# New Advances in Diabetes Management

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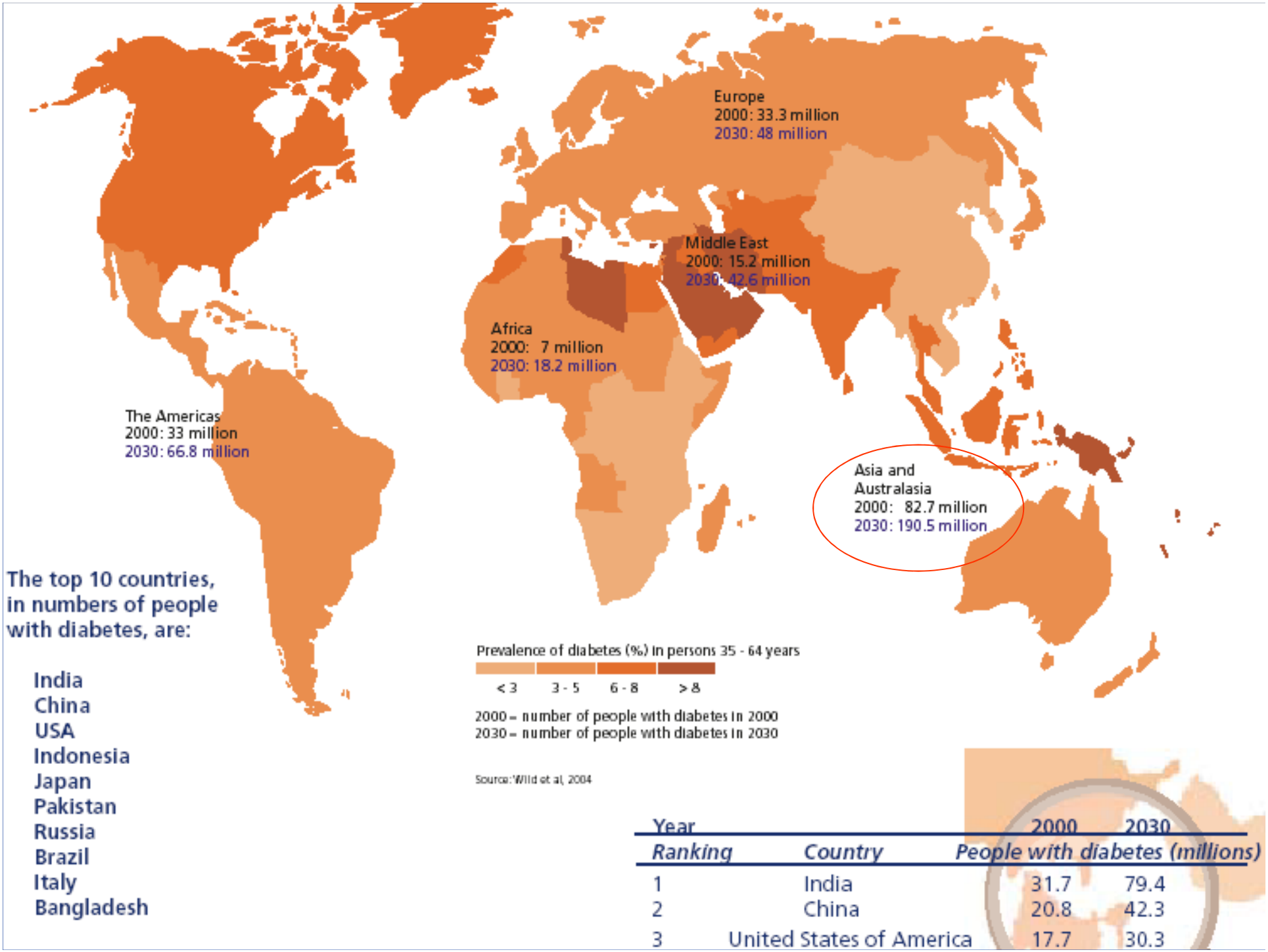
17 Jan 2009

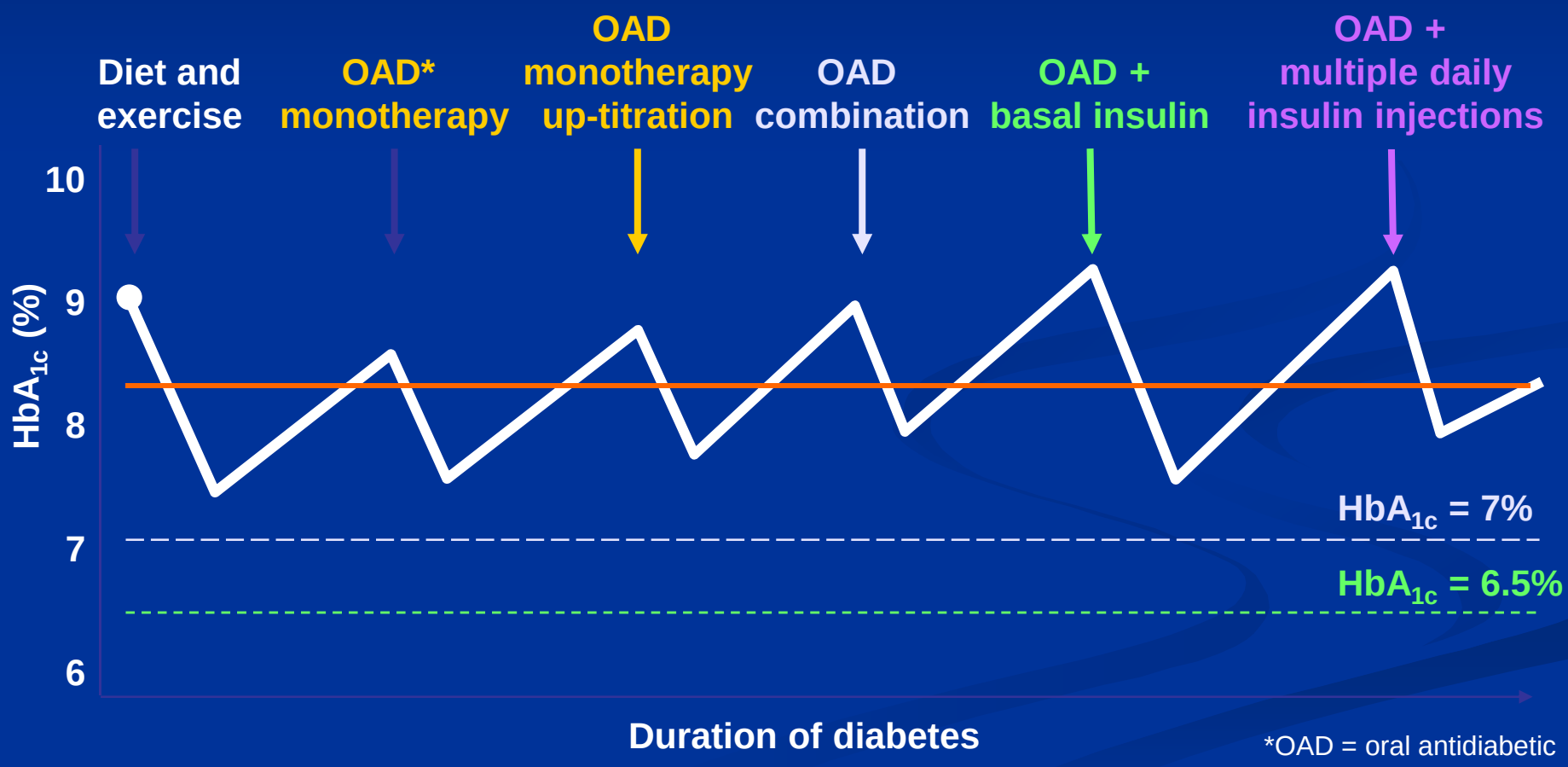



**The top 10 countries, in numbers of people with diabetes, are:**

India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh

| Year | | 2000 | 2030 |
|---|---|---|---|
| *Ranking* | *Country* | *People with diabetes (millions)* | |
| 1 | India | 31.7 | 79.4 |
| 2 | China | 20.8 | 42.3 |
| 3 | United States of America | 17.7 | 30.3 |

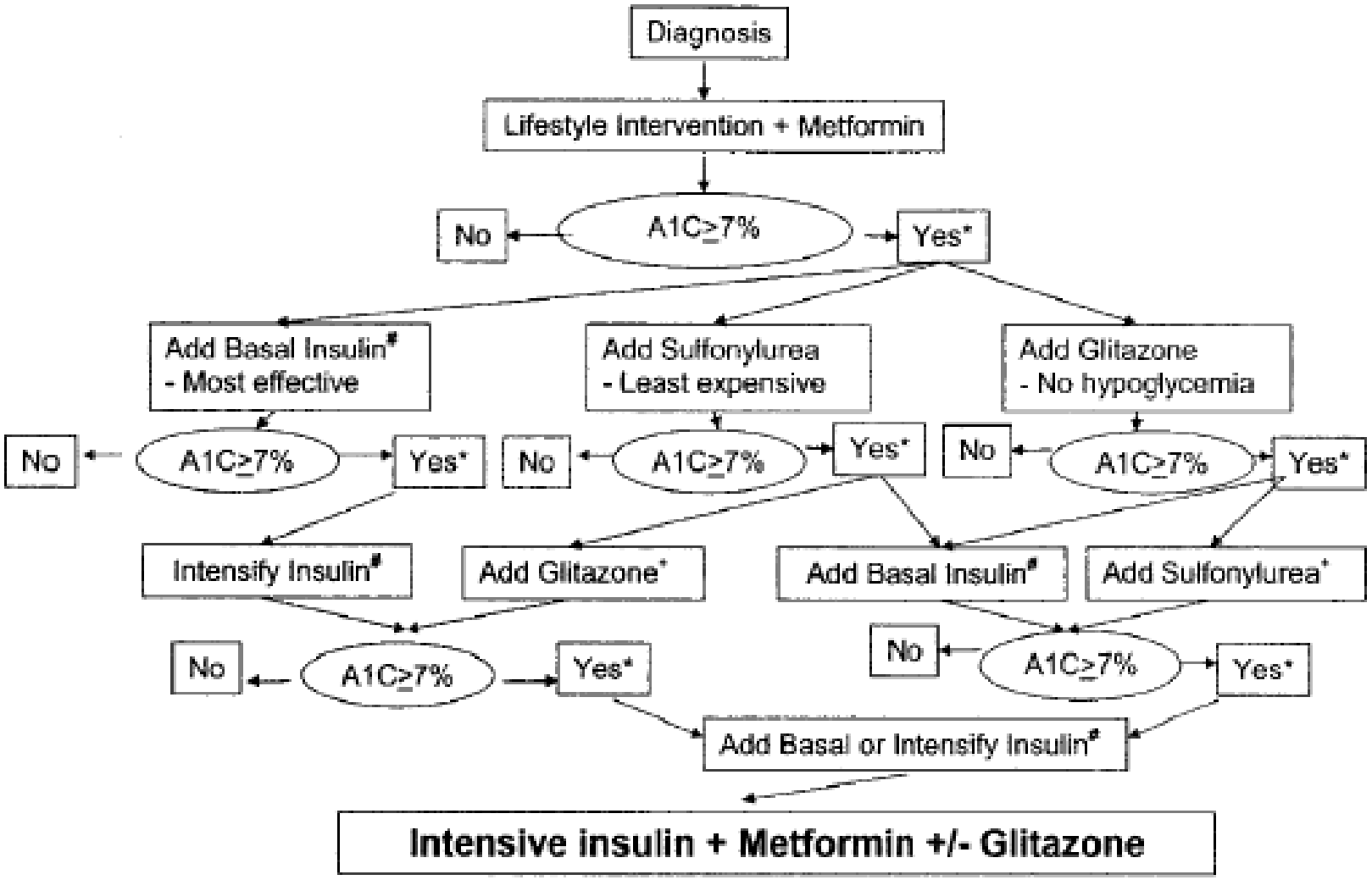
# Traditional Approach to achieve glycemic control




*OAD = oral antidiabetic

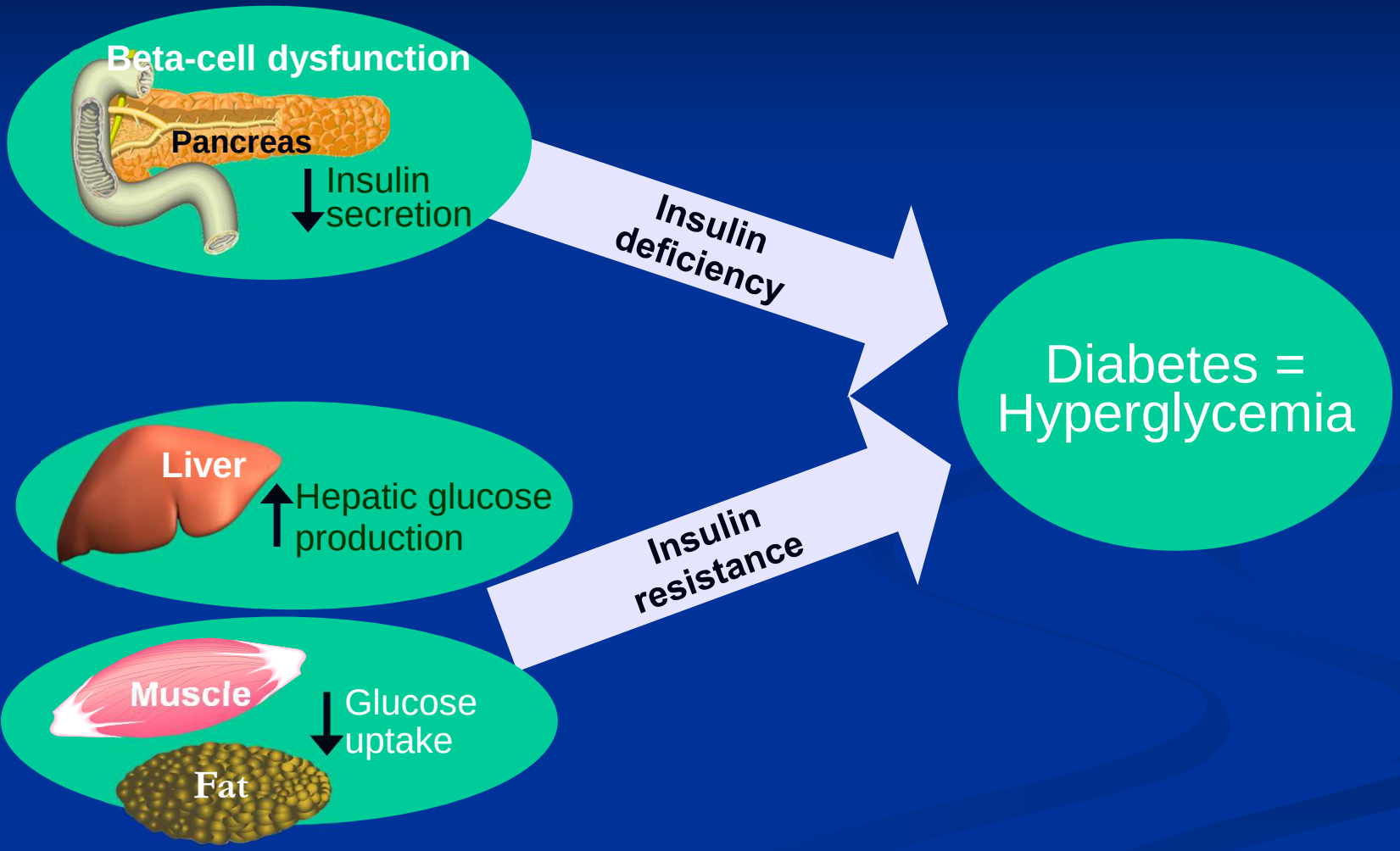
Campbell IW. *Br J Cardiol* 2000; 7:625–631.

