Current Status of Incretin Based Therapies in Type 2 Diabetes

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Greetings from MANIPAL, INDIA



The Diabetes Epidemic: Global Projections, 2010–2030



IDF. Diabetes Atlas 5th Ed. 2011

Disclosures

- Principle investigator from India on multicentre ELIXA trial sponsored by Sanofi Aventis (ongoing)
- Co investigator in Saxagliptin (BMP) & Linagliptin (Boehringer Ingelheim) & Liraglutide (Novo) trials
- Conflict of interest : None


Encarta Interactive World Atlas, Bruce Coleman, Inc./Joe McDonald

Incretins

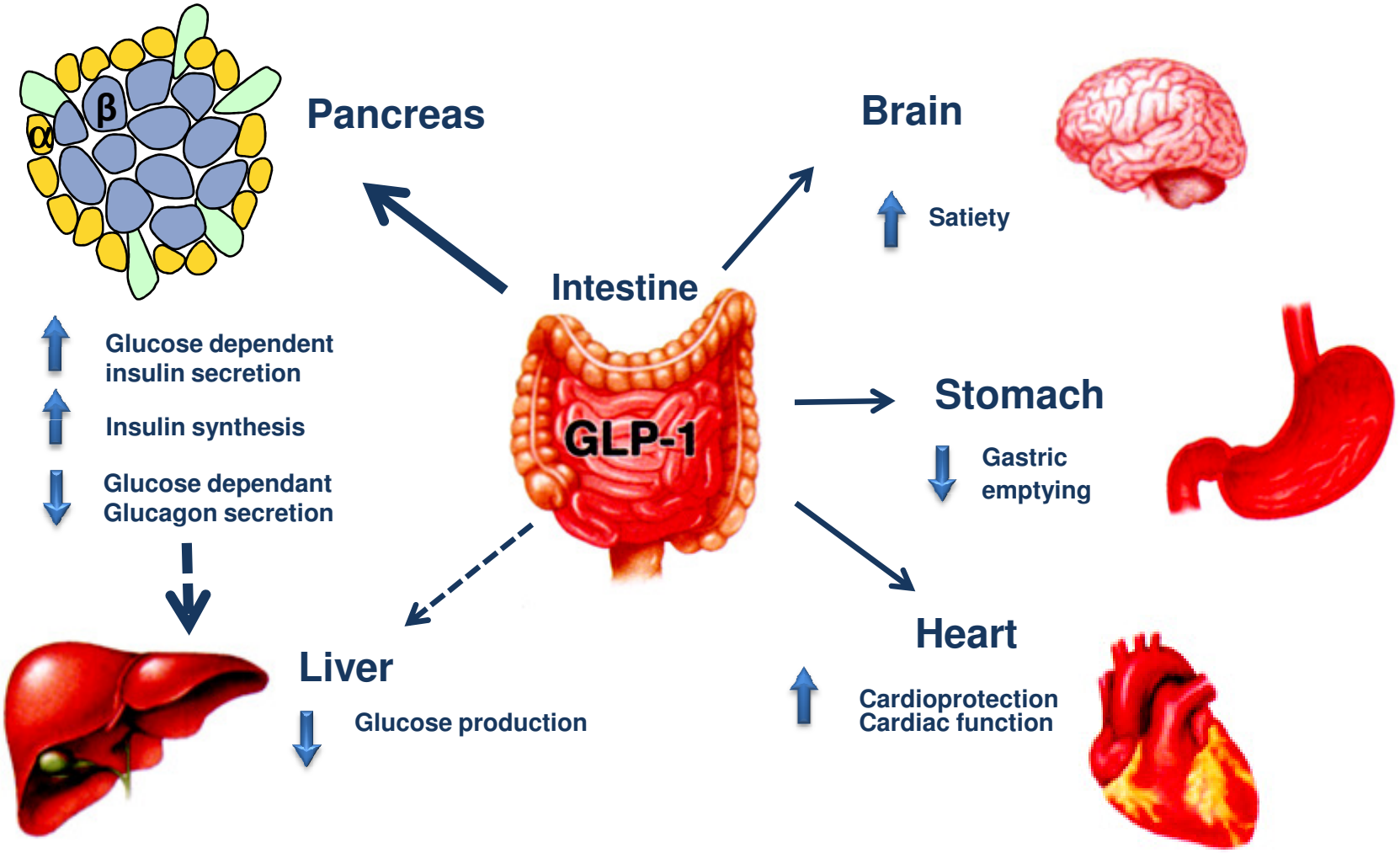
- **Incretins are GI hormones that are released after meals and stimulate insulin secretion**
- **GLP1 and GIP are incretins**
- **GIP is not effective in stimulating insulin**
- **GLP 1 is effective- hence GLP1 signalling system – successful drug target**

Goodman & Gilman's Pharmacological Basis of therapeutics. 12th edition

Flow of Presentation

- Physiological Effects of Incretins
- The Incretin Based Therapies - GLP-1 Analogues
- The Incretin Based Therapies - DPP-4 Inhibitors
- GLP-1 Analogues vs DPP-4 Inhibitors
- The Future of Incretin Based Therapy
- Current Status of Incretin Based Therapy
- Summary & Conclusion

Physiological Effects of GLP-1

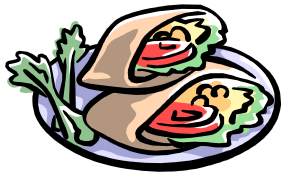


GLP-1: an incretin hormone with multiple direct effects on human physiology.

