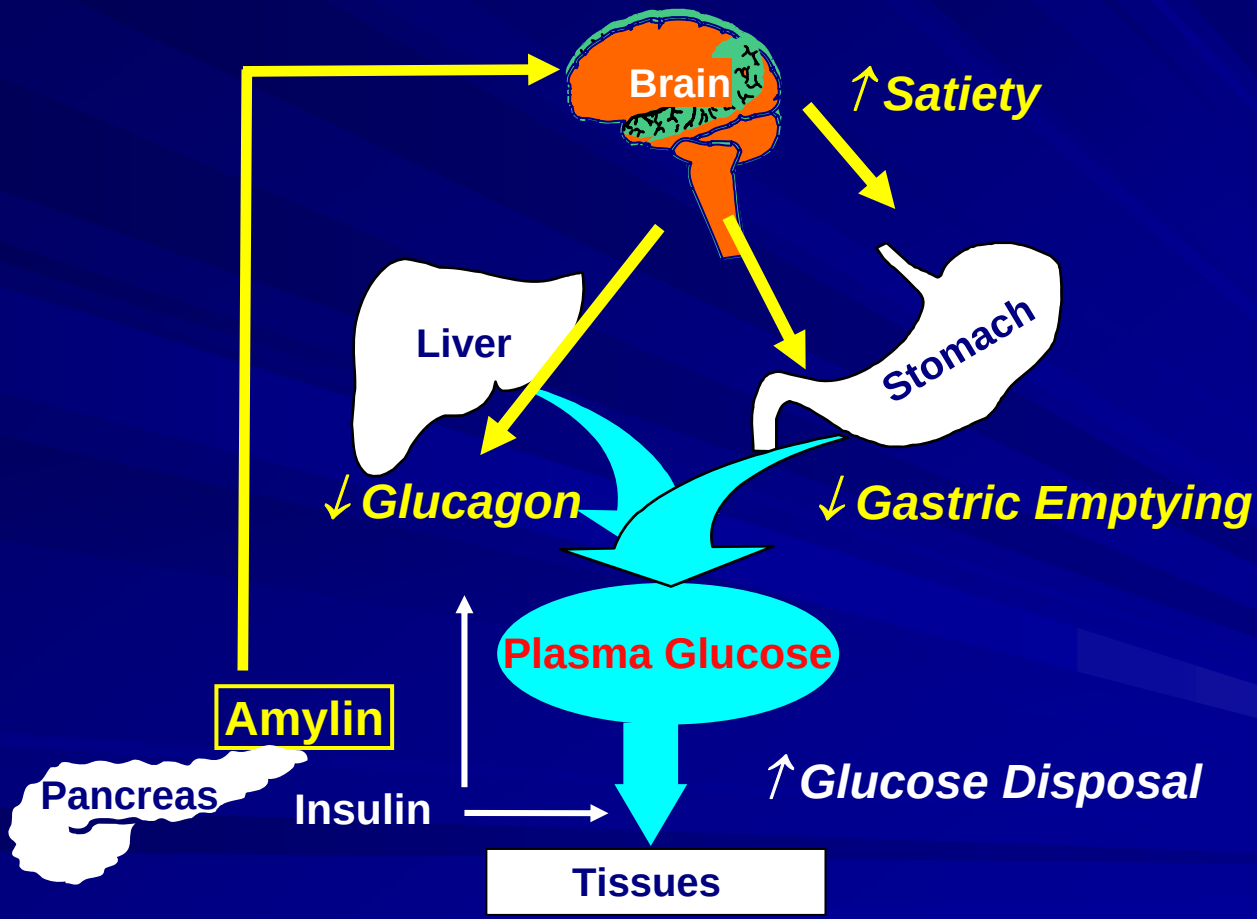
Total fast-acting = 30% (30 +20) =15 units ÷ t.i.d.