## Algorithm for the metabolic management of type 2 diabetes



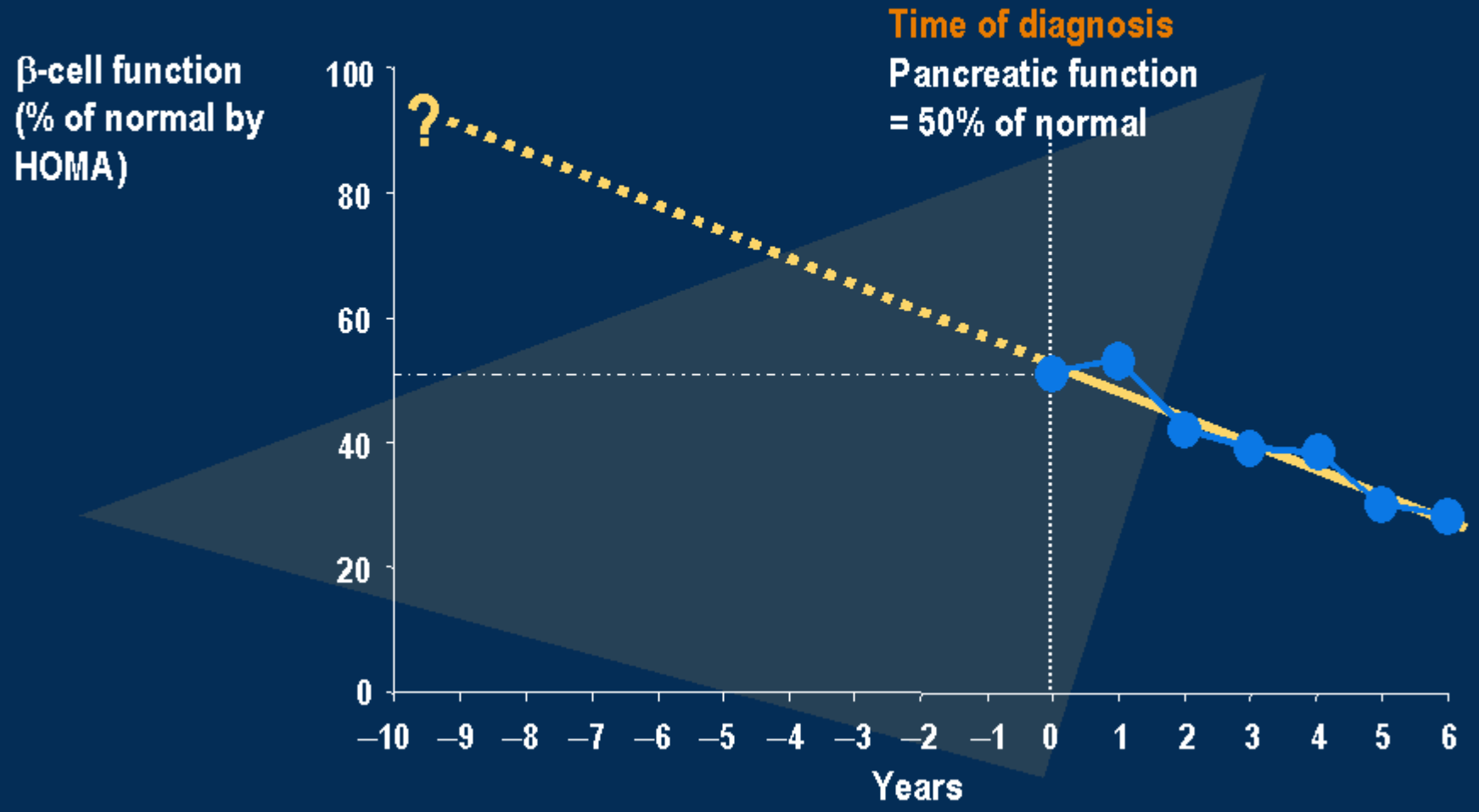

*Source: American Diabetes Association (ADA)/ The European Association for the study of diabetes ADA/EASD-2007 (EASD) 2006*

# Pathogenesis of Type 2 Diabetes




Adapted from American Diabetes Association *Diabetes Care* 2004;27(suppl 1):S5–S10; Beers MH, Berkow R, eds. *Merck Manual of Diagnosis and Therapy*, 17th ed. Whitehouse Station, NJ: Merck Research Laboratories, 1999.

# Decline of β-Cell Function in the UKPDS Illustrates Progressive Nature of Diabetes




HOMA=homeostasis model assessment

Adapted from Holman RR. *Diab Res Clin Pract.* 1998;40(suppl):S21-S25

# Potential causes of progressive beta-cell failure

- Genetically programmed apoptosis
  - May not have specific treatment
- Glucotoxicity and lipotoxicity
  - Cound not explain initial loss
- Insulin resistance
  - Long term insulin hypersectetion
  - Effect on beta-cell metabolism

# As Type 2 Diabetes Progresses…

- Pancreatic beta-cell function declines,
- Glycemic control deterioates,
- Intensified treatment increases hypoglycemia,
- Weight gain…

UKPDS 34. Lancet 1998; 352:854-865.

Kahn et al (ADOPT), New Engl J Med 2006; 355(23):2427-2443.

Lebovitz 1999; 7: 139-153.

# Traditional Pharmacological Agents for Diabetes

# Oral Anti-Diabetic Agents

| | Improving Insulin Resistance | Improving Insulin Secretion | $HbA_{1c}$ Reduction |
|---|---|---|---|
| 傳統磺脲類药物 (sulphonylurea) | 0/+ | ++++ | 1% to 2% |
| 格列奈(repaglinide) | 0 | ++ | 0.9 to 1.7% |
| 雙胍類 (biguanides) | ++++ | 0 | 1% to 2% |
| 格列酮类 (glitazones) | +++ | 0 | 0.5% to 1.3% |
| α-糖苷酶抑制剂 (α-glucosidase inh) | 0 | 0 | 0.5% to 1% |

*Data from Henry. Endocrinol Metab Clin. 1997;26:553-573 - Gitlin, et al. Ann Intern Med. 1998;129:36-38 - Neuschwander-Tetri, et al. Ann Intern Med. 1998;129:38-41*

*Medical Management of Type 2 Diabetes. 4th ed. Alexandria, Va: American Diabetes Association; 1998:1-139 - Fonseca, et al. J Clin Endocrinol Metab. 1998;83:3169-3176*
*Data from Bell & Hadden. Endocrinol Metab Clin. 1997;26:523-537 - De Fronzo, et al. N Engl J Med. 1995;333:541-549 - Bailey & Turner. N Engl J Med. 1996;334:574-579*

*Medical Management of Type 2 Diabetes. 4th ed. Alexandria, Va: American Diabetes Association; 1998:1-139 - Goldberg, et al. Diabetes Care 21:1897-1903*

# *Differences among Current OAD*

| Class | Primary therapeutic effect | Limitations |
|---|---|---|
| Sulfonylureas | ↓ $HbA_{1c}$ | Hypoglycemia, weight gain |
| Meglitinides | ↓ PPG | Hypoglycemia, weight gain |
| Biguanides (metformin) | ↓ $HbA_{1c}$ | GI adverse effects, lactic acidosis (rare) |
| PPARs | ↓ $HbA_{1c}$ | Weight gain, edema, anemia |
| Alpha-glucosidase inhibitors | ↓ PPG | GI adverse effects |

Adapted from DeFronzo RA *Ann Intern Med* 1999;131:281–303; Williams G, Pickup JC, eds. *Handbook of Diabetes*. 3rd ed. Malden, MA: Blackwell Publishing, 2004; Holz GG, Chepurny OG *Curr Med Chem* 2003;10(22):2471–2483; Meneilly GS *Diabetes Care* 2003;26(10): 2835–2841; Ahrén B et al *Diabetes Care* 2002;25(5):869–875; Moller DE *Nature* 2001;414:821–828.

# *Differences among Current OAD*

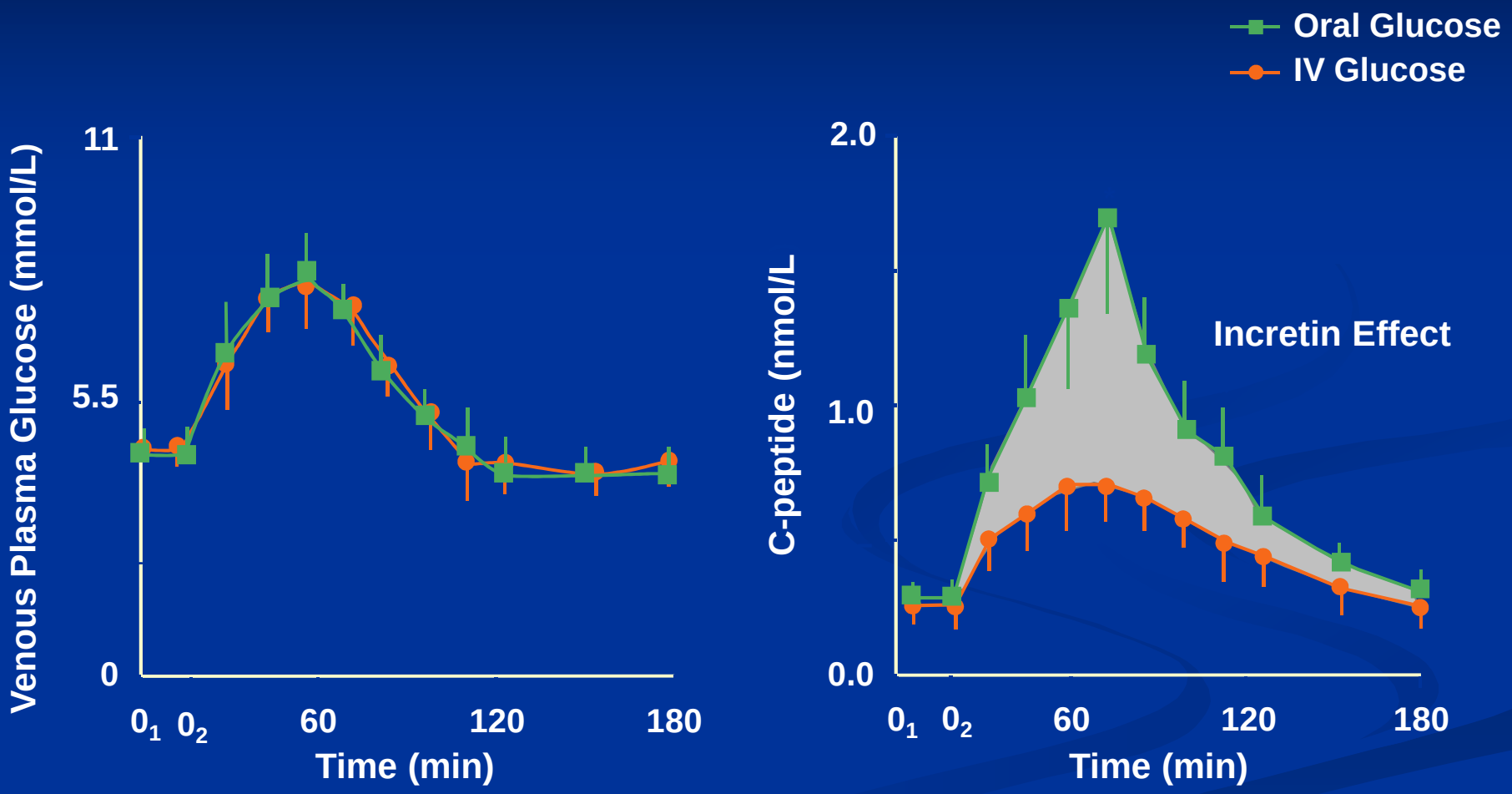
| Class | Effects on beta-cells |
|---|---|
| Sulfonylureas | Stimulation of insulin release; beta-cell exhaustion over long-term exposure |
| Meglitinides | Stimulation of insulin release; beta-cell exhaustion over long-term exposure |
| Biguanides (metformin) | No direct effects |
| PPARγ agonists | Indirect effects via improved insulin sensitivity; evidence of recovery of function |
| Alpha-glucosidase inhibitors | Allow beta-cells time to augment insulin release; no direct effects |

Adapted from Buchanan TA et al *Diabetes* 2002;51:2796–2803; Ovalle F, Bell DS *Diabetes Obes Metab* 2002;4(1):56–59; Wolffenbuttel BH, Landgraf R *Diabetes Care* 1999;22(3):463–467; DeFronzo RA *Ann Intern Med* 1999;131:281–303; Ahrén B *Curr Diab Rep* 2003;3:365–372; Drucker DJ *Expert Opin Invest Drugs* 2003;12(1):87–100; Buse JB et al. In: *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: Saunders, 2003:1427–1483; Skrumsager BK et al *J Clin Pharmacol* 2003;43(11):1244–1256.

# New Pharmacological Agents for Diabetes

# Gut Hormone in Treatment of Diabetes

# The Incretin Effect Demonstrates the Response to Oral vs IV Glucose




Mean ± SE; N = 6; *p≤.05; $0_1$-$0_2$ = glucose infusion time.

Nauck MA, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab.* 1986;63:492-498. 