Baggio & Drucker. Gastroenterol 2007;132;2131–57

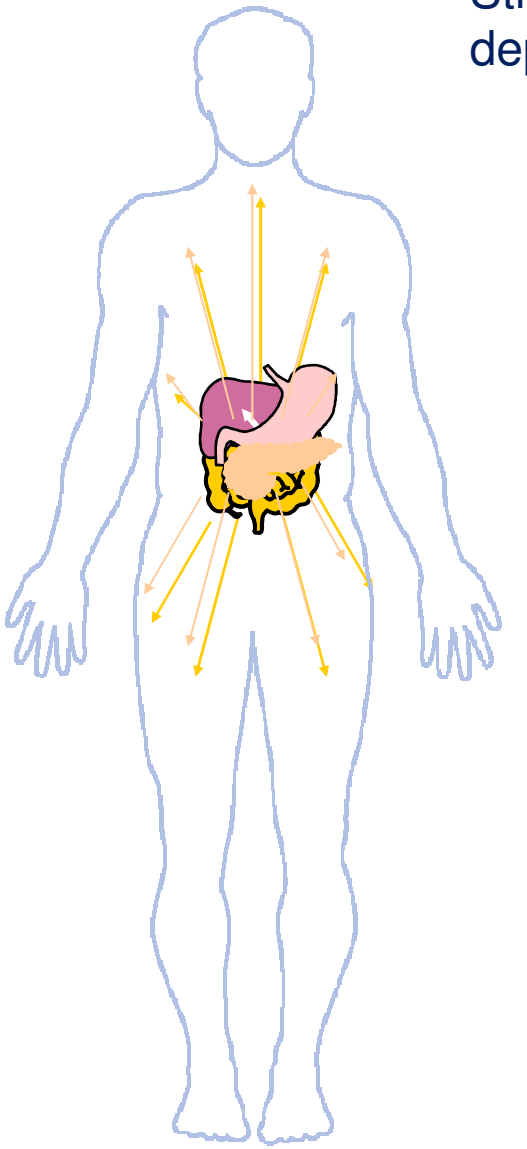
GLP-1: effects in humans

After food ingestion…



GLP-1 is secreted from L-cells of the jejunum and ileum

That in turn…



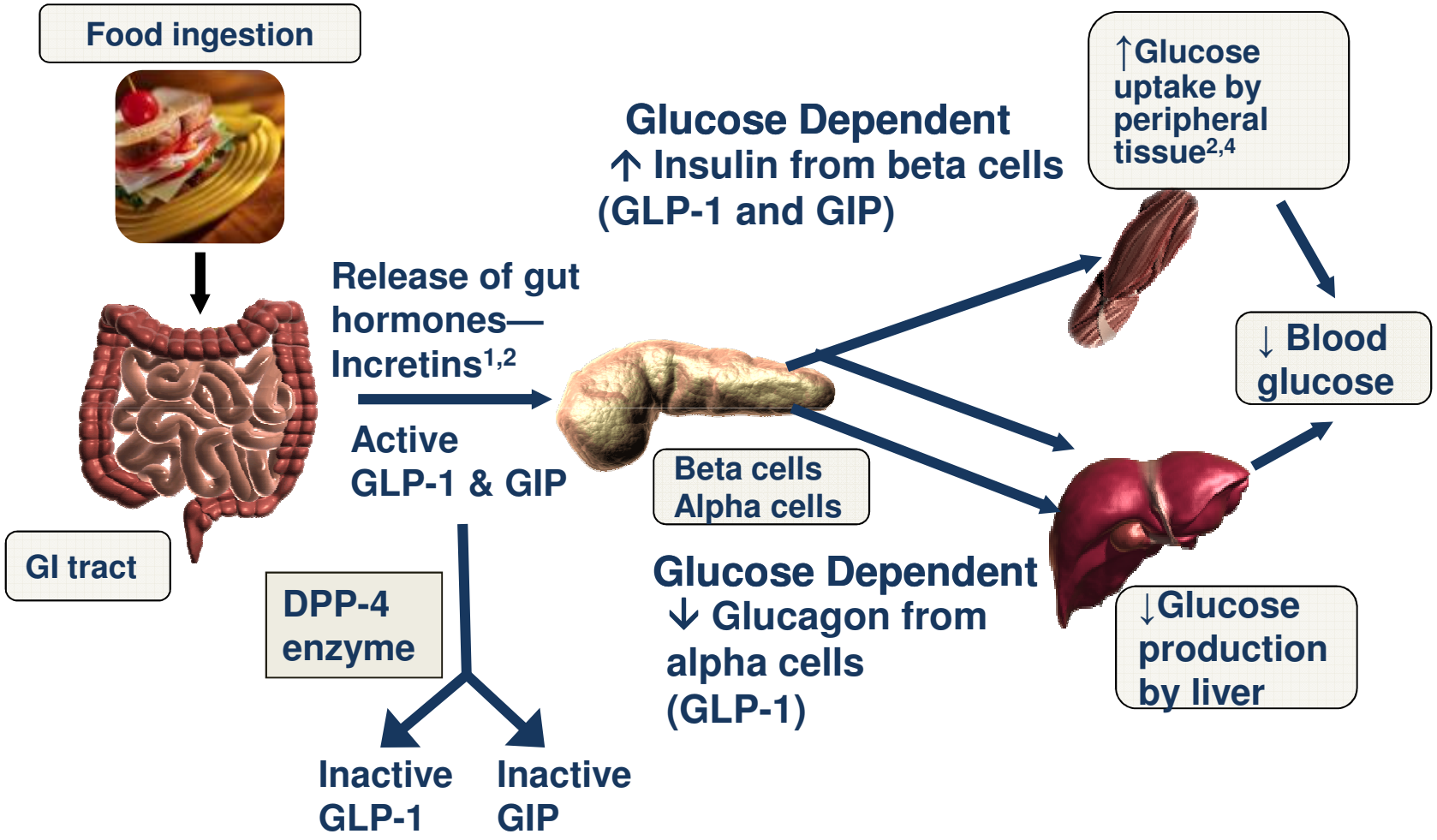
- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake
- Improves insulin sensitivity

Long-term effects in animal models:

- Increase of β-cell mass and improved β-cell function

Drucker. *Curr Pharm Des.* 2001
Drucker. *Mol Endocrinol*. 2003

Incretins: Role in Glucose Homeostasis



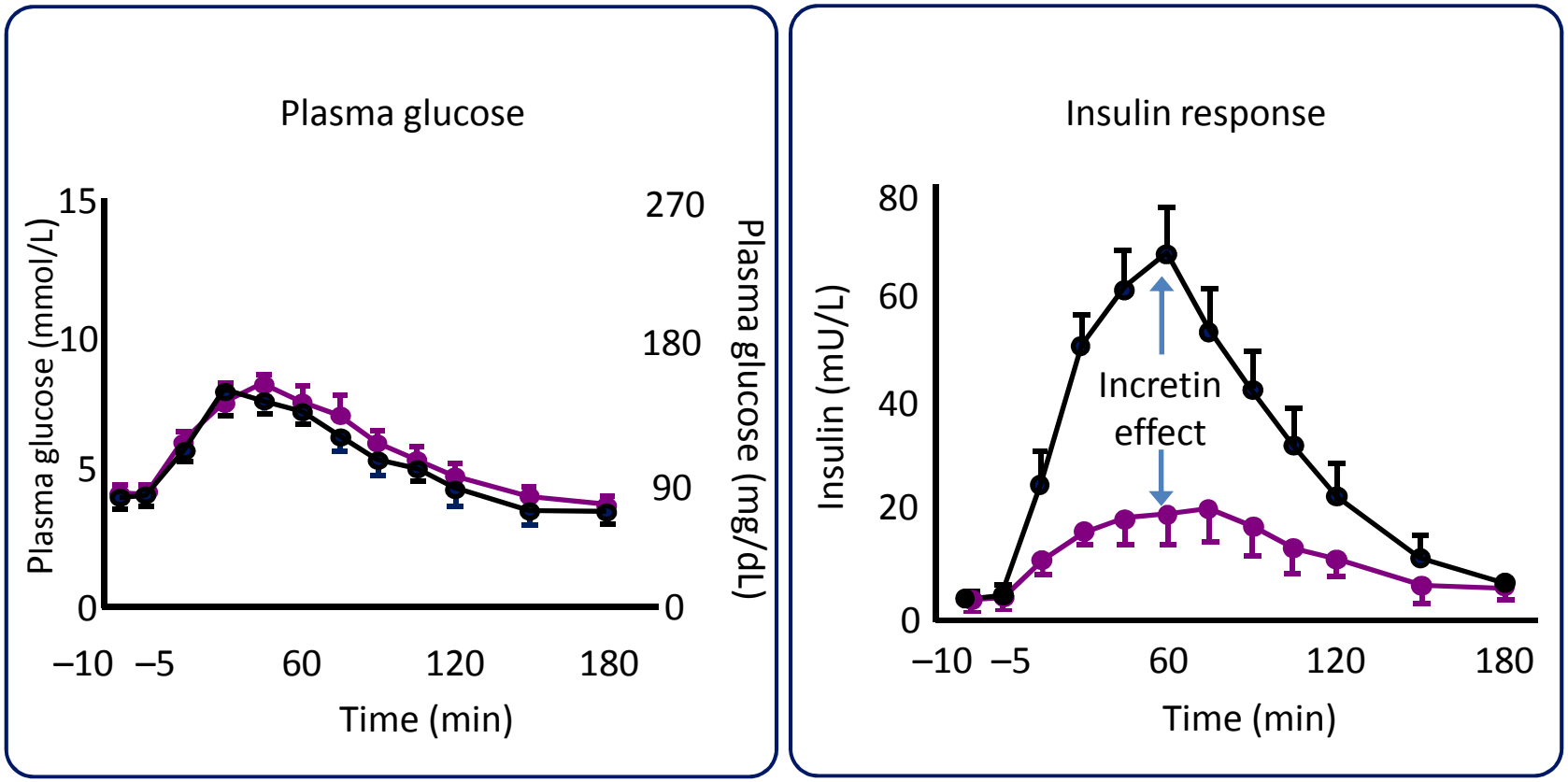
1. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913.
2. Ahrén B. *Curr Diab Rep*. 2003;2:365–372.
3. Drucker DJ. *Diabetes Care*. 2003;26:2929–2940.
4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

The Incretin Effect

The "Incretin Effect" describes the phenomenon whereby a glucose load delivered orally produces a much greater insulin secretion than the same glucose load administered intravenously.

Elrick H J Clin Endocrinol Metab 1964;24:1076–82.