Give 5 units bolus insulin before each meal

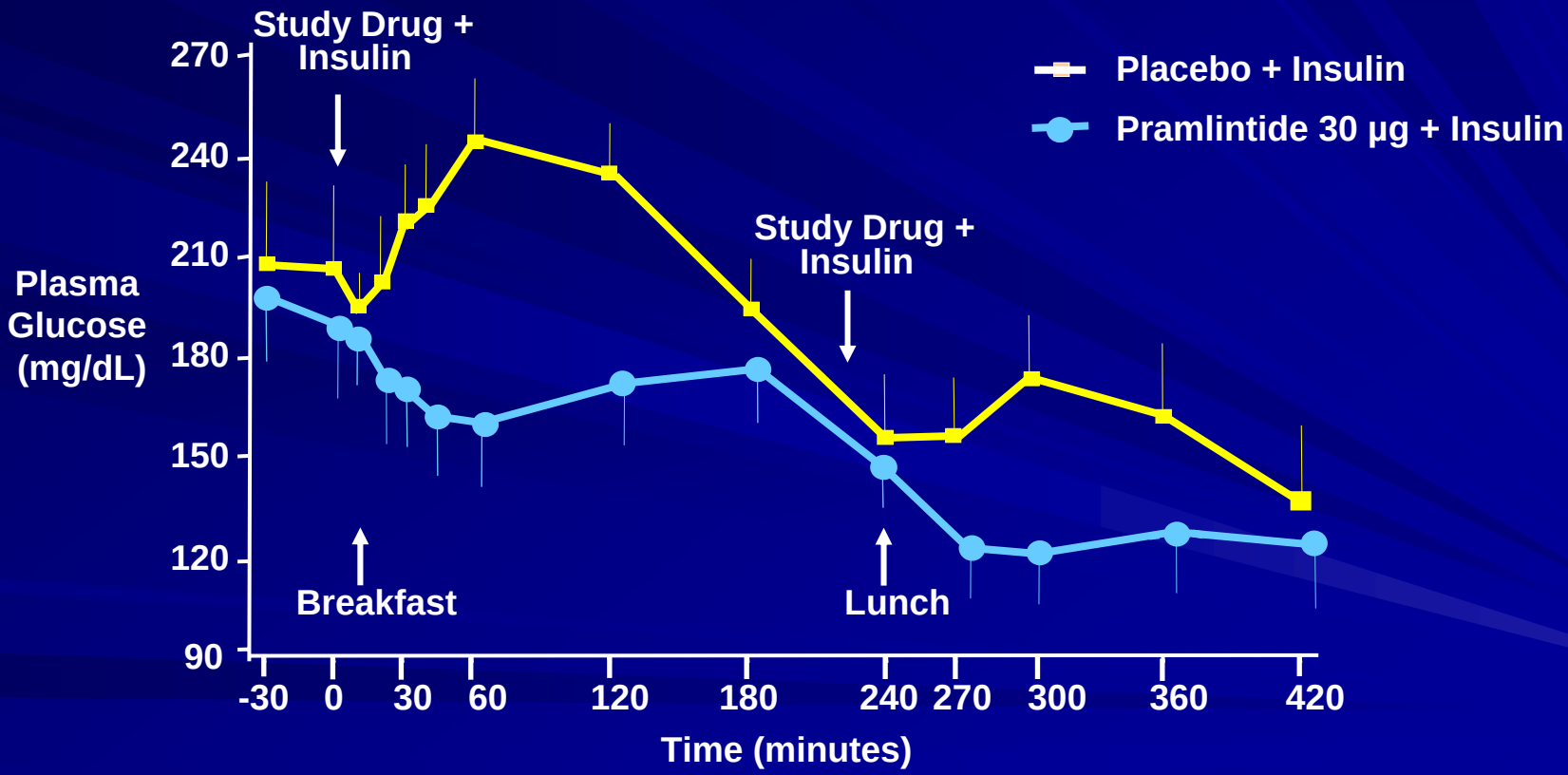
Options For Insulin-Managed Patients Who Cannot Obtain Postprandial Control

- Repeat education!
  - Medical Nutrition Therapy and Carb Counting
  - Diabetes Education
  - Insulin Management
- Insulin pump therapy is appropriate for some patients….. *but not for all patients*
- Consider Pramlinitide, a synthetic amylin analog, for postprandial control