# Incretin Hormones are Gastrointestinal Peptides

- Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the 2 major incretins in humans
- Both are peptide hormones (30 and 42 amino acids)
- Secreted from open-type endocrine cells (L- and K-cells, respectively) mainly in the distal (GLP-1, ileum, colon) or proximal (GIP, duodenum) small intestinal mucosa
- Released in response to meal ingestion

GLP-1 positive endocrine L-cells in human small intestine

# GLP-1 and GIP are 2 Major Incretins

## GLP-1

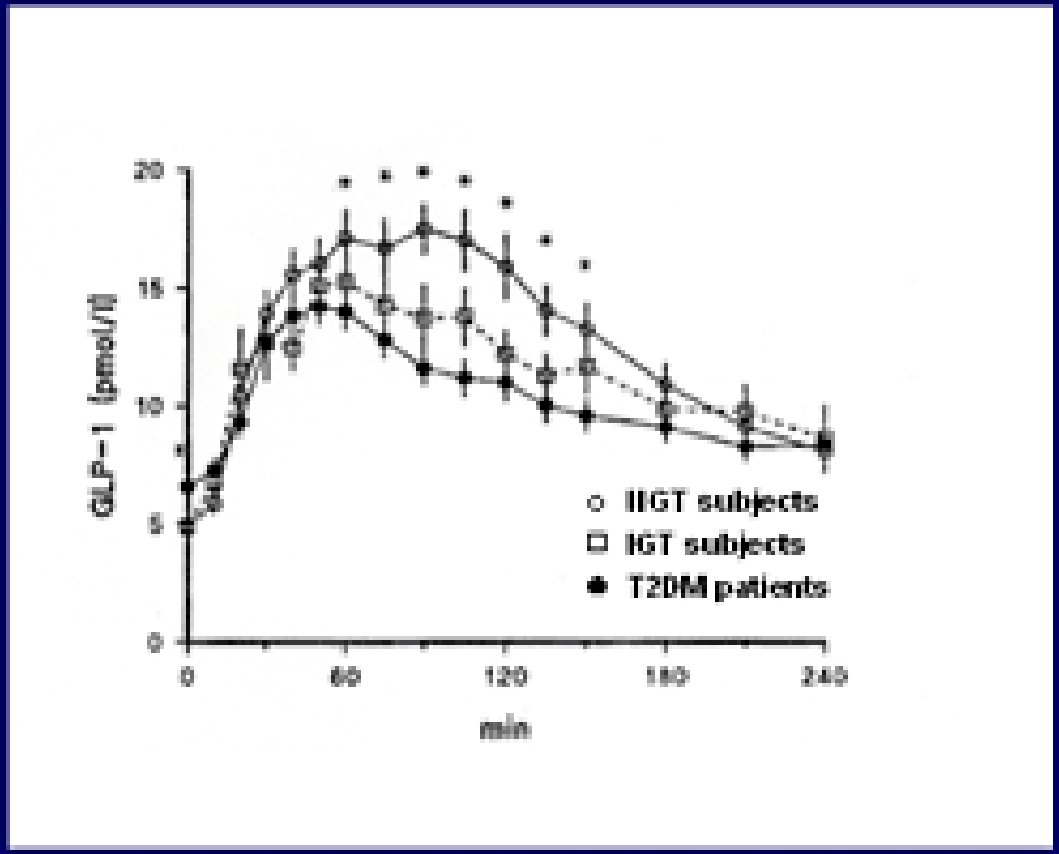
- Potentiates glucose-induced insulin secretion
- Upregulates insulin gene expression and all steps in insulin biosynthesis
- Upregulates expression of other genes essential for β-cell function
- Enhances β-cell proliferation and survival in animal models and isolated human islets
- Other effects:
  - ↓ hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner
  - ↓ gastric emptying and appetite
  - ↓ food intake
  - ↓ body weight

## GIP

- Potentiates glucose-induced insulin secretion
- Upregulates insulin gene expression and all steps in insulin biosynthesis
- Upregulates expression of other genes essential for β-cell function
- Enhances β-cell proliferation and survival in islets cell lines

- Does not inhibt glucagon secretion
- Minimal effects on gastric empyting
- No significant effects on appetite or body weight

# Postprandial GLP-1 Levels Are Decreased in Patients With IGT and Type 2 Diabetes




*P <0.05

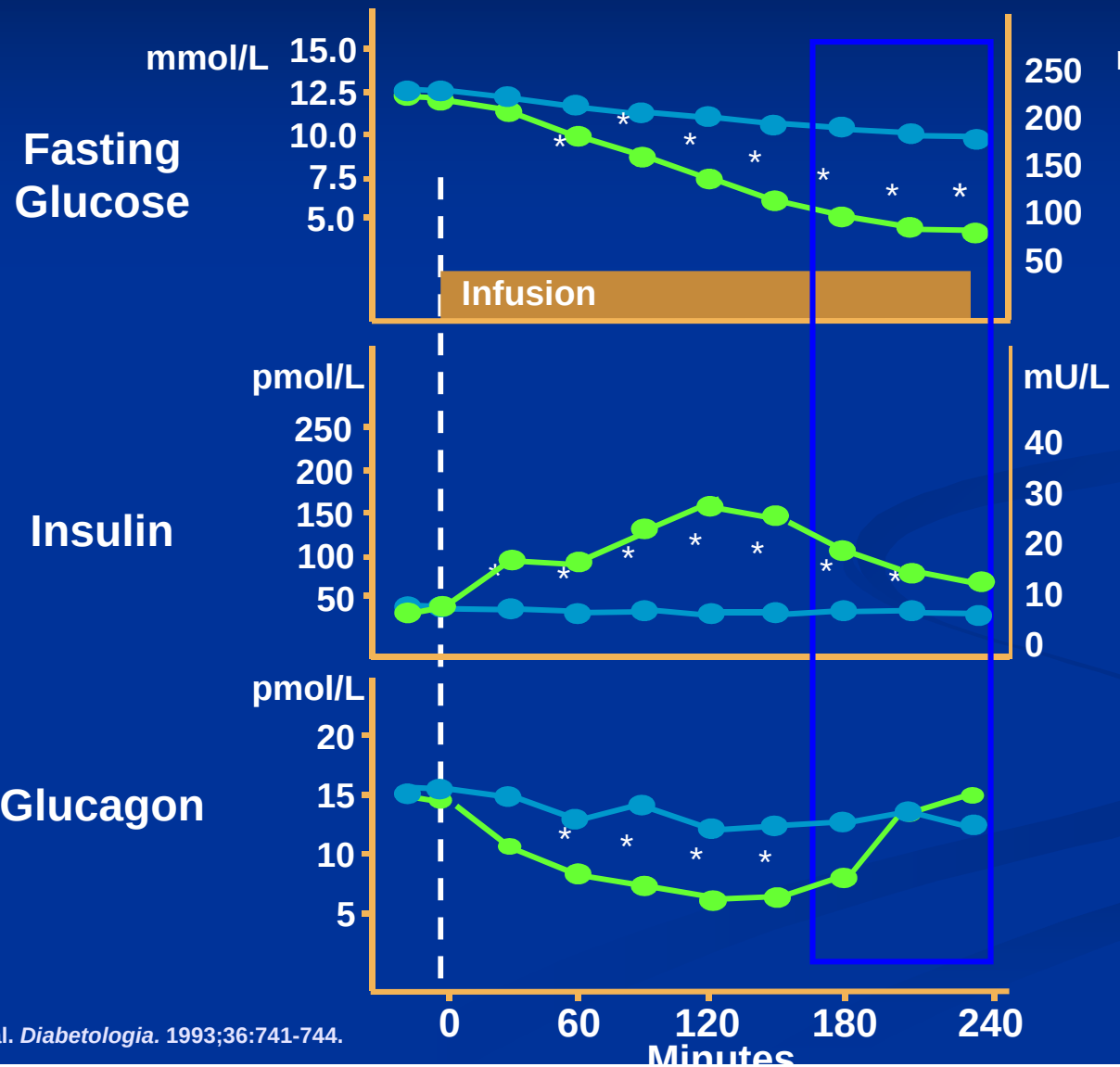
Toft-Nielsen. *J Clin Endocrinol Metab.* 2001;86(8):3717.

# The Incretin Effect is Reduced in Type 2 Diabetes

- Secretion of GLP-1 impaired
- β-cell sensitivity to GLP-1 decreased
- Secretion of GIP normal (or slightly impaired)
- Effect of GIP abolished or grossly impaired
- Inhibition of glucagon is impaired
- The loss occurs at even slight hyperglycaemia

Can metabolism be normalised if incretin function is restored by exogenous GLP-1?

# *GLP-1 Actions are Glucose Dependent in Patients with Type 2 Diabetes*




Placebo
GLP-1
*$P$ <0.05
n = 10

**Effect declines as glucose reaches normal**

Nauck NA, et al. *Diabetologia.* 1993;36:741-744.

# The Therapeutic Potential of GLP-1 Is Limited by its Rapid Inactivation

Rapid inactivation (DPP-4),
Short elimination half-life (~1-2 min)

↓

GLP-1 must be administered continuously (infusion)

↓

Inconvenient for treating a chronic disease like type 2 diabetes

Drucker DJ, et al. *Diabetes Care*. 2003;26:2929-2940.

# Current Strategies for Improving the Therapeutic Potential of GLP-1

- Agents that mimic the actions of GLP-1 (incretin mimetics)
  - DPP-4–resistant GLP-1 derivatives
    - Examples: GLP-1 analogues, albumin bound GLP-1
  - Novel peptides that mimic some of the glucoregulatory actions of GLP-1
    - Exenatide
- Agents that prolong the activity of endogenous GLP-1
  - DPP-4 Inhibitors

Drucker DJ, et al. *Diabetes Care*. 2003;26:2929-2940.; Baggio LL, et al. *Diabetes*. 2004;53:2492-2500.

# Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

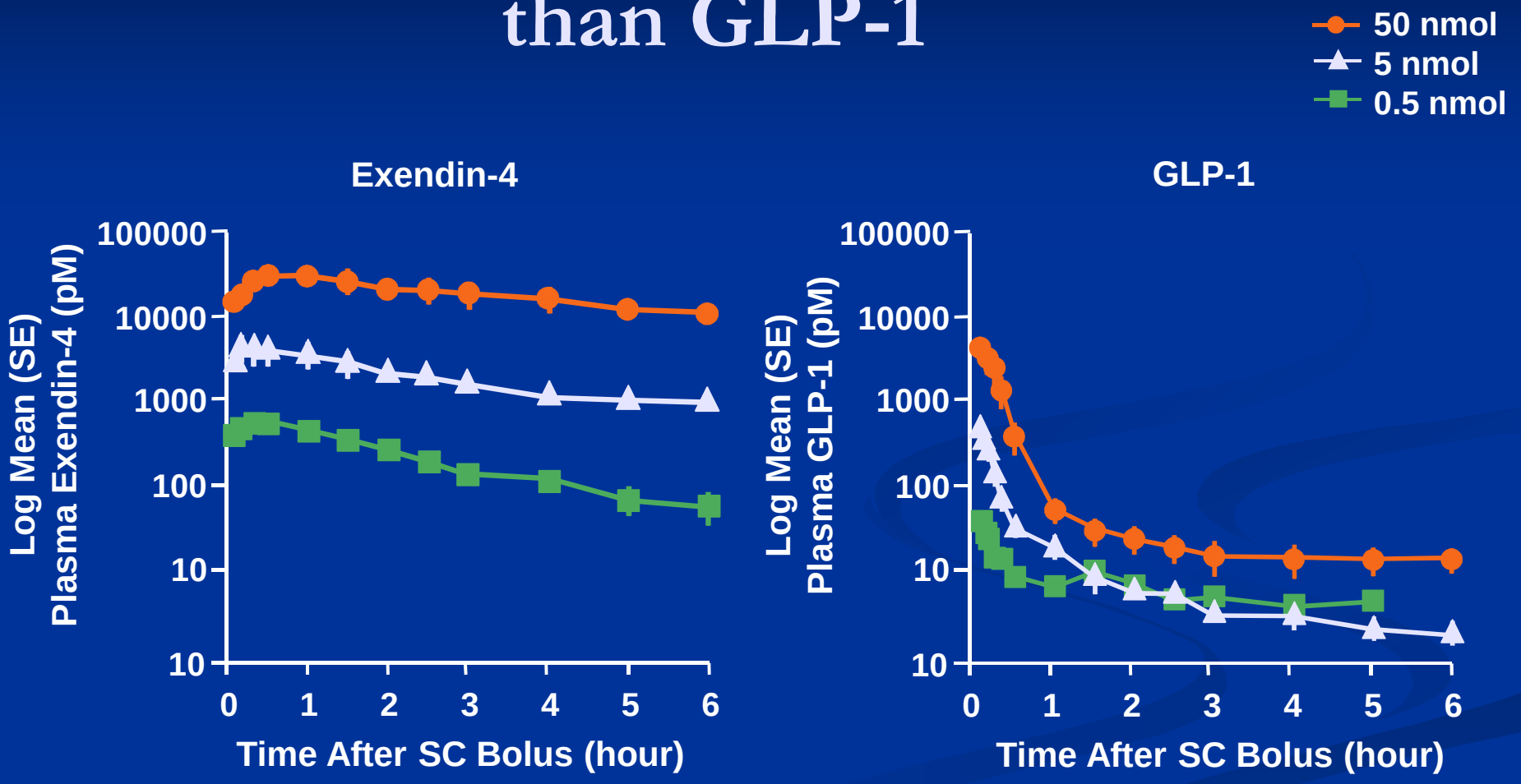
- Synthetic version of salivary protein found in the Gila monster
- Approximately 50% identity with human GLP-1
  - Binds to known human GLP-1 receptors on β cells *in vitro*
  - Resistant to DPP-4 inactivation

| | |
|---|---|
| **Exenatide** | **H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S – $NH_2$** |
| GLP-1 Human | H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R – $NH_2$ |

**Site of DPP-4 Inactivation**

**Adapted from Nielsen LL, et al. *Regulatory Peptides*. 2004;117:77-88. Reprinted from *Regulatory Peptides*, 117, Nielsen LL, et al, Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycaemic control of type 2 diabetes, 77-88, 2004, with permission from Elsevier for English use only.**

# Exenatide (Exendin-4) Remains in the Circulation Longer than GLP-1

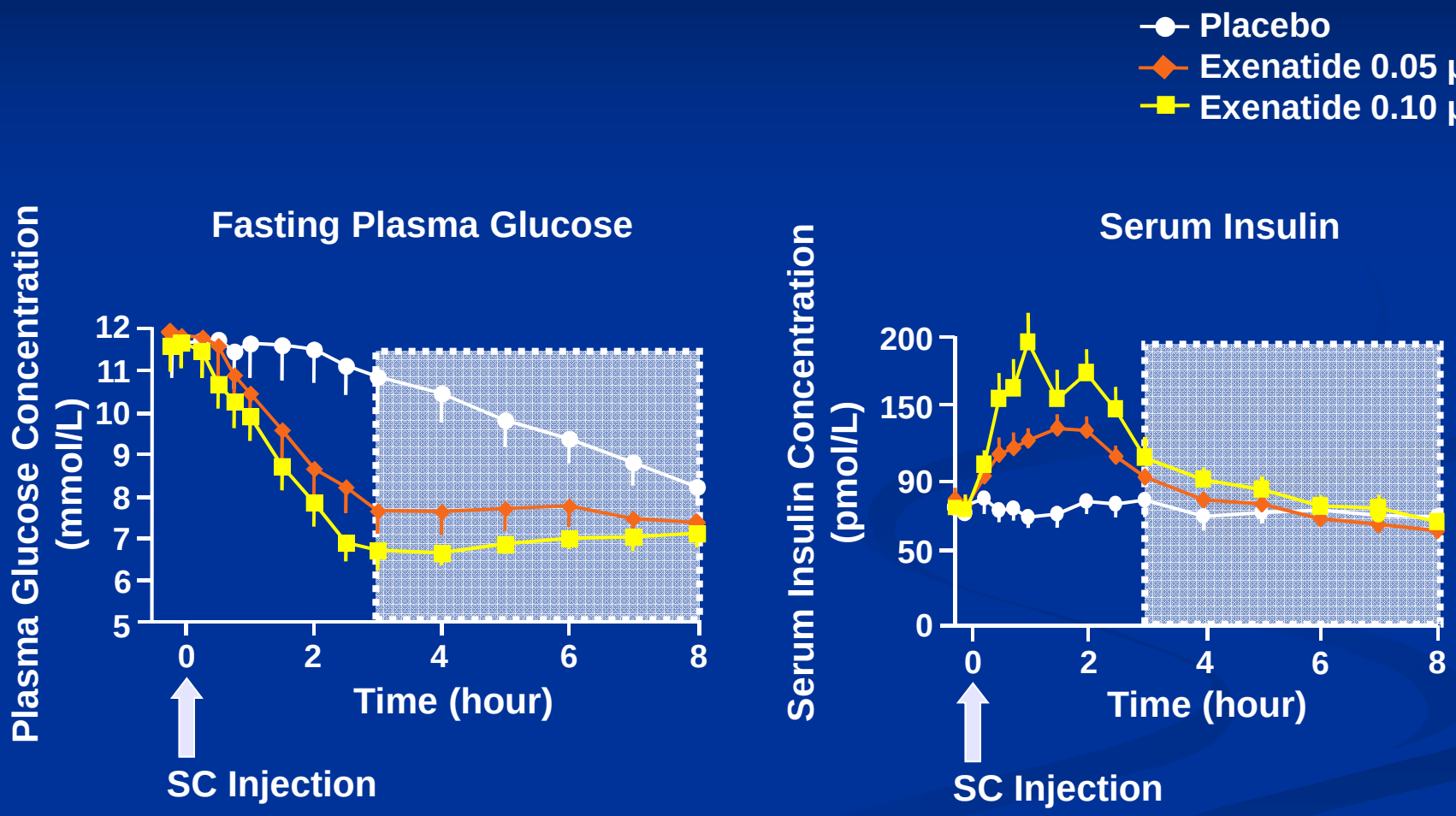



N = 4-7 (rats); p<.05.