The Incretin Effect



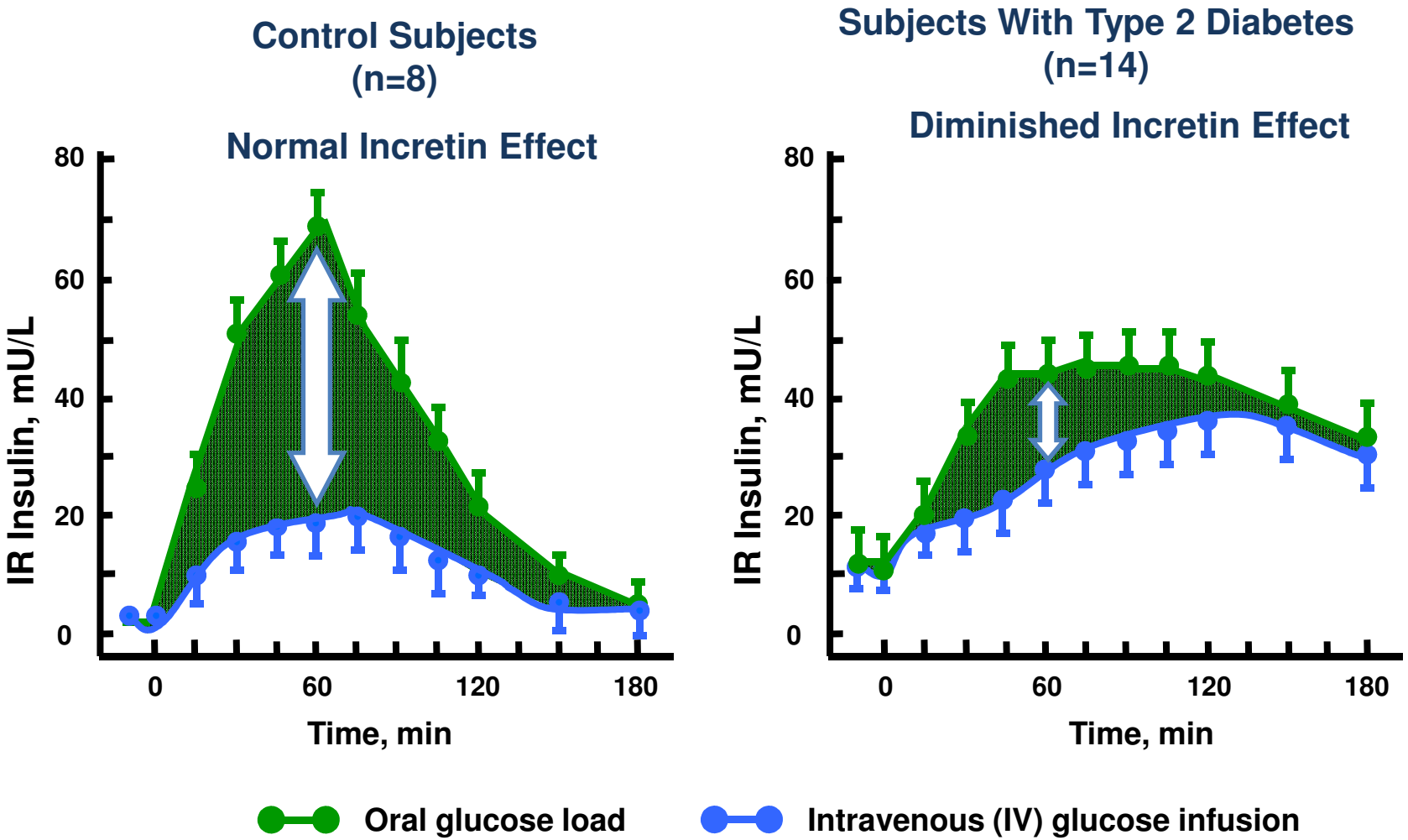
● Oral glucose load (50 g/400 mL)

● IV glucose infusion

Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration.

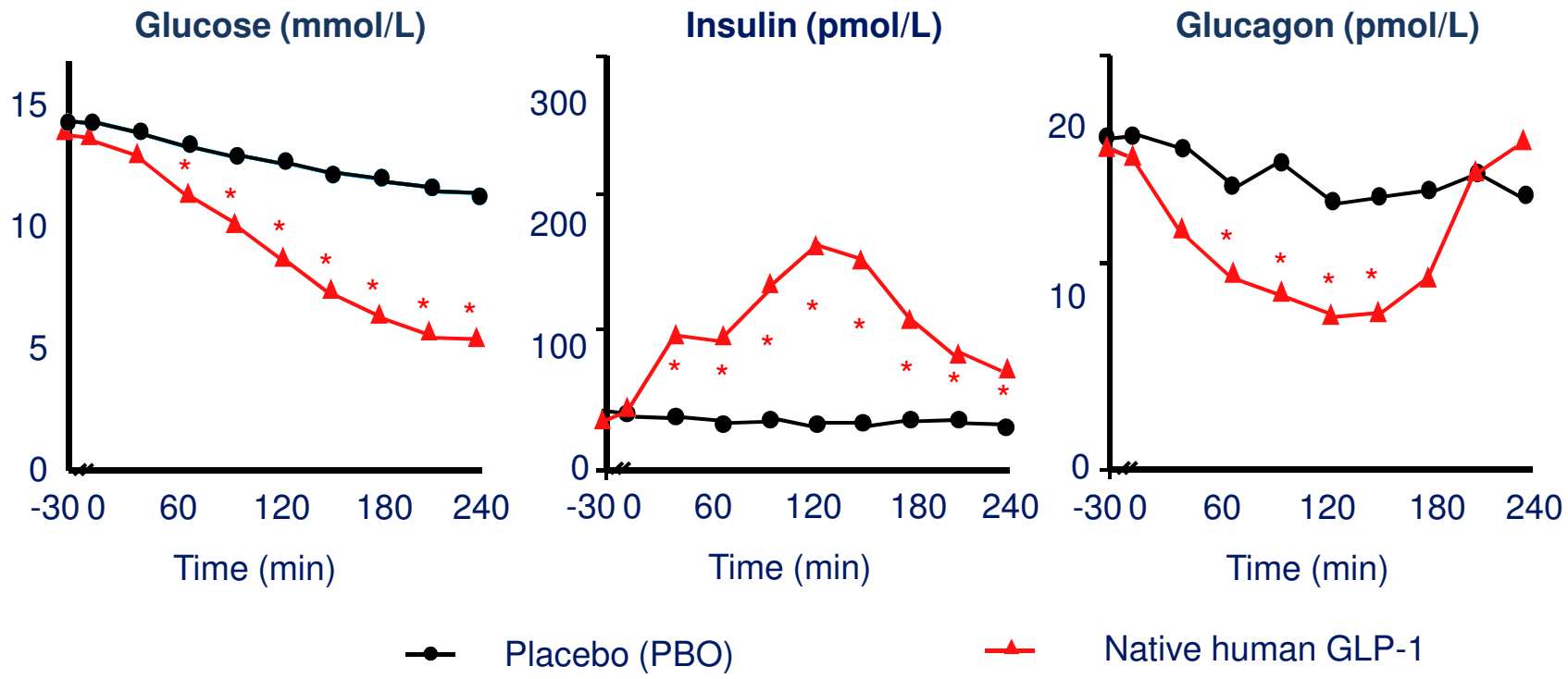
Nauck *et al. Diabetologia* 1986;29:46–52,

The Incretin Effect : Diminished in Type 2 Diabetes



Nauck M et al. *Diabetologia* 1986;29:46–52.

GLP-1 Infusion Has Glucose-dependent Effects

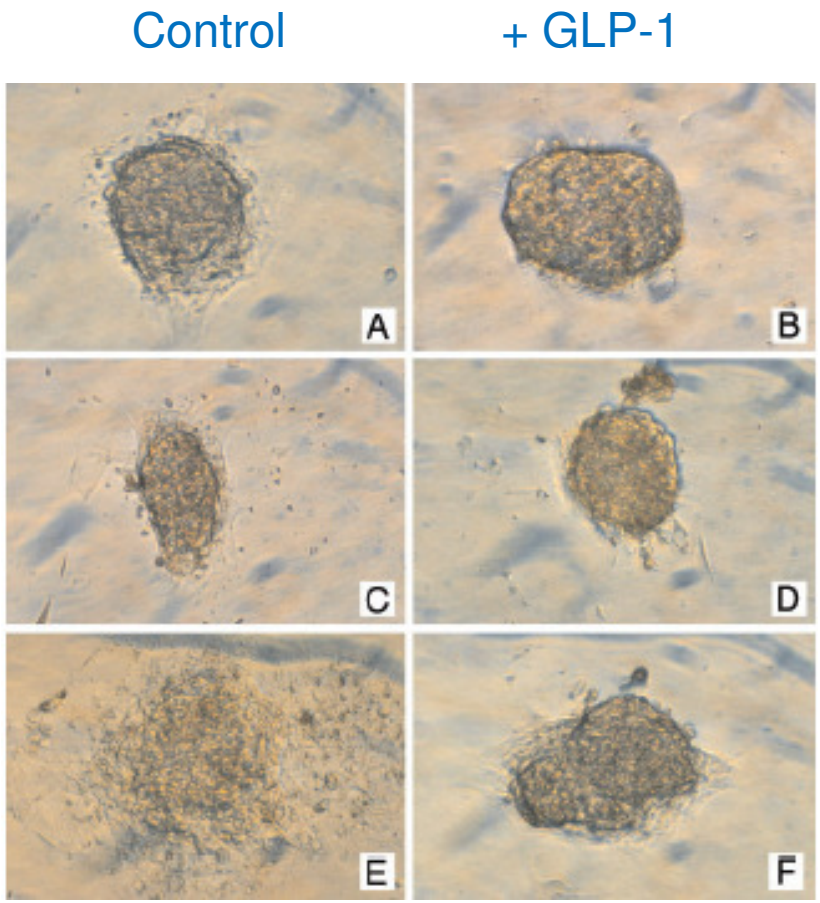


Effects of 4-hour GLP-1 infusion (1.2 pmol/kg/min) in 10 patients with type 2 diabetes.

Mean (SE); n=10; *p<0.05.