Amylin Is A Neuroendocrine Hormone

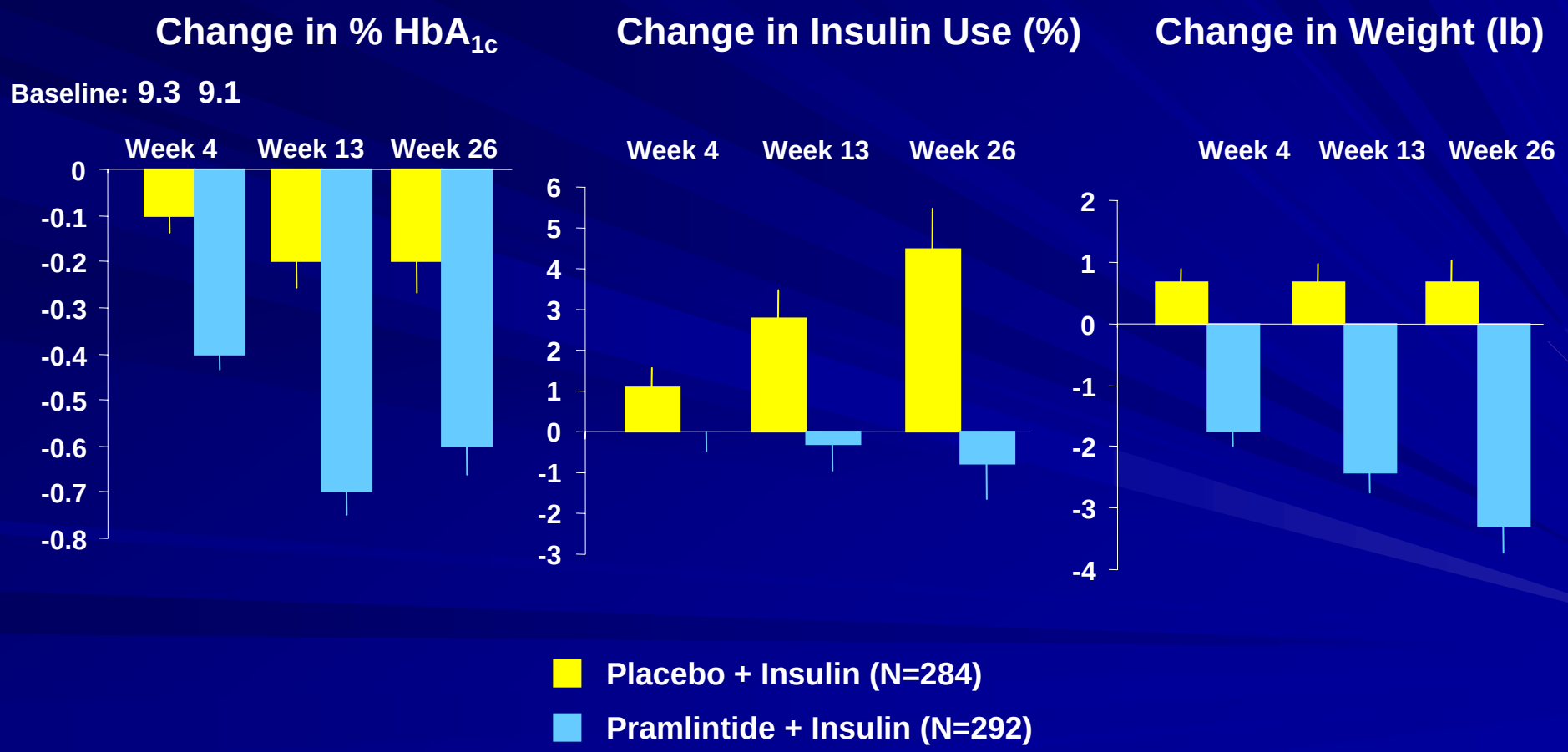


The Amylin Analog Pramlintide Plus Insulin: Effect on Postprandial Glucose Concentration



Data on file, Amylin Pharmaceuticals Inc.

Effects of Pramlintide Therapy in T2DM



Data on file, Amylin Pharmaceuticals, Inc.

Options For Insulin-Managed Patients Who Cannot Obtain Postprandial Control

- Continue basal glargine, same dose
- Decrease each bolus dose ~50%
- Begin Pramlintide

  T1DM 15 mcg a.c. and titrate

  T2DM 30 mcg a.c. ± titrate