Adapted from Parkes D, et al. *Drug Dev Res.* 2001;53:260-267. Reprinted with permission from John Wiley & Sons, Inc.

# The Glucoregulatory Actions of Exenatide

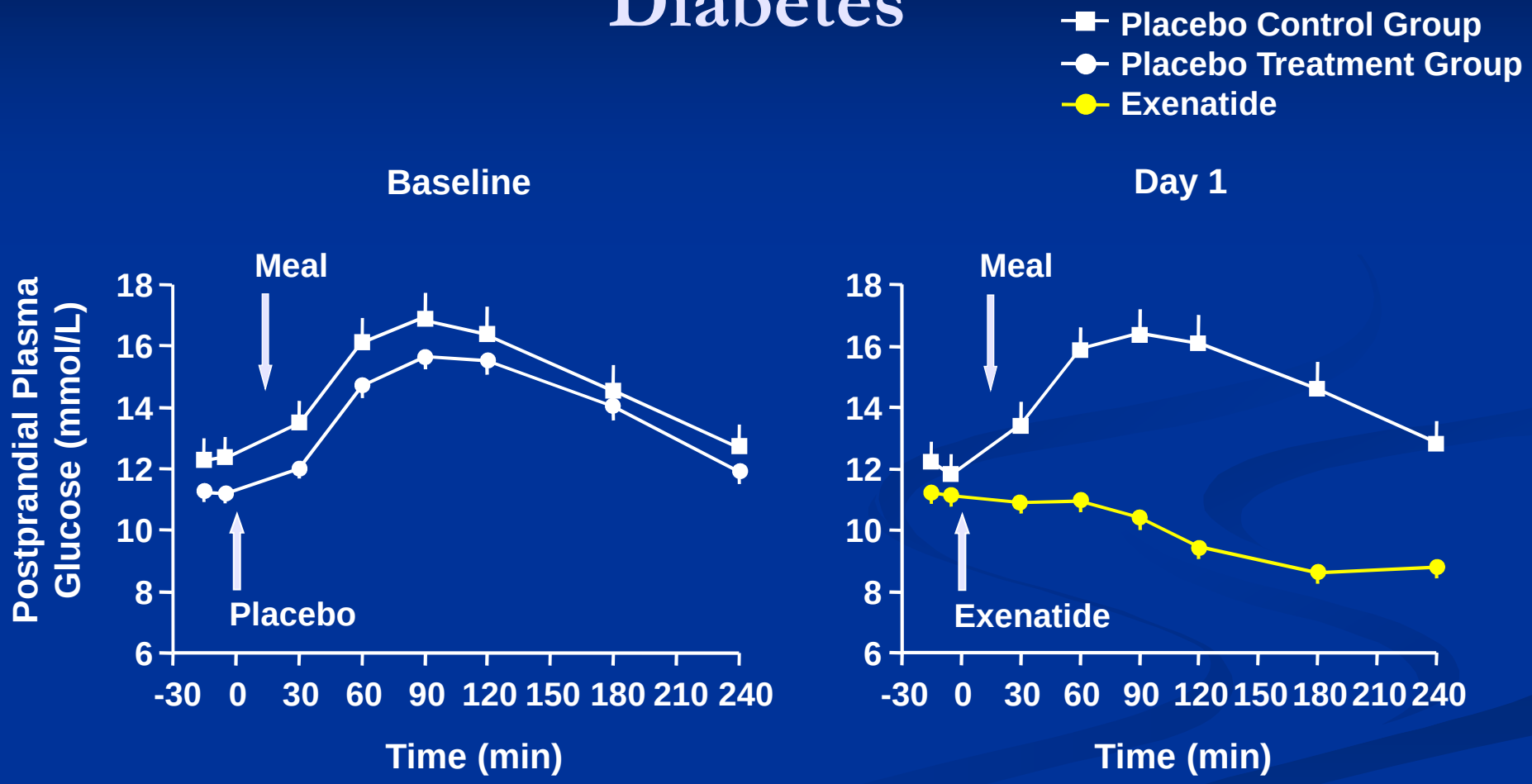
# Exenatide Reduced Fasting Hyperglycaemia in Patients With Type 2 Diabetes




Mean (SE); N = 12; p<.0001 for glucose; p<.001 for insulin.

Adapted from Kolterman OG, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88:3082-3089. Copyright 2003, The Endocrine Society.

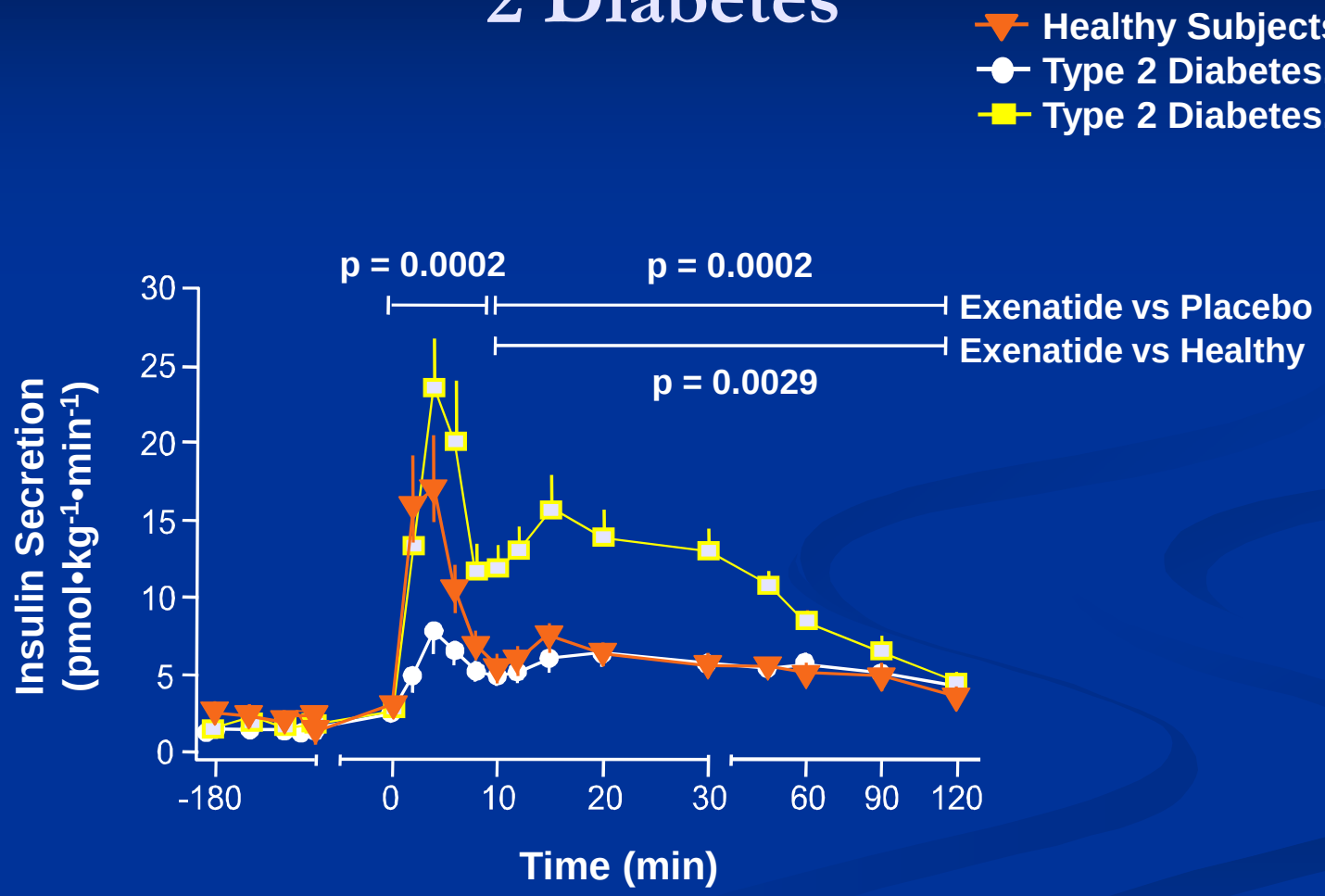
# Exenatide Reduced Postprandial Hyperglycaemia in Patients With Type 2 Diabetes




Mean (SE); N = 109; p≤.004.

Fineman MS, et al. *Diabetes Care.* 2003;26:2370-2377. Reprinted with permission from The American Diabetes Association.

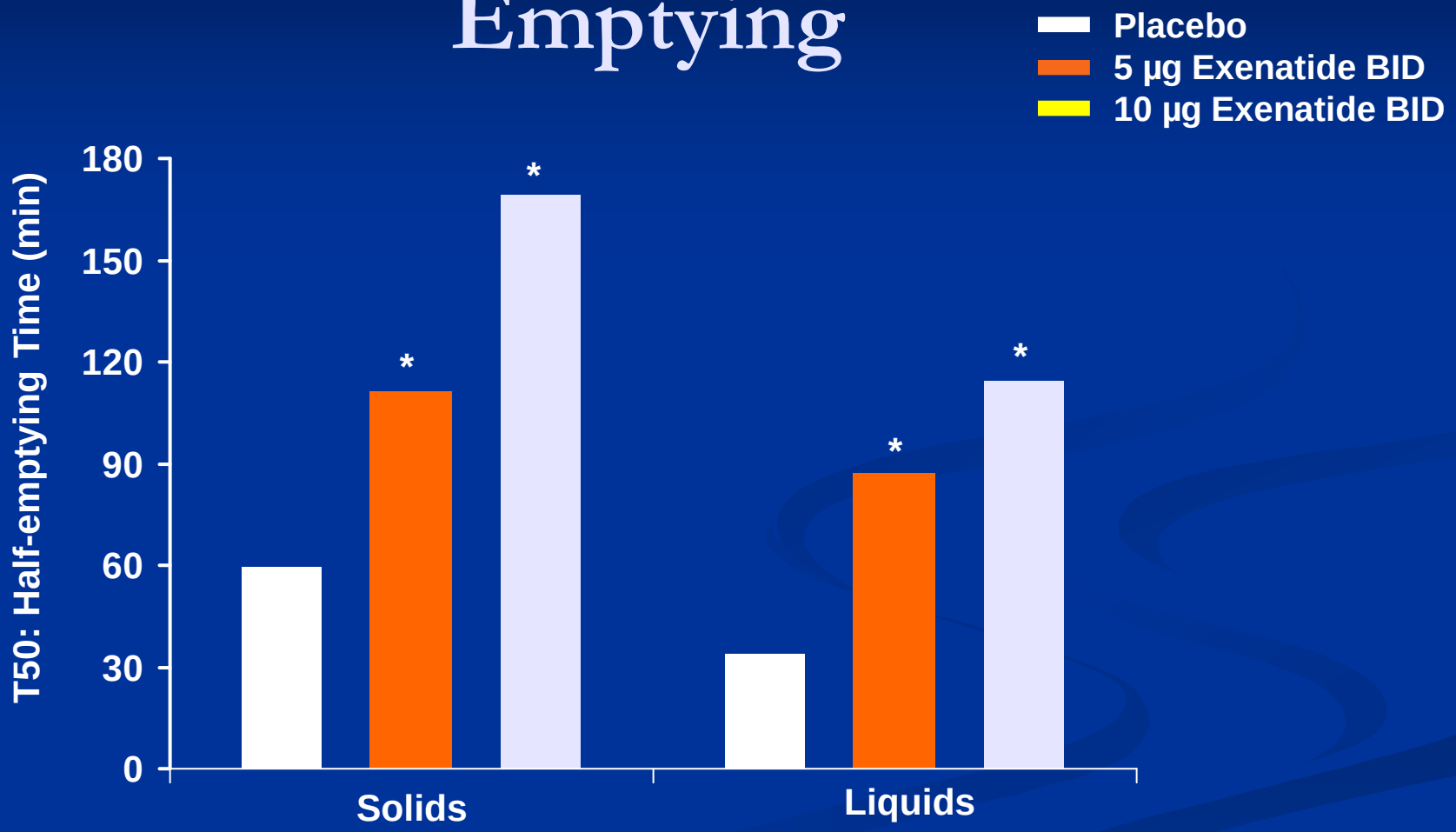
# Acute Exenatide Infusion Restored First-Phase Insulin Response in Patients With Type 2 Diabetes




Mean (SE); N = 25.

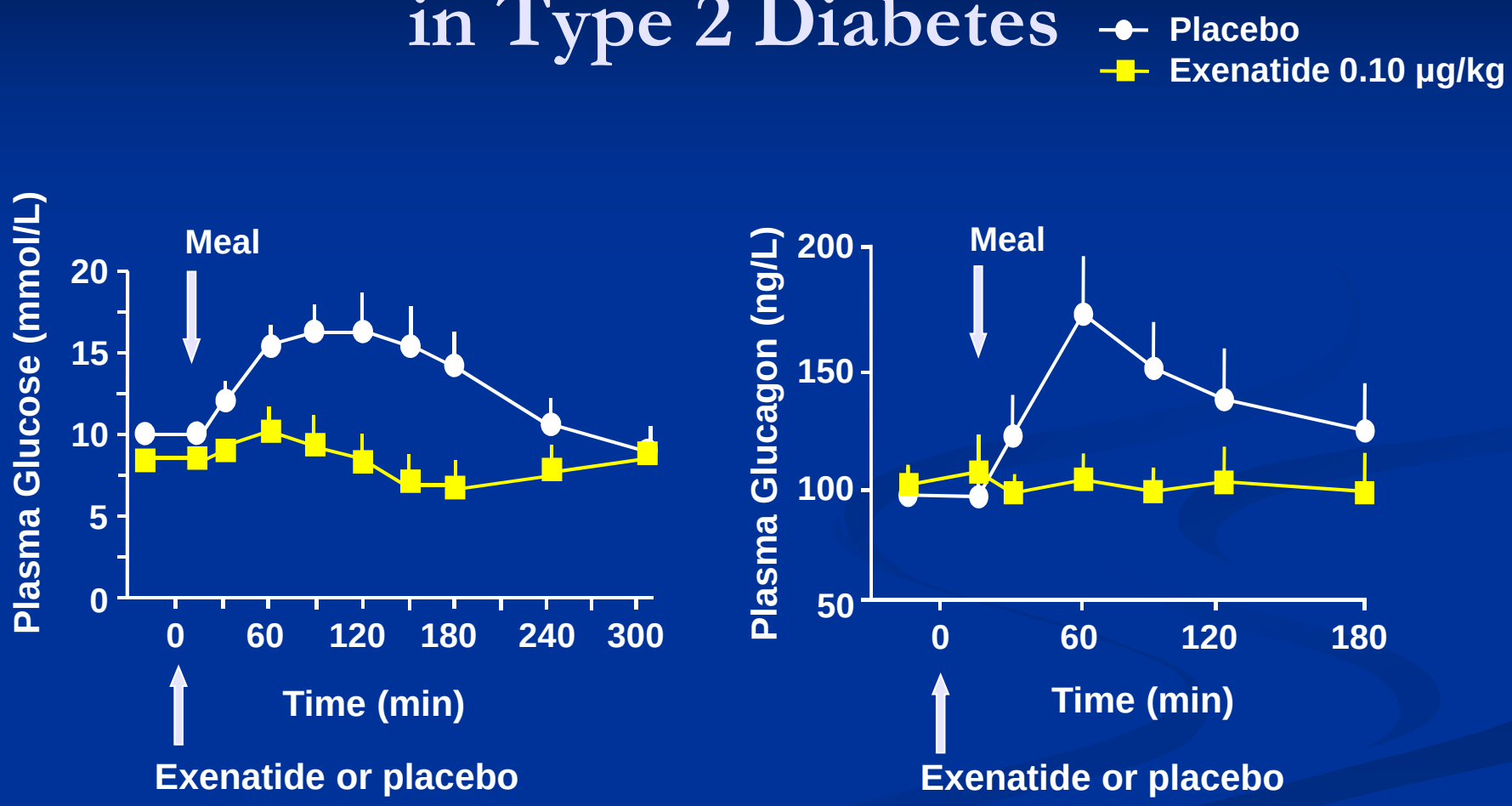
Fehse F, et al. *J Clin Endocrinol Metab*. 2005 Nov;90(11):5991-5997. 