Nauck *et al. Diabetologi*a 1993;36:741–4

GLP-1 preserves human islet morphology and function in cultured islets in vitro



Farilla et al. *Endocrinology.* 2003

Incretin Based Therapies

GLP-1 secretion is impaired in Type 2 diabetes

Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:

- Exenatide
- Liraglutide
- Lixisenitide

Injectables

Block DPP- 4, enzyme that degrades GLP-1:

- Sitagliptin
- Saxogliptin
- Vildagliptin
- Saxagliptin
- Linagliptin

Oral agents

GLP1 receptor agonists

- Short acting- exenatide and lixisenatide
- Lower postprandial glucose levels and insulin concentrations via retardation of gastric emptying
- Long acting- albiglutide, dulaglutide, exenatide long-acting release and liraglutide
- Lower blood glucose levels through stimulation of insulin secretion and reduction of glucagon levels

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* 8, 728–742 (2012);

Mechanism of action

- Activation of the GLP-1 receptor
- GLP1 receptors are expressed on beta cells, cells in the peripheral and central nervous system, the heart and vasculature, kidney, lung, and GI mucosa
- Binding of agonists to the GLP-1 receptor activates the cAMP-PKA pathway and several GEFs (guanine nucleotide exchange factors)

Goodman & Gilman's Pharmacological Basis of therapeutics. 12th

Mechanism of action

- The end result of these actions is increased insulin biosynthesis and exocytosis in a glucose-dependent manner

Goodman & Gilman's Pharmacological Basis of therapeutics. 12th

Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Pharmacokinetics

- Exenatide –
  - S.C twice daily
  - Rapidly absorbed, reaches peak concentrations in ~2 hours
  - Little metabolism in circulation
  - Vd is 30 L
  - Clearance is glomerular filtration

Goodman & Gilman's Pharmacological Basis of therapeutics. 12th

Pharmacokinetics

- Liraglutide
  - S.C once daily
  - Peak in 8-12 hrs
  - elimination $t_{1/2}$ is 12-14 hours
  - clearance is primarily through the metabolic pathways of large plasma proteins

Goodman & Gilman's Pharmacological Basis of therapeutics. 12th

Advantages of long acting agents

- Provide better glycaemic control than the short-acting GLP-1 receptor agonists, as patients have higher insulin levels in the fasting state (and presumably during the night) following administration of long-acting receptor agonists

- Greater reductions in plasma HbA1c levels than those observed with the intermittent activation of the GLP 1 receptor resulting from administration of short-acting compounds

- They are also effective during the night and early morning

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* 8, 728–742 (2012);

Adverse effects

- Nausea- most frequent- incidence is between 25% and 60%
- Occurrence in a specific individual seems to be dependent upon various factors, such as meal size and frequency—and, potentially, BMI
- Lower in Asian patients

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* 8, 728–742 (2012);

Adverse effects

- Incidence of vomiting 5-15 %

- Long-acting GLP-1 receptor agonists seem to exhibit improved gastrointestinal tolerability, and the incidence of nausea declines over time (tolerance)

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol*. 8, 728–742 (2012);

Adverse effects

- 5–10% of patients discontinue treatment owing to nausea & vomiting
- Diarrhoea in ~10–20% of patients- more with long acting compounds
- Few cases of acute pancreatitis have been reported during treatment with exenatide and other GLP-1 receptor agonists
- An association between treatment with GLP-1-based drugs and an increased risk of pancreatitis cannot be ruled out

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol*. 8, 728–742 (2012);

Adverse effects

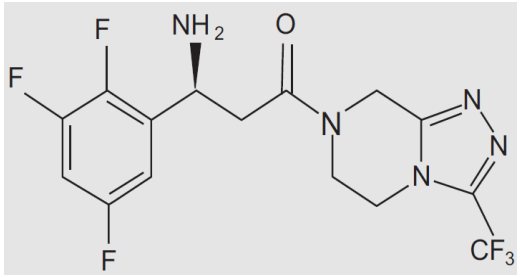
- Liraglutide- increase in mean lipase concentrations of >10 IU, an effect that was reversible after treatment was discontinued.

- Cessation of treatment with GLP-1 receptor agonists in patients with clinical signs of acute pancreatitis is, therefore, advisable, and avoiding these drugs in patients with a history of pancreatitis would be prudent

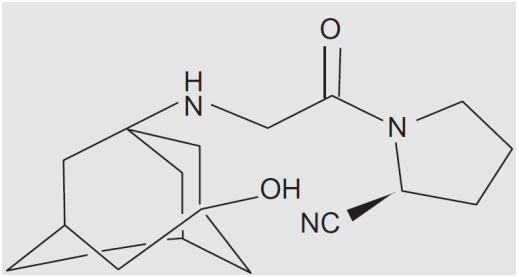
- Should be avoided in patients with a history of thyroid cancer or multiple endocrine neoplasia- increased incidence of C-cell hyperplasia and medullary thyroid cancer was reported in rats and mice

Meier J. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol*. 8, 728–742 (2012);

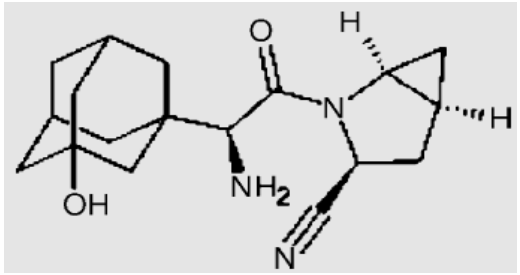
Incretin Based Therapies: DPP4 Inhibitors



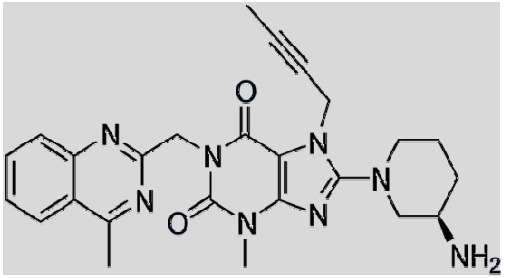
Sitagliptin



Vildagliptin



Saxagliptin



Linagliptin

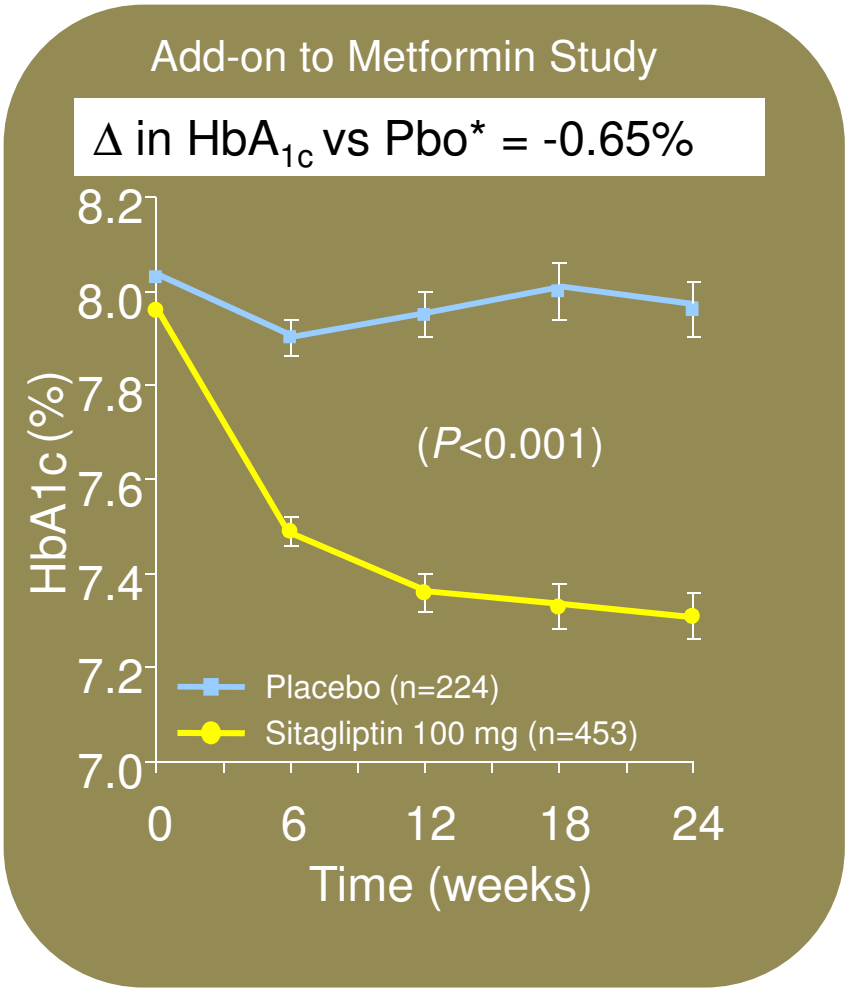
Overview of Sitagliptin

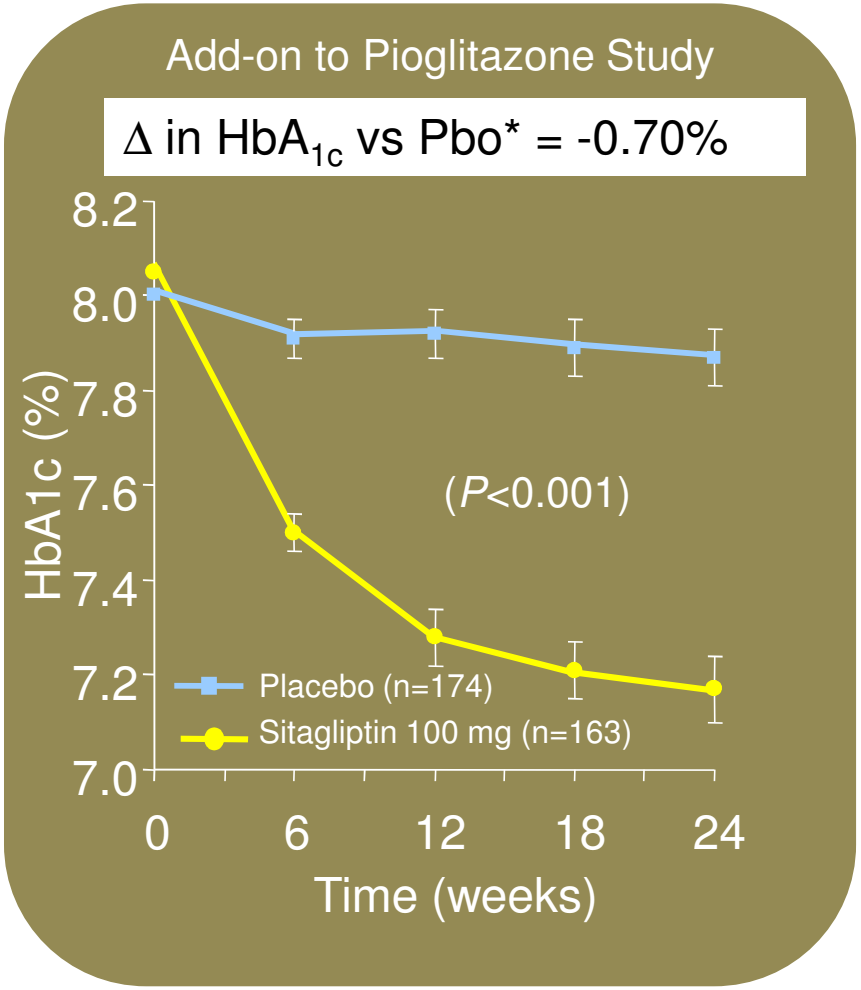
- Sitagliptin is a triazolopiperazine based DPP-4 inhibitor that binds selectively and reversibly to the active site of DPP-4.
- The recommended dosage of Sitagliptin is 100 mg once/day.
- Sitagliptin is primarily (79%) eliminated unchanged by the kidney. Dosing should be reduced to 50 mg once/day in patients with moderate renal insufficiency and to 25 mg once/day in cases of severe renal impairment or ESRD.
- Only about 16% of sitagliptin undergoes hepatic metabolism; hence, its pharmacokinetics have been shown to be unaffected by mild-to-moderate hepatic failure.

Drab SR Pharmacotherapy 2010;30(6):609–624.
Neumiller JJ *Clin Ther. 2011;33:528–576*

Sitagliptin: Effects on HbA1c

The efficacy and safety of sitagliptin, added to ongoing metformin & pioglitazone therapy for 24 weeks, were assessed in patients with type 2 diabetes who had inadequate glycaemic control.





*Compared with placebo.

Charbonnel B et al *Diabetes Care.* 2006;29:2638-2643.
Rosenstock J et al. *Clin Ther.* 2006;28:1556-1568.

Sitagliptin: FDA Alert

- Eighty-eight post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported to the Agency between October 16, 2006 and February 9, 2009.
- FDA recommended that healthcare professionals should monitor patients carefully for the development of pancreatitis after initiation or dose increases of sitagliptin or sitagliptin/metformin, and to discontinue sitagliptin or sitagliptin/metformin if pancreatitis is suspected while using these products.



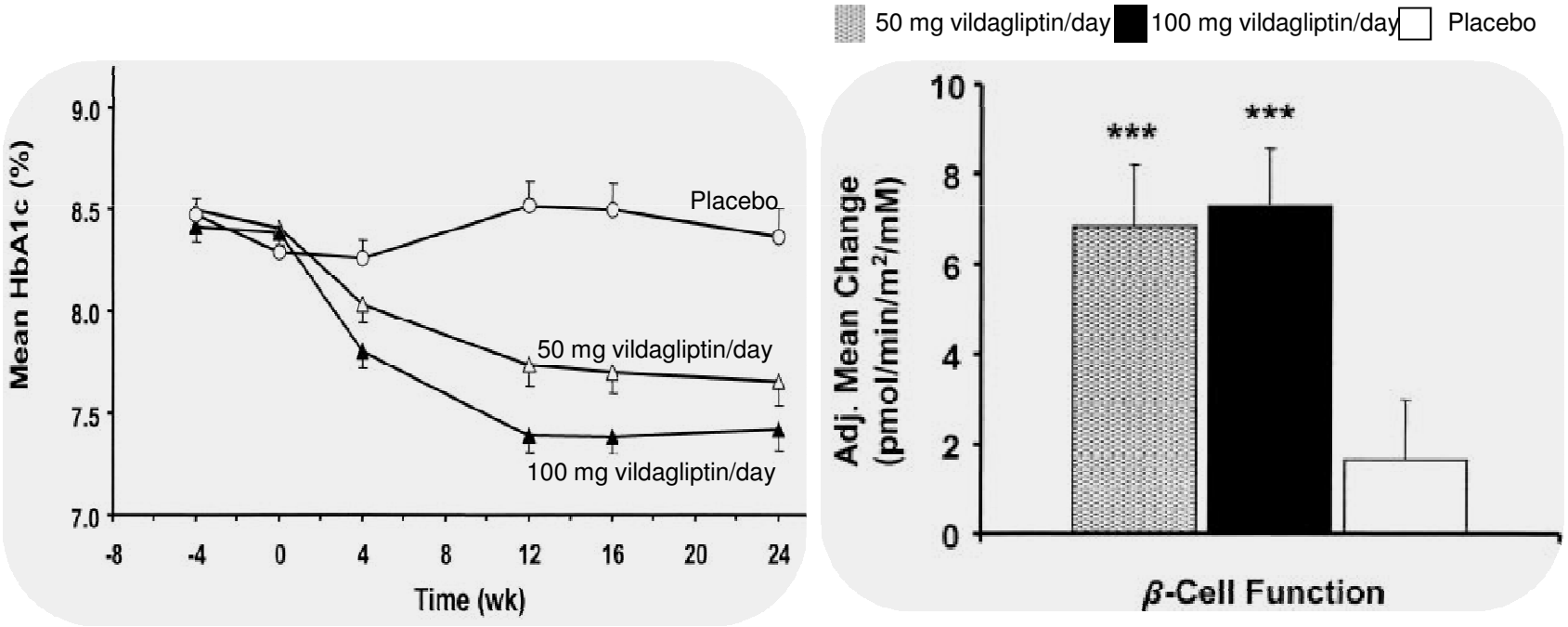
Overview of Vildagliptin

- Vildagliptin is a cyanopyrrolidine compound.
- According to EU labeling, vildagliptin is dosed at 50 mg once or twice daily.
- The approval of this drug in the United States has been delayed by a request from the FDA for additional data on the use of vildagliptin in patients with renal impairment, reportedly due to concern about the potential for an elevated risk for skin lesions resulting from increased drug exposure in this patient group.

Drab SR Pharmacotherapy 2010;30(6):609–624.
Neumiller JJ *Clin Ther. 2011;33:528–576*

Vildagliptin: Effects on HbA1c & ß-Cell function

This was a double-blind, randomized, multicenter, parallel group study of a 24-week treatment with 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo in patients continuing a stable metformin dose regimen (≥1,500 mg/day) but achieving inadequate glycaemic control.



Vildagliptin produced clinically meaningful, decrease in HbA1c & improvement in measures of β-cell function.

***P <0.001; **P <0.001 vs. placebo.

Bosi E et al. Diabetes Care 2007;30:890–95.