# Exenatide Dose-Dependently Slowed Gastric Emptying




Least Squares Geometric Means shown.
*p<.01 vs placebo.
Linnebjerg H, et al. *Diabetes.* 2006;55(Suppl 1):A28 Abstract 116-OR.

# Exenatide Reduced Glucagon Secretion in Type 2 Diabetes




N = 20; Mean (SE).

Adapted from Kolterman OG, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab*. 2003;88:3082-3089. Copyright 2003, The Endocrine Society.

# Summary of Clinical Data

- Exenatide is a first-in-class incretin mimetic that shares several glucoregulatory actions with GLP-1:
  - Enhances glucose-dependent insulin secretion
  - Reduces postprandial glucagon levels
  - Slows gastric emptying rate
  - Reduces food intake and body weight
  - Beta cell effects
- In Phase III placebo-controlled trials, exenatide:
  - Lowered $HbA_{1c}$ ~1%
  - Reduced body weight 4-5 lbs
  - Demonstrated sustained effects in extension studies (2-year data)
- When compared to insulin, exenatide provides similar $HbA_{1c}$ improvements, with the potential advantages of tighter postprandial control and reduced body weight

# Summary of Safety Data:

- The most common adverse events associated with exenatide are mild-to-moderate gastrointestinal effects, most common at initiation of therapy
- Exenatide treatment is associated with low rates of hypoglycaemia
  - When co-administered with MET alone, exenatide was not associated with an increased risk of hypoglycaemia
  - When co-administered with an SFU, exenatide was associated with an increased incidence of hypoglycaemia compared to SFU alone
    - Generally manageable by reduction in SFU dose

# *JANUVIA® (Sitagliptin)*

# *A Selective DPP-4 Inhibitor*

# DPP-IV Inhibitors: Overview

| | |
|---|---|
| Mechanism of action | **Inhibit degradation of incretins (e.g., GLP-1) resulting in**<br>■ **Increased insulin release**<br>■ **Decreased glucagon secretion**<br>■ **Delayed gastric emptying**<br>■ **Reduced food intake**<br>■ **Potentially improved beta-cell function** |
| Route of administration | **Oral** |
| Potential benefits | **Preservation or restoration of beta-cell function**<br>**Durable glucose control** |

Adapted from Ahrén B *Curr Diab Rep* 2003;3:365–372; Schirra J et al *J Endocrinol* 1998;156(1):177–186; Meier JJ et al *Clin Endocrinol Metab* 2003;88(6):2719–2725; Holz GG, Chepurny OG *Curr Med Chem* 2003;10(22):2471–2483; Drucker DJ *Expert Opin Invest Drugs* 2003;12(1): 87–100; Gutzwiller JP et al *Am J Physiol* 1999;76(5 pt 2):R1541–1544; Drucker DJ *Endocrinology* 2001;142(2):521–527; Holst JJ, Deacon CF *Diabetes* 1998;47(11):1663–1670.

# Mechanism of Action of Sitagliptin

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Pancreas

Beta cells

Alpha cells

Glucose dependent

↑ Insulin (GLP-1and GIP)

↑ Glucose uptake by peripheral tissue

↓ Blood glucose in fasting and postprandial states

JANUVIA (DPP-4 inhibitor)

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Glucose-dependent

↓ Glucagon (GLP-1)

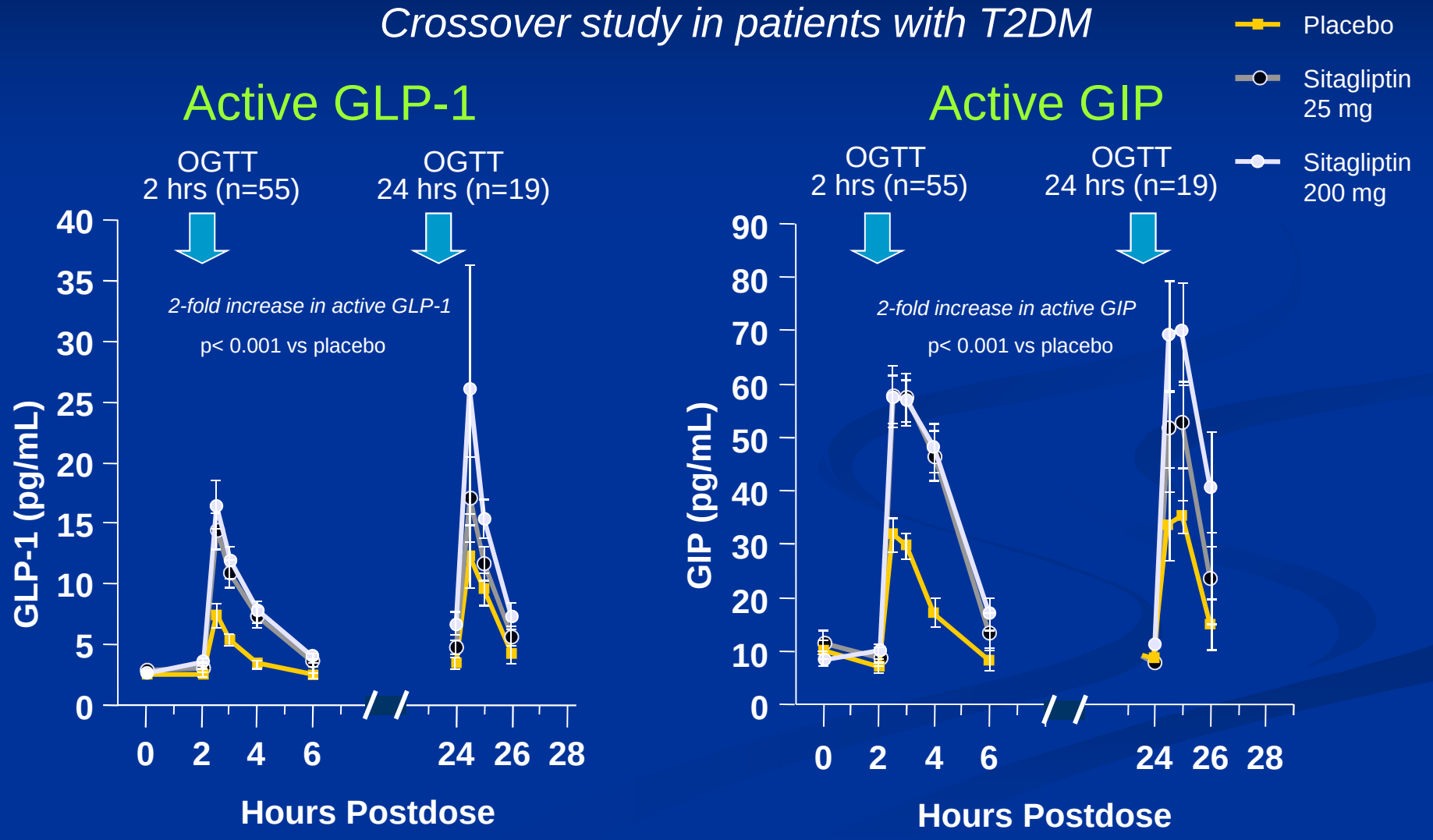
↓ Hepatic glucose production

- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

**Concentrations of the active intact hormones are increased by JANUVIA™ (sitagliptin phosphate), thereby increasing and prolonging the actions of these hormones.**

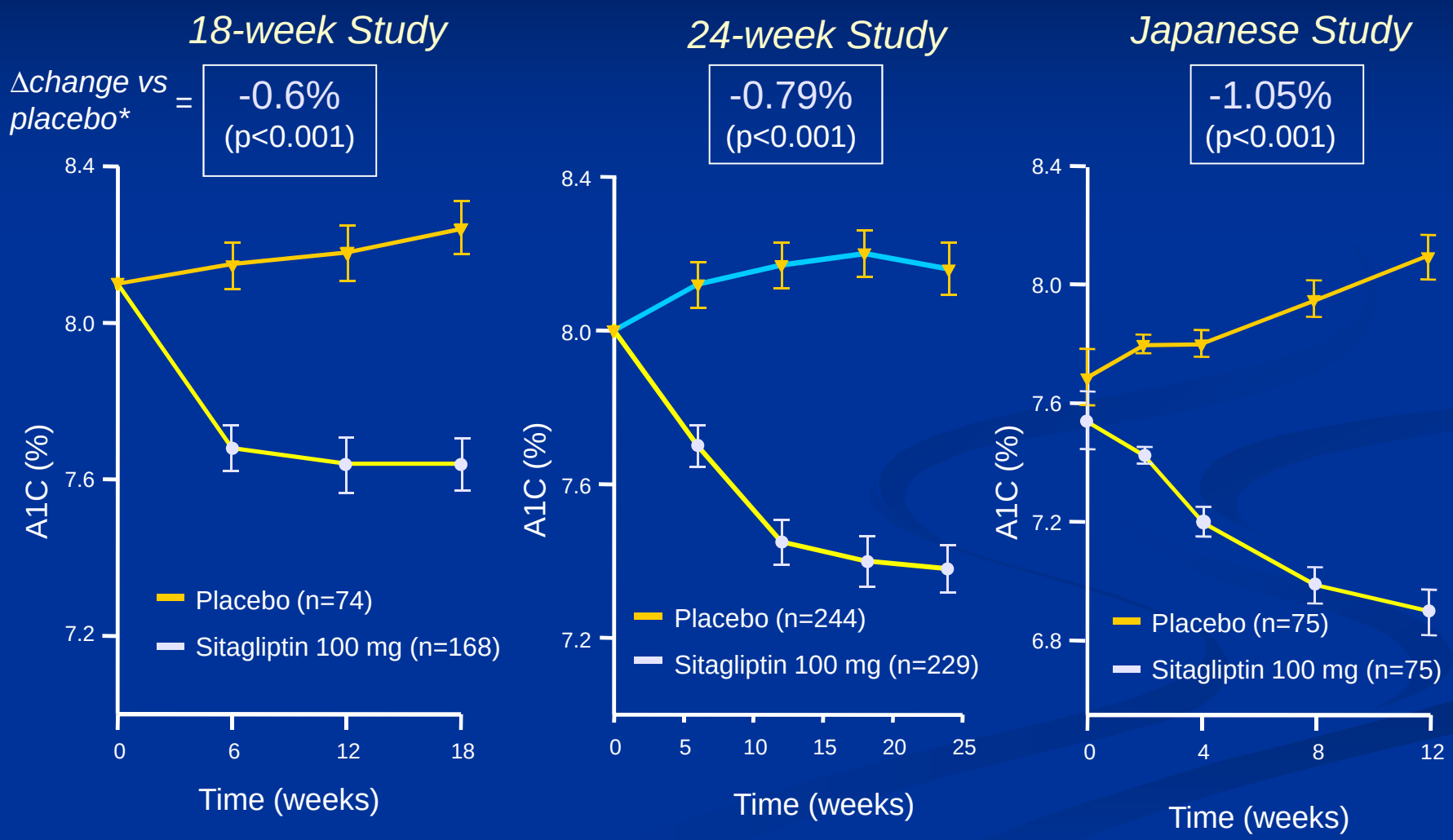
# A Single Dose of Sitagliptin Increased Active GLP-1 and GIP Over 24 Hours

*Crossover study in patients with T2DM*




Herman et al. *Diabetes*. PN005, 2005.

# *Sitagliptin Consistently and Significantly Lowers A1C with Once-Daily Dosing in Monotherapy*

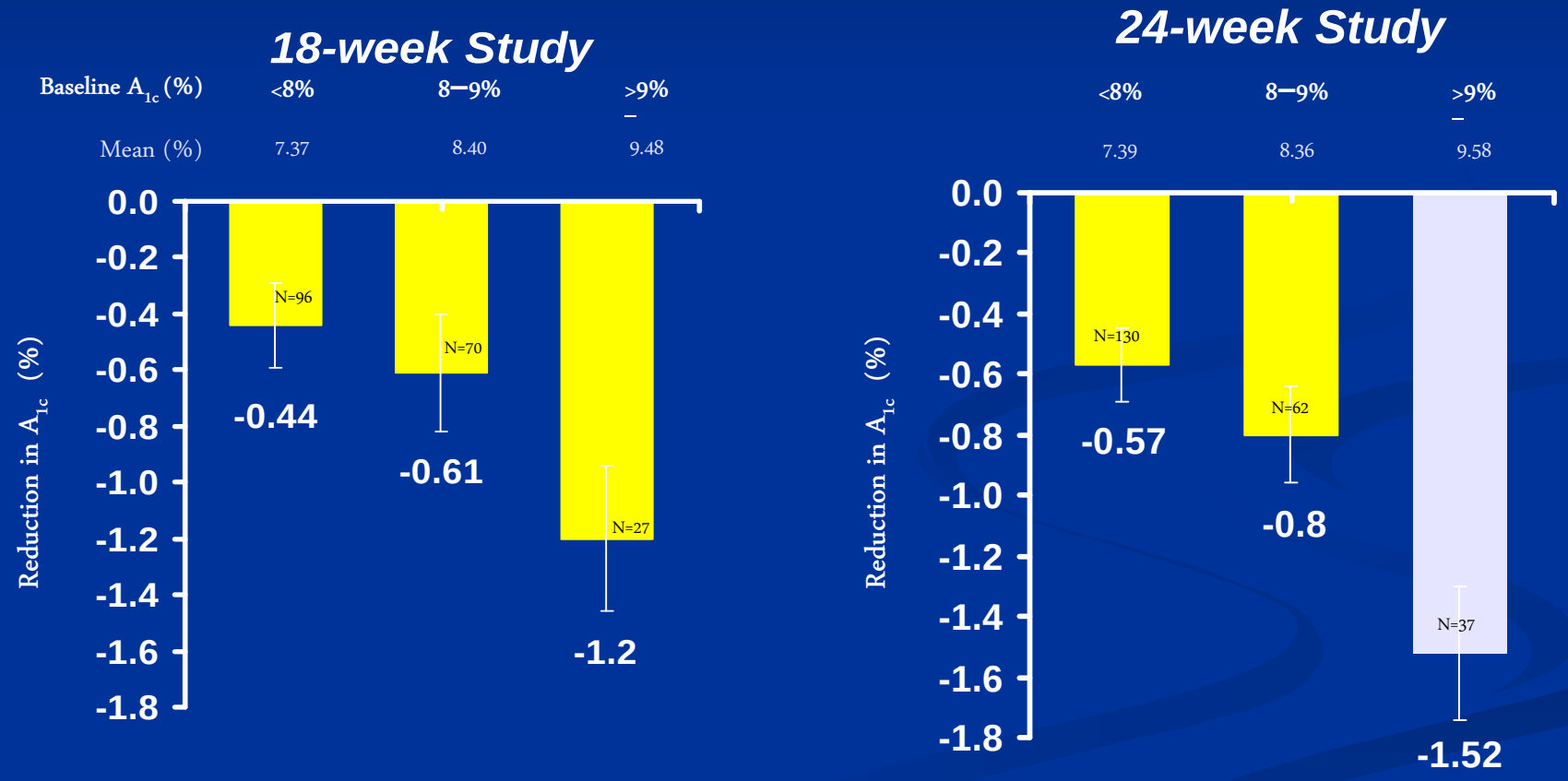



*between group difference in LS means

Raz I et al; PN023; Aschner P et al. PN021; Nonaka K et al; A201. Abstracts presented at: ADA 2006