Overview of Saxagliptin

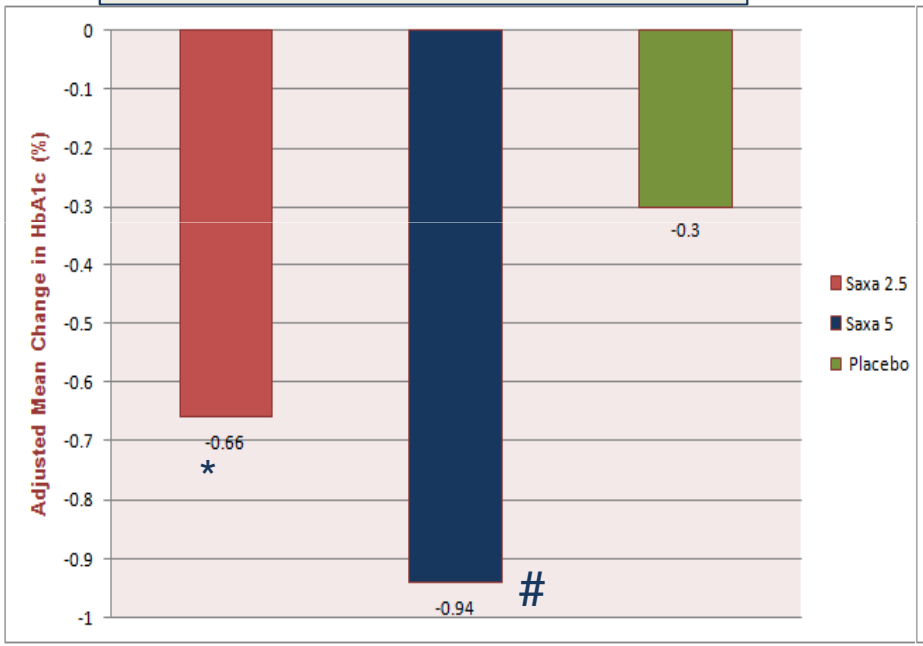
- Saxagliptin is a cyanopyrrolidine DPP-4 inhibitor with a high selectivity for DPP-4.
- The recommended dosage is 2.5 or 5 mg/day.
- Both the Saxagliptin and its metabolite are renally excreted, and accumulation can occur in patients with renal impairment, necessitating a daily dose limit of 2.5 mg.
- The 2.5-mg dose is recommended in patients taking strong CYP3A4/5 inhibitors.
- Compared with sitagliptin or vildagliptin, saxagliptin is at least 10-fold more potent inhibitor of DPP-4.

Drab SR Pharmacotherapy 2010;30(6):609–624.
Neumiller JJ *Clin Ther. 2011;33:528–576*

Saxagliptin: Effects on HbA1c

This two 24-weeks trials assessed the efficacy and safety of saxagliptin as add-on therapy in patients with T2 DM with inadequate glycaemic control with TZDs & metformin alone.

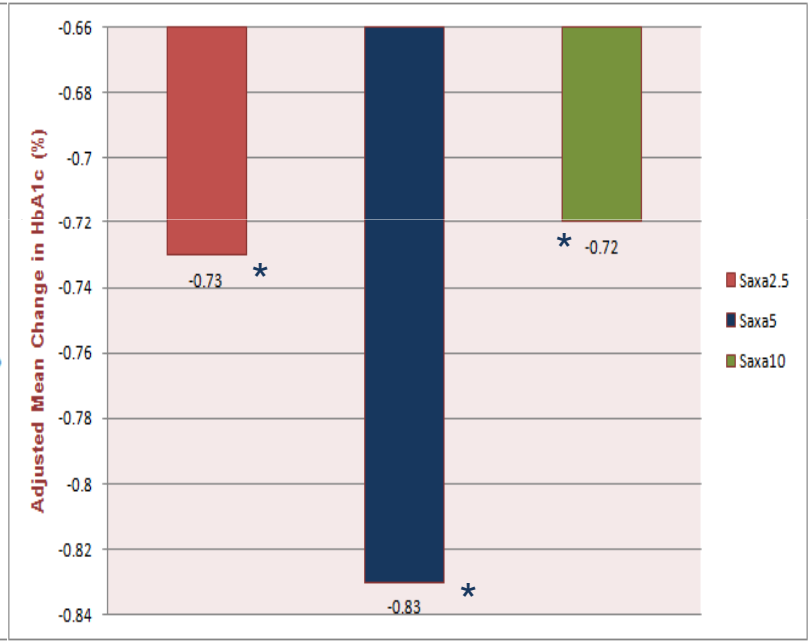
Saxagliptin added to TZDs



Adjusted mean change in HbA1c from baseline to wk 24

*P=0.0007, #p<0.0001 vs Placebo

Saxagliptin added to Metformin



Adjusted mean change in HbA1c from baseline versus placebo

*p<0.0001

Hollander P et al. J Clin Endocrinol Metab. December 2009, 94(12):4810–19
Defronzo RA et al. Diabetes Care 2009, 32:1649–1655.

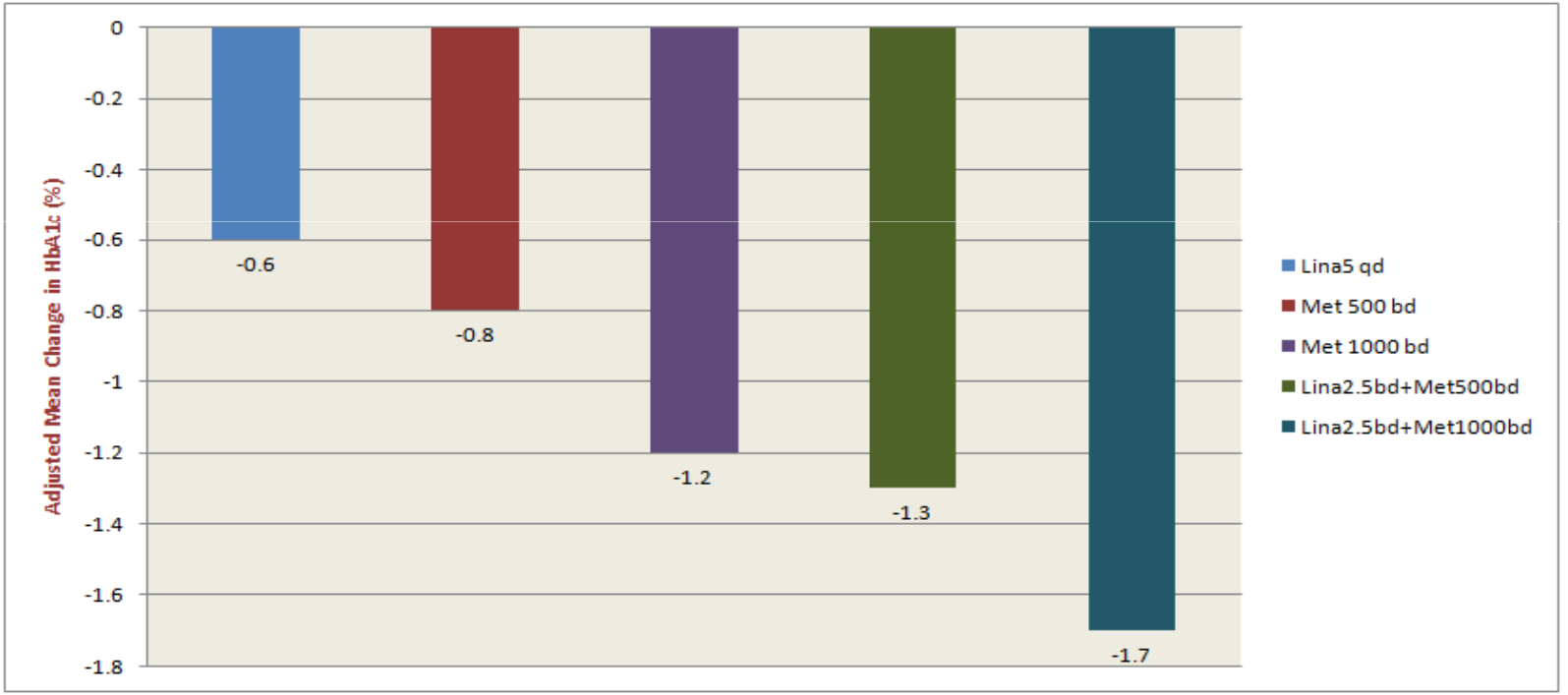
Linagliptin: The New Prospect

- FDA on May 2nd, 2011 approved linagliptin, a dipeptidyl peptidase-4 inhibitor, for the improvement of blood glucose control in adults with type 2 diabetes mellitus.
- Linagliptin is predominantly excreted via enterohepatic system, with 84.7% of the drug eliminated in the faeces and only 5% eliminated via urine.
- Data to date suggest that linagliptin would not need dose adjustment in patients with type 2 diabetes, regardless of the degree of renal impairment.

www.boehringeringelheim.com/content/dam/.../Linagliptin.pdf
Heise et al Diabetes Obes Metab. 2009 Aug;11(8):786-94.
Edelman SV, Basile J Paper Presented at ADA 2011
Scott LJ. Drugs 2011; 71 (5): 611-624

Linagliptin: Effects on HbA1c

This 24-week, double-blind, placebo-controlled study randomized 791 individuals with T2 DM that were drug naïve with an A1c> 7.5% and <11% or that were using one oral antidiabetic drug (metformin) with an A1c >7.0 and <10.5%.