# Sitagliptin: Provides Significantly and Progressively Greater Reductions in $HbA_{1C}$

Inclusion Criteria: 7%–10%

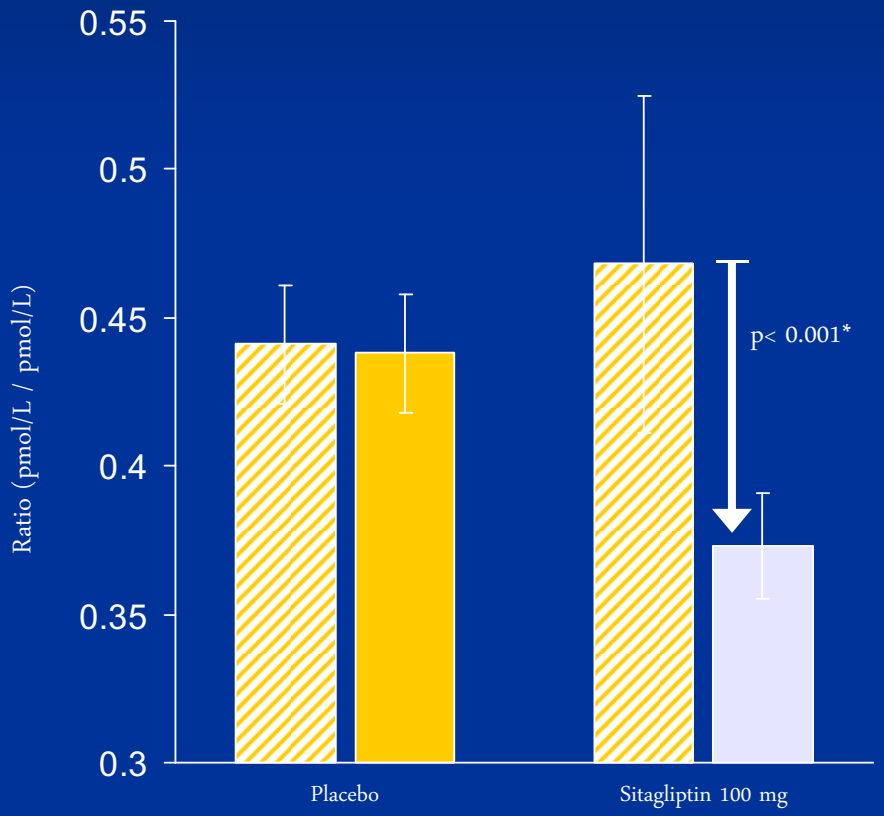



*Reductions are placebo-subtracted*

Adapted from Raz I et al. PN023; Aschner P et al. PN021. Abstracts presented at: ADA2006

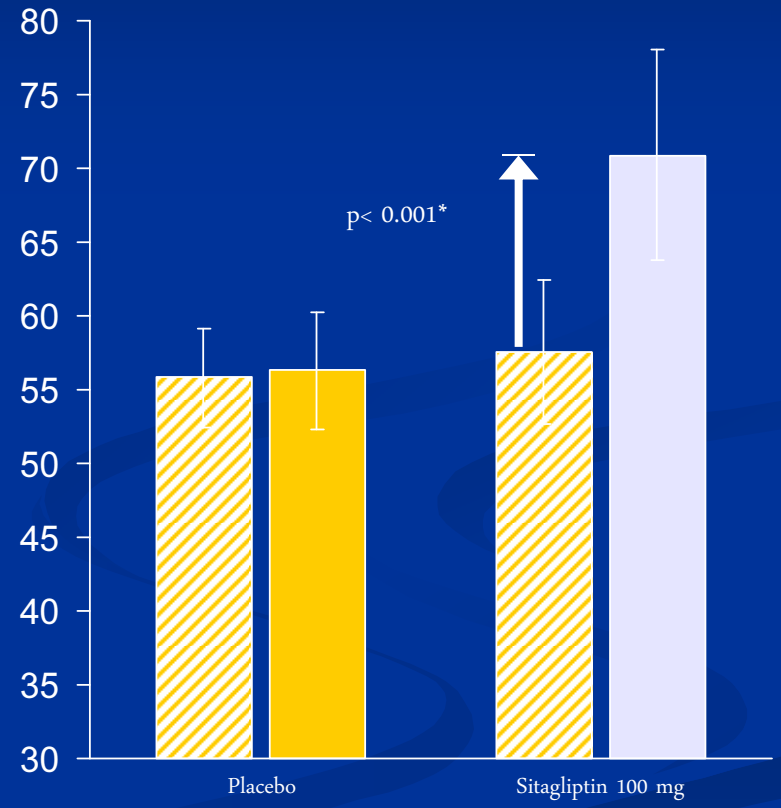
# Sitagliptin Improved Markers of Beta-Cell Function: 24-Week Monotherapy Study

## Proinsulin/insulin ratio




Δ from baseline vs pbo = 0.078
(95% CI -0.114, -0.023

## HOMA-β



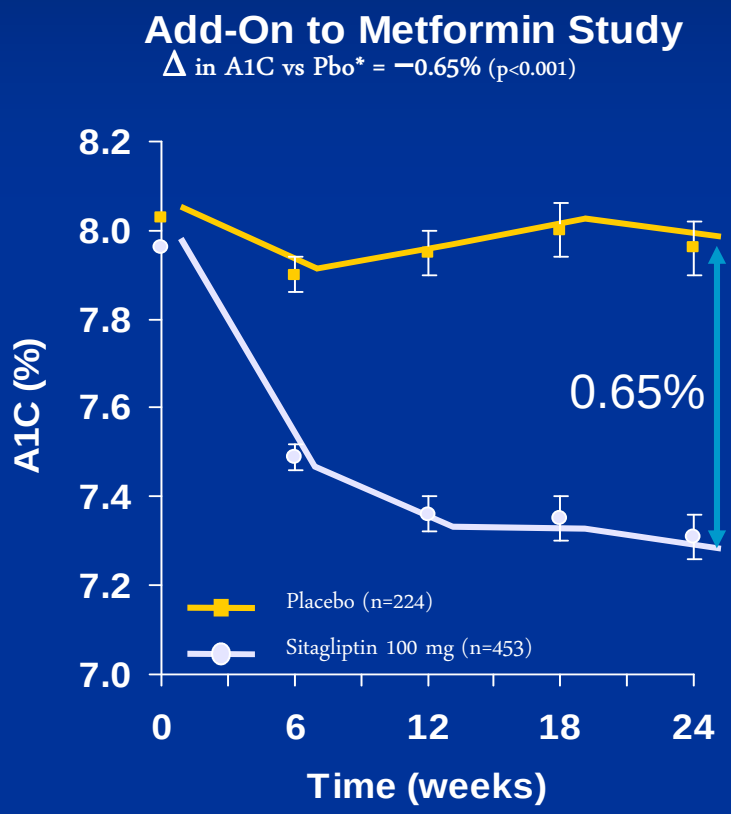

Hatched = Baseline
Solid = Week 24

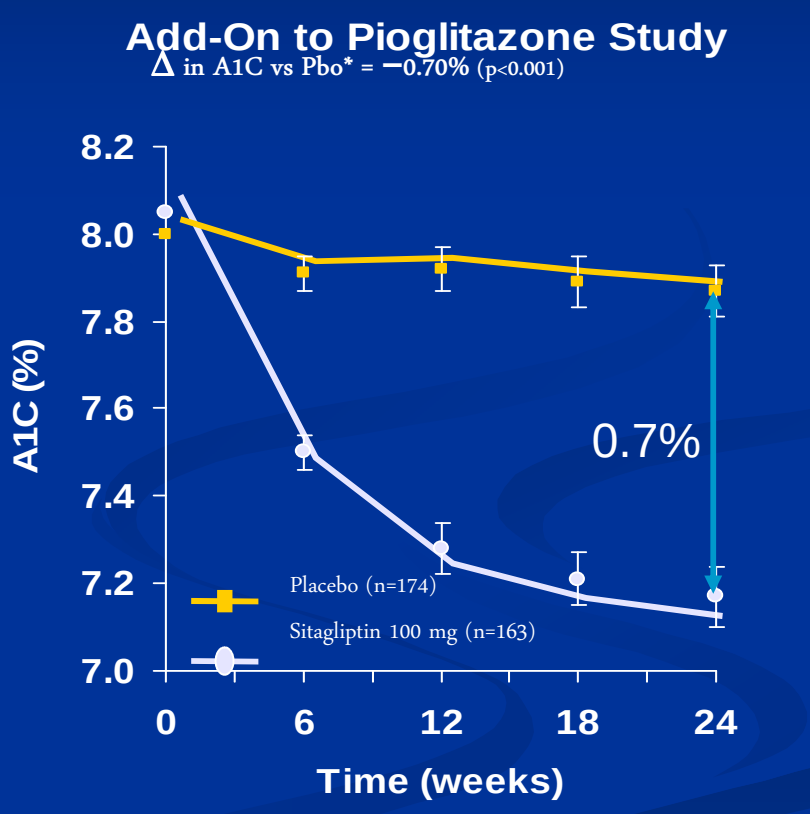
Δ from baseline vs pbo = 13.2
(95% CI 3.9, 21.9)

*P value for change from baseilne compared to placebo

Aschner P et al. PN021; Abstract presented at: American Diabetes Association; June 10, 2006; Washington, DC.