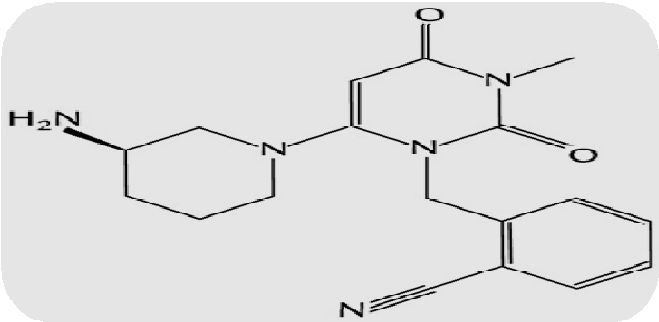


The combination therapy of metformin and linagliptin provided superior improvements in both A1c ($p<0.0001$) and fasting plasma glucose ($p<0.001$) than monotherapy comparators.

Thomas Haak,Paper Presented at ADA 2011

Overview of Alogliptin

- Alogliptin is an orally available, quinazolinone based, noncovalent DPP-4 inhibitor.
- Alogliptin is primarily excreted unchanged by the kidneys. So, dose adjustment is required in patients with moderate to severe renal impairment.

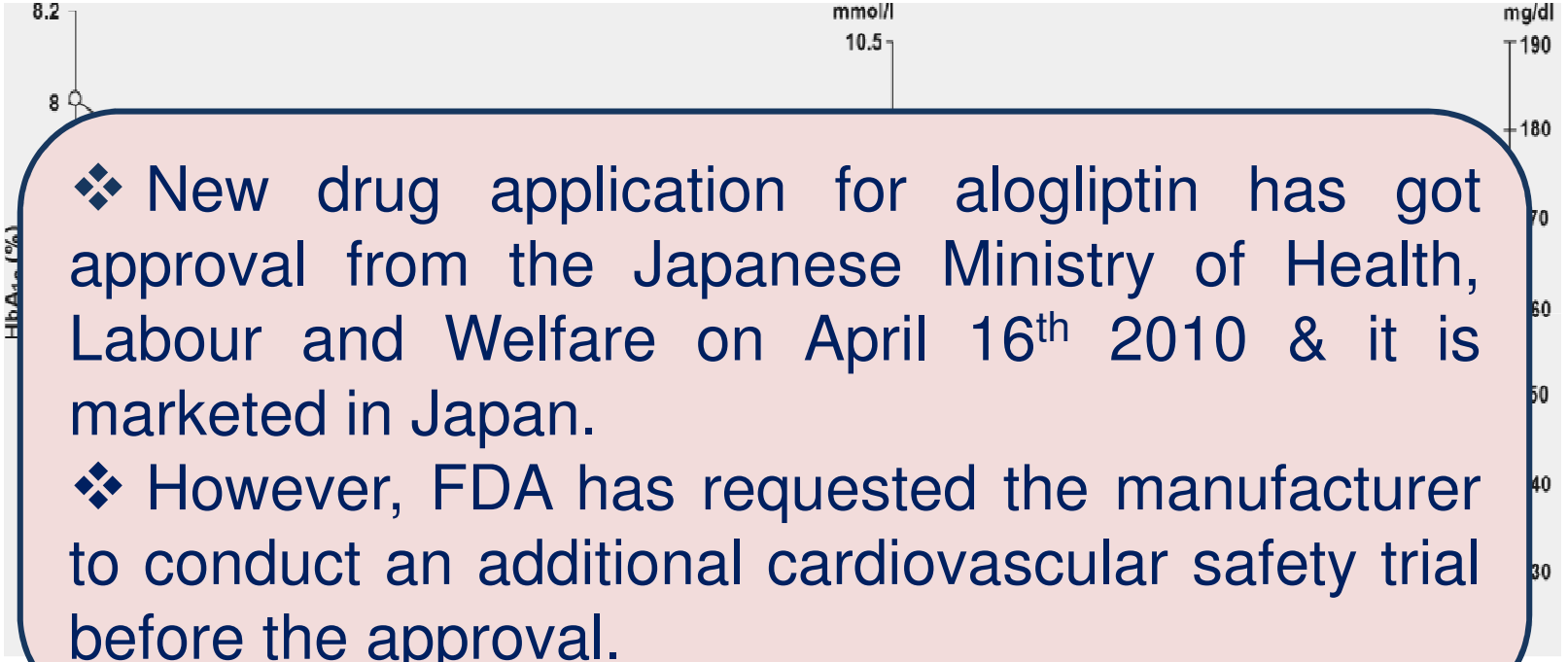


Chemical Structure of Alogliptin

Drab SR Pharmacotherapy 2010;30(6):609–624.
Neumiller JJ *Clin Ther. 2011;33:528–576*

Alogliptin: Effects on Glycaemic Parameters

Evaluation of the efficacy and safety of alogliptin for 26 weeks at once-daily doses of 12.5 and 25 mg in combination with metformin in patients whose HbA1c levels were inadequately controlled on metformin alone.



- New drug application for alogliptin has got approval from the Japanese Ministry of Health, Labour and Welfare on April 16th 2010 & it is marketed in Japan.
- However, FDA has requested the manufacturer to conduct an additional cardiovascular safety trial before the approval.

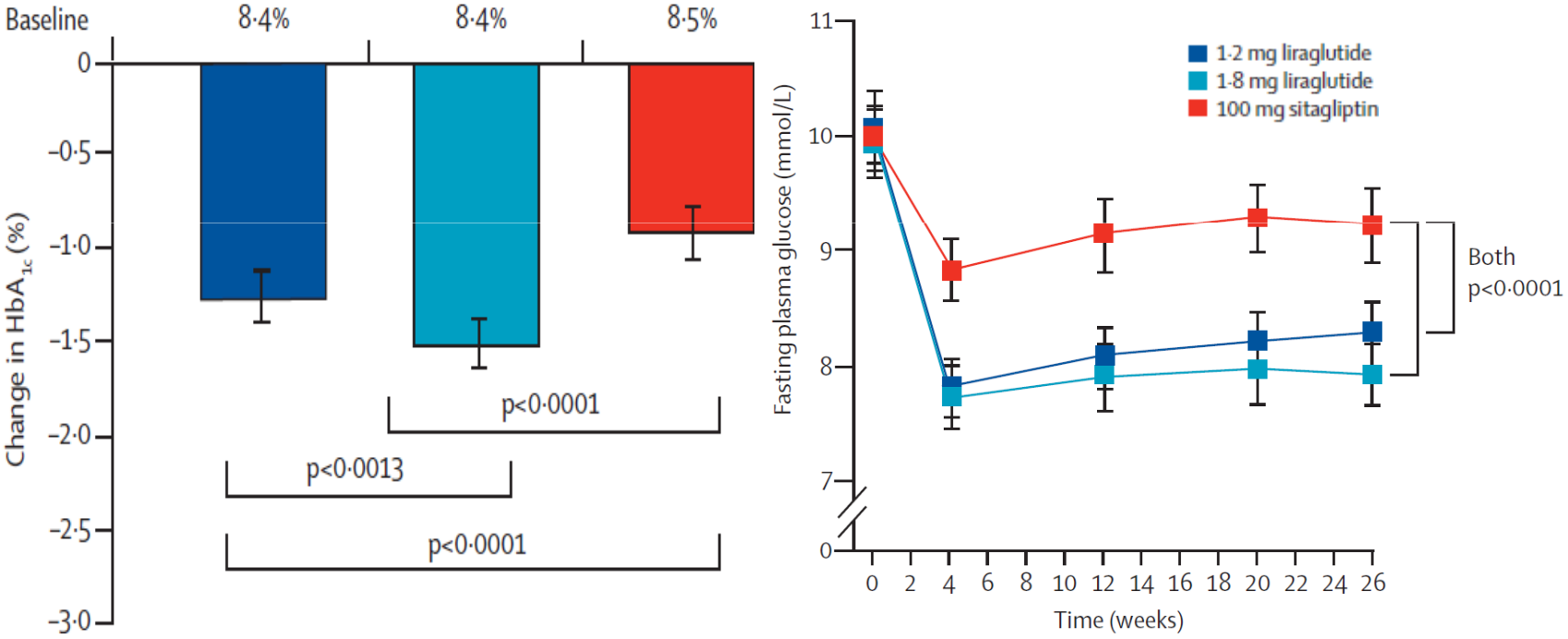
Alogliptin at either dose produced least squares mean (SE) decreases from baseline in HbA1c of - 0.6 (0.1)% and in FPG of -17.0 (2.5) mg/dl, decreases that were significantly (*p < 0.001) greater than those observed with placebo.

Nauck MA et al. Int J Clin Pract 2009; 63: 46–55

GLP-1 Analogues
vs
DPP-4 Inhibitor

Liraglutide vs Sitagliptin

In this parallel-group, open-label trial, participants with T2 DM who had inadequate glycaemic control on metformin were randomly allocated to receive 26 weeks' treatment with 1.2 mg or 1.8 mg subcutaneous liraglutide once daily, or 100 mg sitagliptin once daily.