# *Sitagliptin Once Daily Significantly Lowers $HbA_{1C}$ When Added On to Metformin or Pioglitazone*

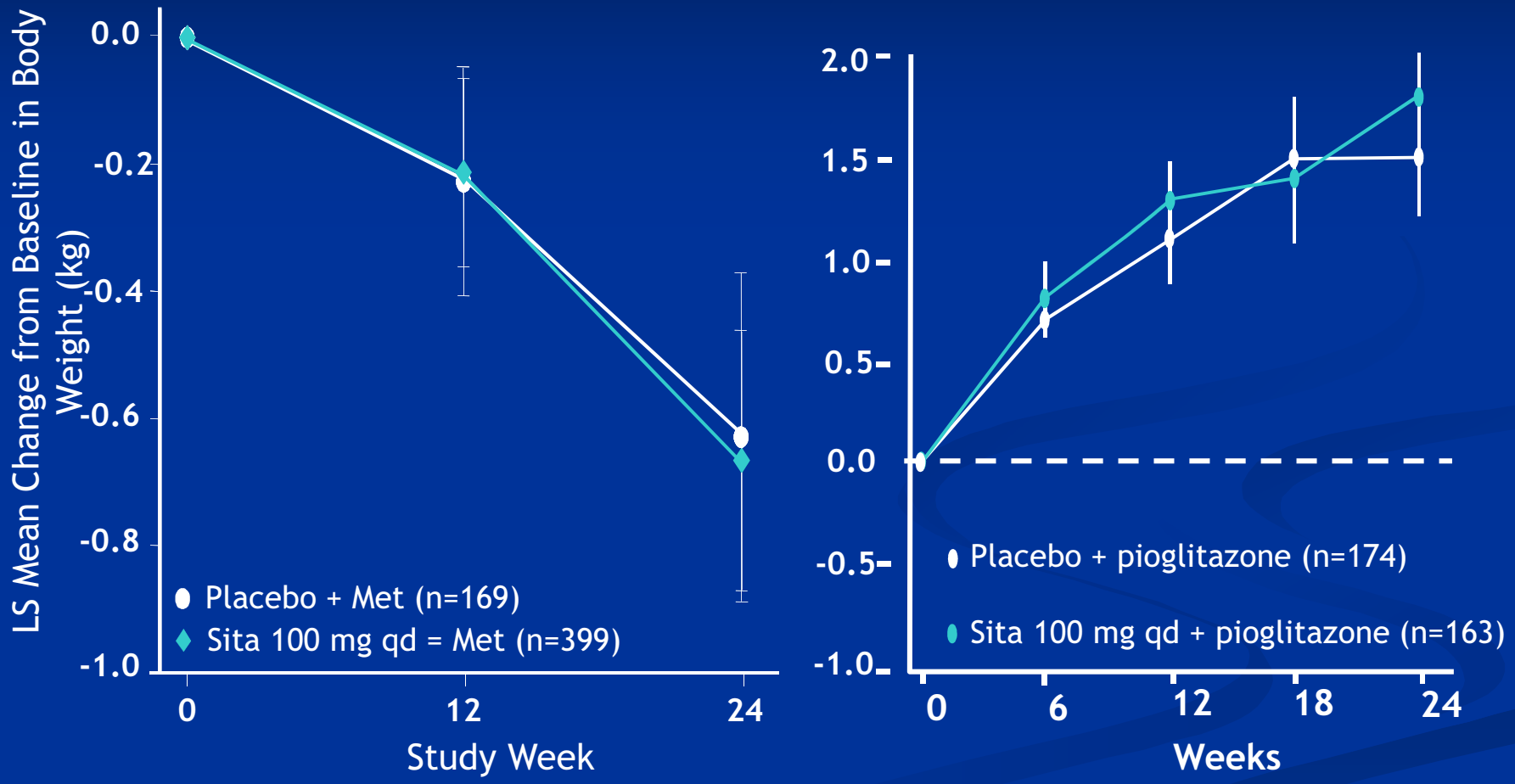



**Placebo Subtracted Difference in LS Means.*

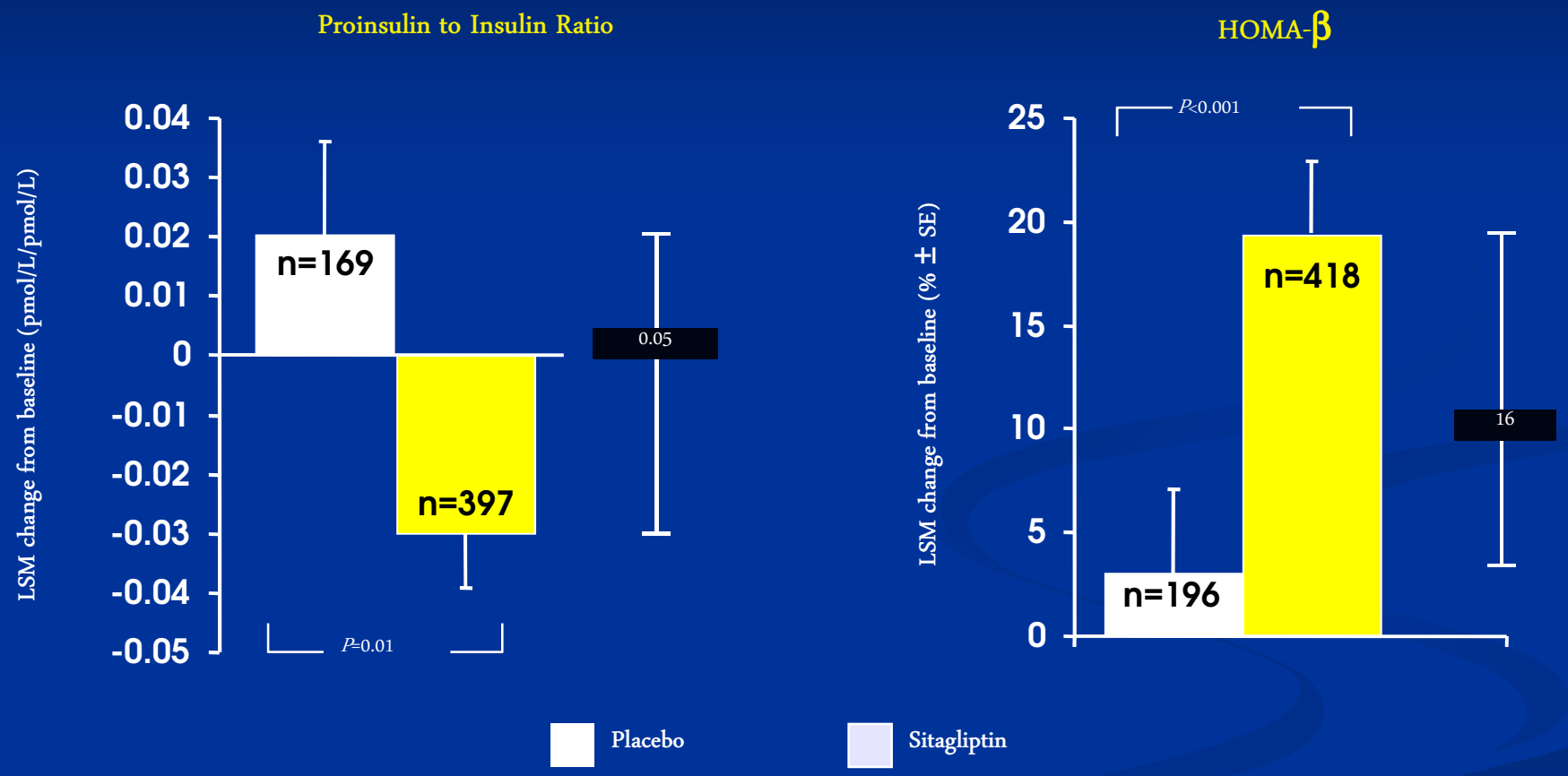
Rosenstock J et al. PN019. Hashomer T et al. PN020. Abstracts presented at: ADA2006

# *Sitagliptin Added to Ongoing Metformin or Pioglitazone: Change in Body Weight Over Time*




Karasik A et al. Presented at: The 66th Scientific Session of the American Diabetes Association; June 11, 2006; Washington, D.C. Abstract 020. Rosenstock J et al. Presented at: The 66th Scientific Session of the American Diabetes Association; June 11, 2006; Washington, D.C. Abstract 019.

# *24-week Add-on Therapy to Metformin Study*
# Measures of Beta-cell Function at Week 24




Baseline: proinsulin to insulin ratio (sitagliptin = 0.357 pmol/L/pmol/L, placebo = 0.369 pmol/L/pmol/L), HOMA-β (sitagliptin = 46.4%, placebo = 45.1%)

All-patients-as-treated population

LSM = least square mean; HOMA-β = homeostasis model assessment-β

Adapted from Charbonnel et al. *Diabetes Care.* 2006;29:2638–2643.

# *24-week Add-on Therapy to Metformin Study*
# Number of Patients With Selected GI-related AEs

| | Sitagliptin 100 mg (n=464) | | Placebo (n=237) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Abdominal pain | 10 | (2.2) | 9 | (3.8) |
| Diarrhea | 12 | (2.6) | 6 | (2.5) |
| Nausea | 6 | (1.3) | 2 | (0.8) |
| Vomiting | 5 | (1.1) | 2 | (0.8) |

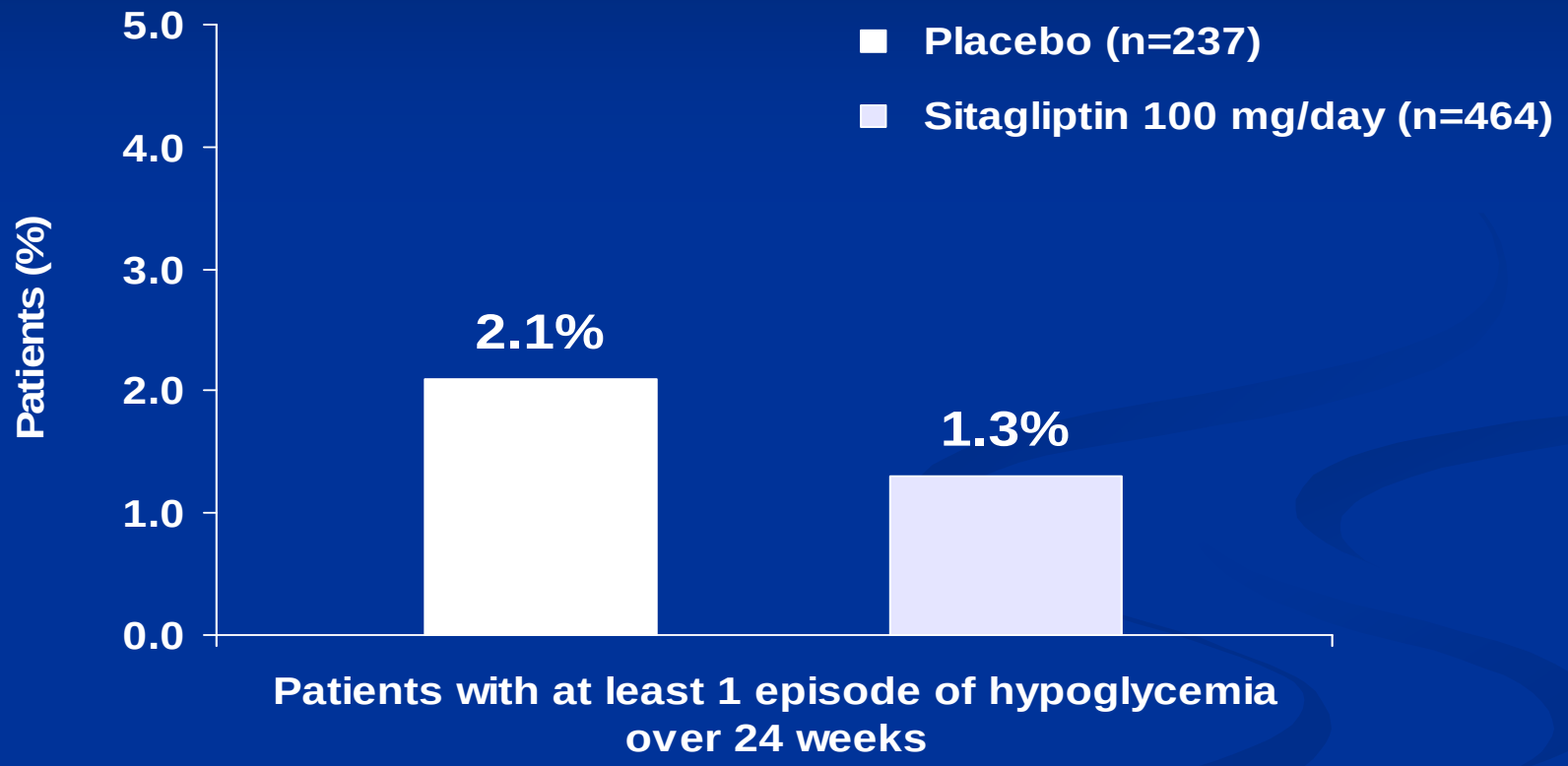
All-patients-as-treated population

GI = gastrointestinal

Adapted from Charbonnel et al. *Diabetes Care.* 2006;29:2638–2643.

# *24-week Add-on Therapy to Metformin Study*

# Incidence of Hypoglycemia




All-patients-as-treated population

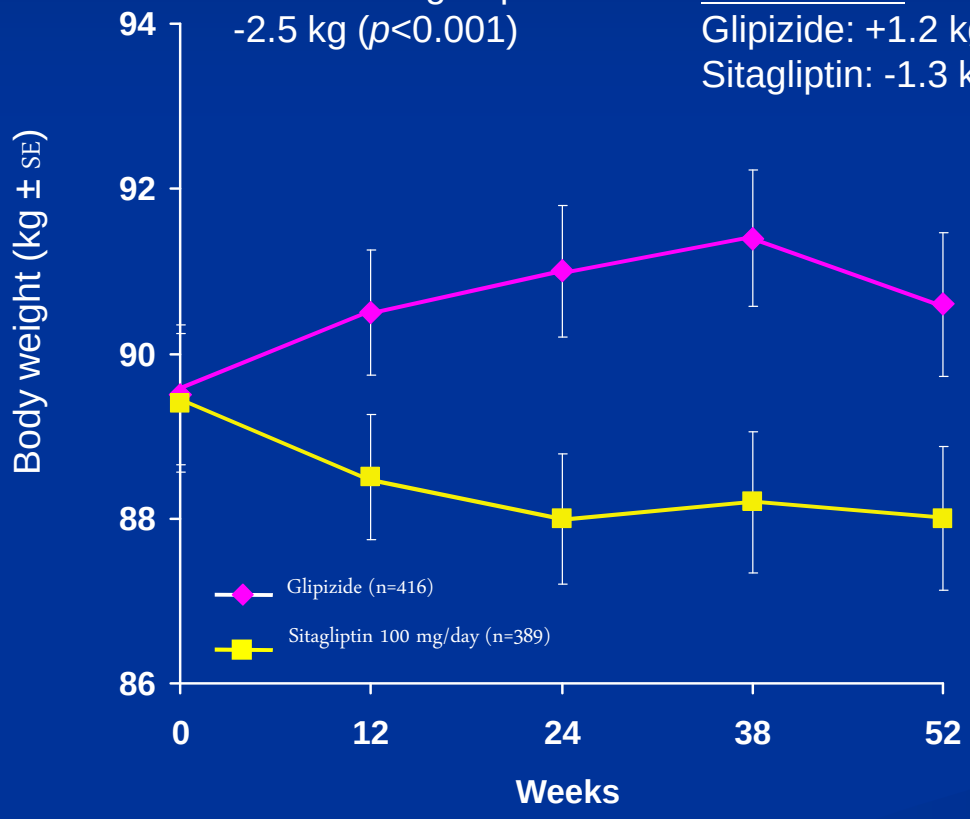
Adapted from Charbonnel et al. *Diabetes Care*. 2006;29:2638–2643.

# 52-Week Sitagliptin vs Glipizide Add-on Therapy to Metformin Study

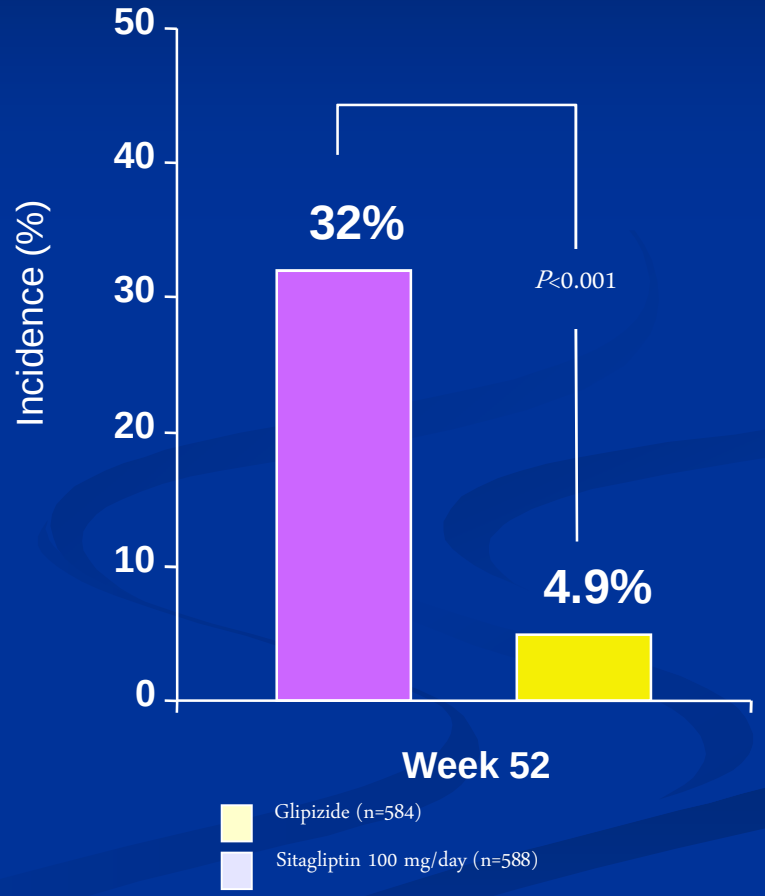
## Change in Body Weight Over Time[a]

△Between groups =
-2.5 kg ($p$<0.001)

At 52 weeks
Glipizide: +1.2 kg
Sitagliptin: -1.3 kg




## Hypoglycemia[b]




[a]All-patients-as–treated population; [b]patients with at least one episode; all–patients–treated population

LSM between-group difference at week 52 (95% CI): Δ in body weight = –2.5 kg [–3.1, –2.0] ($P$<0.001);
LSM change from baseline at week 52: glipizide: +1.1 kg; sitagliptin: –1.5 kg

Diabetes, Obesity and Metabolism, 9, 2007, 194-205

# Summary: Sitagliptin

- Orally active, 100 mg once daily
- Generally well tolerated
- Low incidence of hypoglycemia (1.2% vs 0.9%)
- Weight neutral
- Efficacy: reduce fasting and postprandial blood glucose, lowers HbA1c 0.6 to 1%
- Current approved indications for type 2 DM:
  - Monotherapy, or
  - Add-on therapy to sulfonlyureas, metformin or glitazone
  - Combination with metformin and a sulfonylurea
- No significant drug interactions

# *Patients With Renal Insufficiency*

| Renal Insufficiency | Mild | Moderate | Severe and ESRD* |
|---|---|---|---|
| Increase in Plasma AUC of Sitagliptin† | ~1.1 to 1.6-fold increase‡ | ~2-fold increase | ~4-fold increase |
| Recommended Dose | 100 mg no dose adjustment required | 50 mg | 25 mg |

To achieve plasma concentrations similar to patients with normal renal function, lower doses of JANUVIA® (sitagliptin phosphate) are recommended in moderate and severe renal insufficiency.

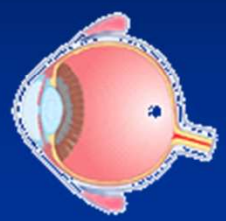
**ESRD=end-stage renal disease; AUC=area under the curve.**
***Includes patients on hemodialysis or peritoneal dialysis.**
**†Compared with normal healthy control subjects.**
**‡Not clinically relevant.**

# What is the difference between DPP-IV Inhibitors and Exenatide

| | Sitagliptin | Exenatide |
|---|---|---|
| Route of administration | p.o. | s.c. |
| GLP elevation | 2-4 fold | 10 fold |
| HbA1c reduction | -0.7% | -1.1% |
| Weight effects | neutral | -4.7 kg |
| Hypoglycemia potency | none | none |
| B-cell protection | possible | possible |

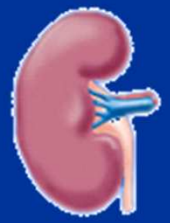
# Type 2 diabetes and CV risk

# Type 2 diabetes is NOT a mild disease



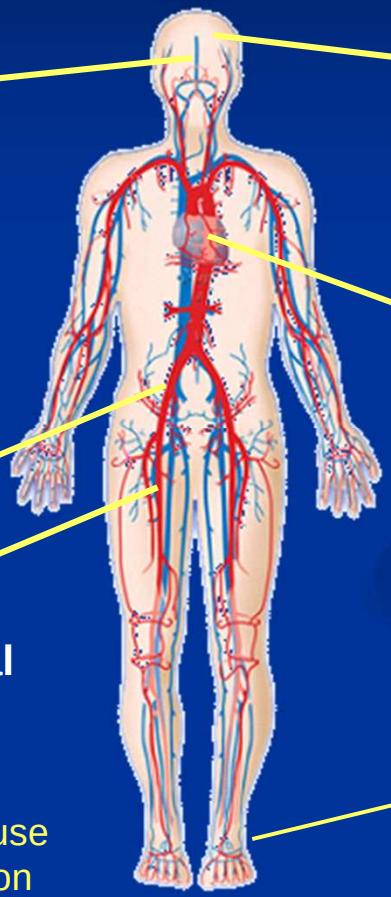
**Diabetic retinopathy**

Leading cause of blindness in working-age adults[1]



**Diabetic nephropathy**

Leading cause of end-stage renal disease[2]

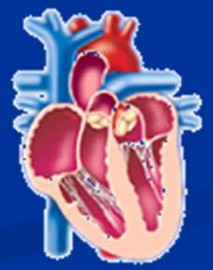


**Peripheral vascular disease**

Leading cause of amputation

**Stroke**

1.2- to 1.8-fold increase in stroke[3]



**Cardiovascular disease**

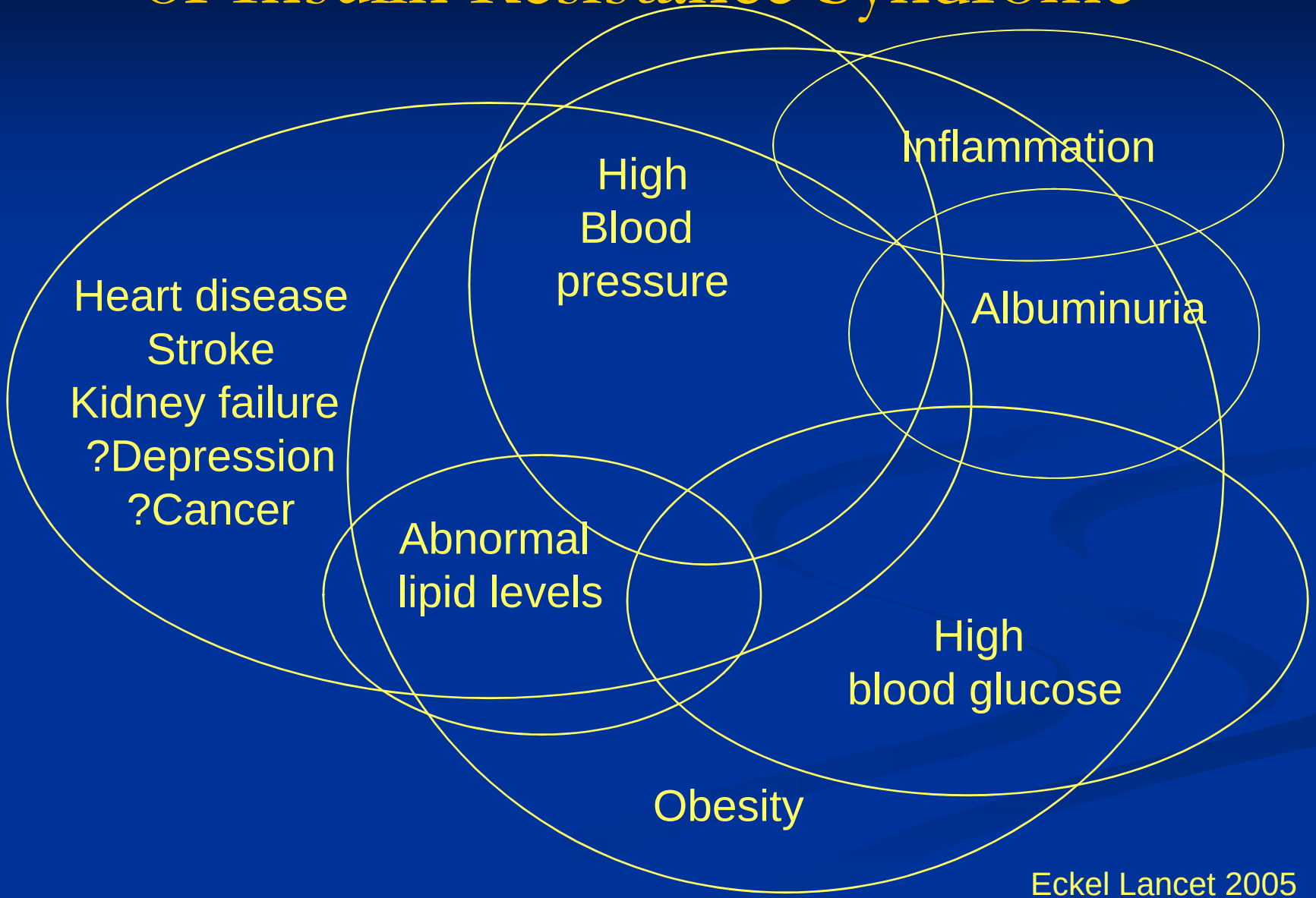
75% diabetic patients die from CV events[4]

**Diabetic neuropathy**

Leading cause of non-traumatic lower extremity amputations[5]

[1]Fong DS, *et al. Diabetes Care* 2003;26 (Suppl. 1):S99–S102. [2]Molitch ME, *et al. Diabetes Care* 2003;26 (Suppl. 1):S94–S98. [3]Kannel WB, *et al*. *Am Heart J* 1990;120:672–676. [4]Gray RP & Yudkin JS. In *Textbook of Diabetes* 1997. [5]Mayfield JA, *et al. Diabetes Care* 2003;26 (Suppl. 1):S78–S79.

# Metabolic Syndrome or Insulin Resistance Syndrome




Eckel Lancet 2005

# ABC + 2A + 2S

- HbA1c
- Blood Pressure
- Cholesterol (Low density lipoprotein cholesterol)

+ Aspirin

+ ACEI or ARB

+ Stop Smoking

Cardiovascular and Metabolic Risk
ORIGINAL ARTICLE

# Effects of Treatment Targets on Subsequent Cardiovascular Events in Chinese Patients With Type 2 Diabetes

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CLIVE S. COCKRAM, MD[2]
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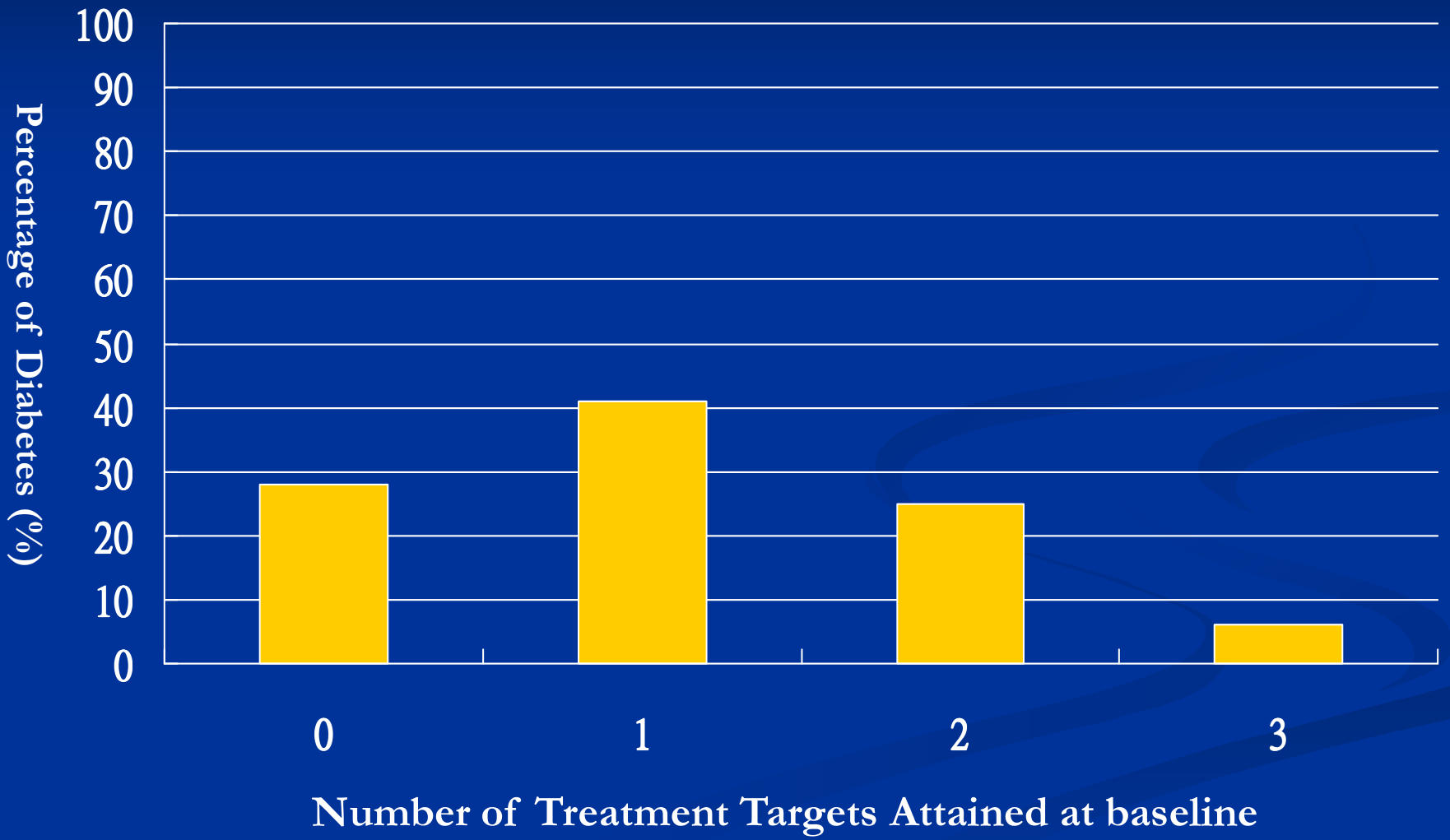
JULIANA C.N. CHAN, MD[2]

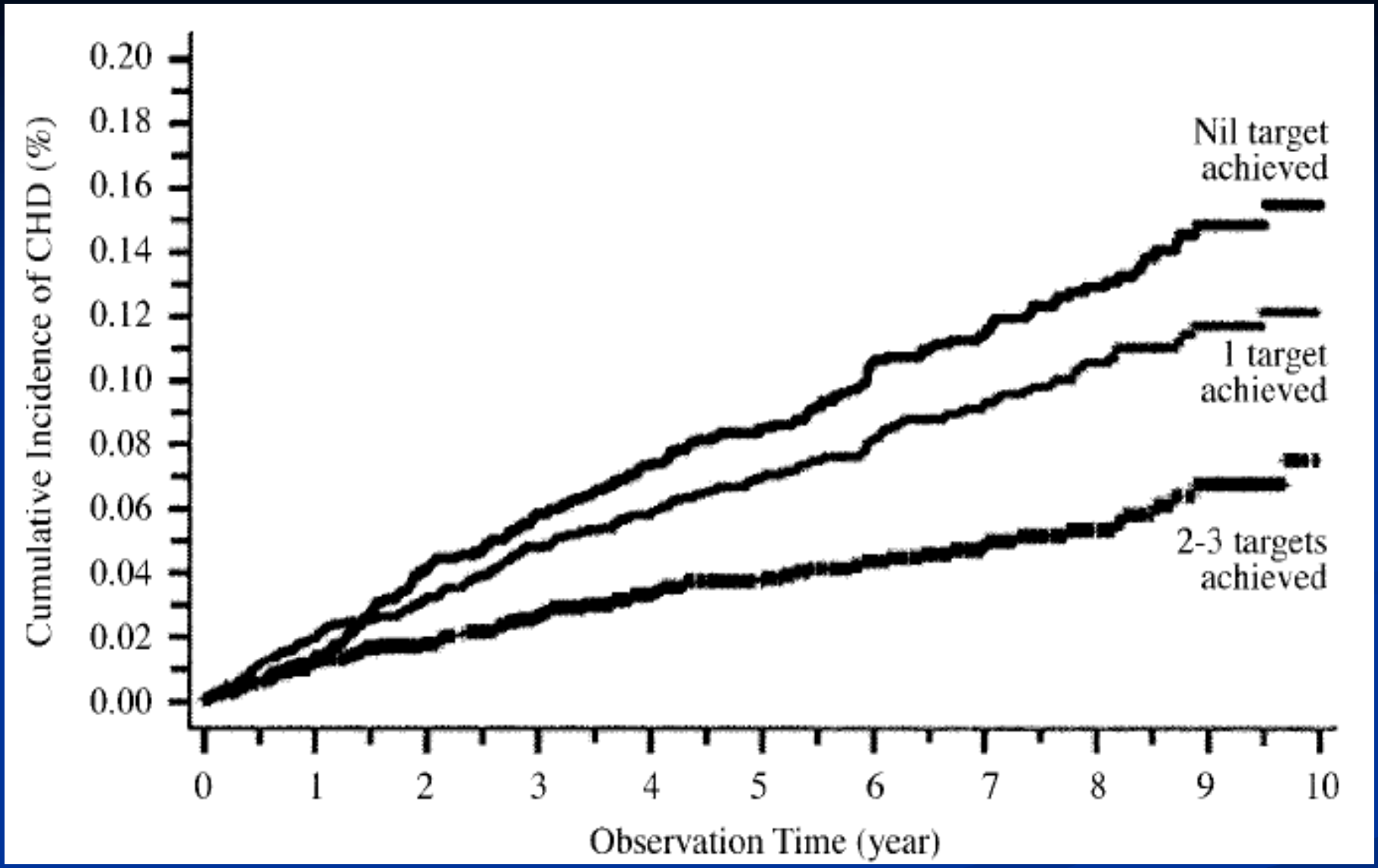
Hong Kong Diabetes Registry. Diabetes Care 2007; 30:953-959

- Between 1995 and 2005, 6,386 Chinese type 2 diabetic patients without history of CHD or stroke were recruited.
- Classified according to the number of treatment targets attained at baseline, and their cardiovascular outcomes were compared.

# ABC targets in Hong Kong T2DM




Kong AP, et al. Diabetes Care 2007




- Attainment of 2 or more treatment targets at baseline was associated with reduced risk of CHD compared with those with no target achieved.