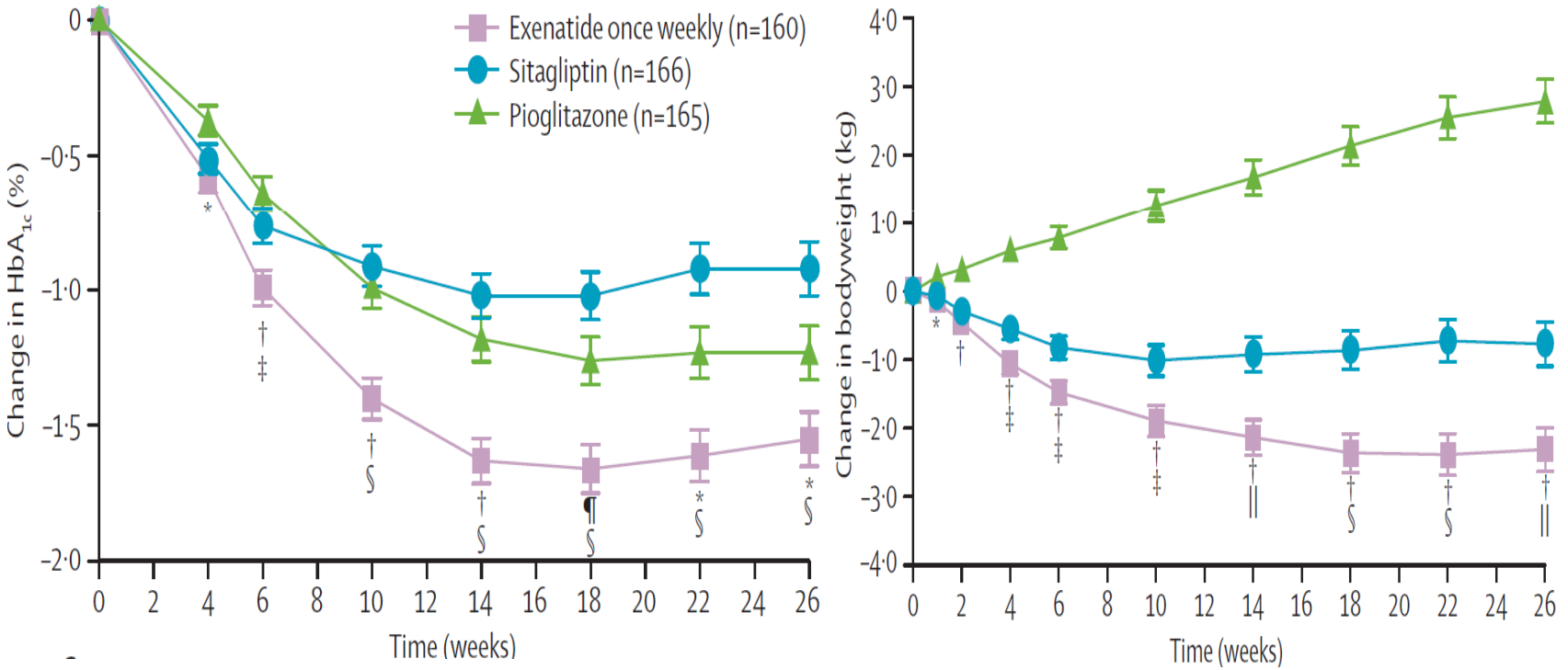


Liraglutide was superior to sitagliptin for reduction of HbA1c & FPG, and was well tolerated with minimum risk of hypoglycaemia.

Pratley RE et al Lancet 2010; 375: 1447–56

Exenatide LAR vs Sitagliptin (DURATION-2)

In this 26-week randomised, double-blind, double-dummy, superiority trial, patients with T2DM treated with metformin were randomly assigned to receive: 2 mg exenatide once weekly; 100 mg sitagliptin once daily; or 45 mg pioglitazone once daily.



Treatment with once weekly exenatide resulted in a significantly greater reduction in HbA1c & bodyweight as compared to sitagliptin.

‡p<0 · 05 for exenatide versus sitagliptin. §p<0 · 0001 for exenatide versus sitagliptin.
||p<0 · 001 for exenatide versus sitagliptin.

Bergenstal RM et al. Lancet 2010; 376: 431–39

GLP-1 Analogues vs DPP-4 Inhibitors

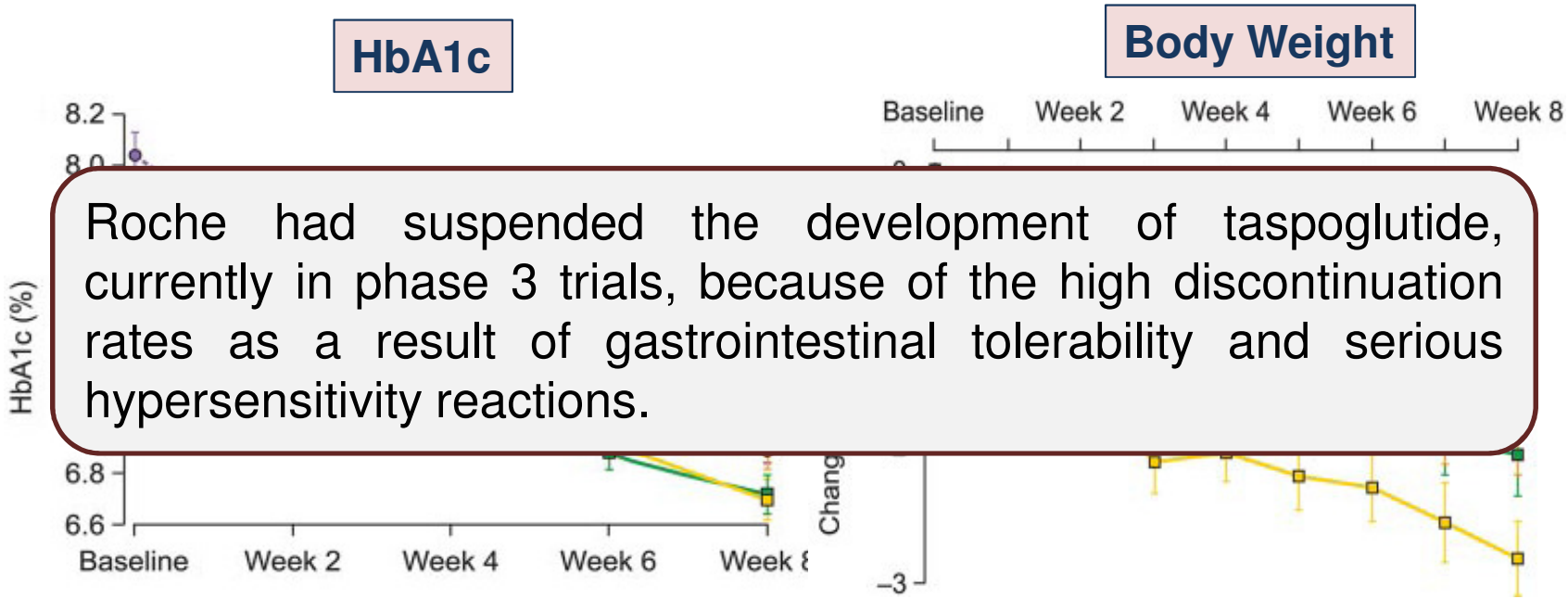
Properties/Effects	DPP-4 Inhibitors	GLP-1 Analogues
↑ Glucose-dependent insulin secretion	Yes	Yes
↓ Glucagon secretion	Yes	Yes
Effect on incretins	Endogenous incretins enhanced to physiological levels	Exogenous GLP-1: Possible Immune response (antibody formation)
Effect on body weight	Weight neutral	Body weight decreased
Inhibition of gastric emptying	Marginal	Yes
Hypoglycaemia	No	No
Side Effects	No nausea, vomiting	Reported nausea, vomiting
Administration	Oral	Subcutaneous

Barnett A Clinical Endocrinology 2009; 70: 343–53

The Future of Incretin Based Therapy

Overview of Taspoglutide

Type 2 diabetic patients who failed to obtain glycaemic control despite 1,500 mg metformin daily were randomly assigned to 8 weeks of double-blind subcutaneous treatment with placebo or taspoglutide.



Roche had suspended the development of taspoglutide, currently in phase 3 trials, because of the high discontinuation rates as a result of gastrointestinal tolerability and serious hypersensitivity reactions.

Black, placebo; magenta, 5 mg once weekly; green, 10 mg once weekly; yellow, 20 mg once weekly; purple, 10 mg once every 2 weeks; orange, 20 mg once every 2 weeks.

Taspoglutide used in combination with metformin significantly improves fasting and postprandial glucose control and induces weight loss.

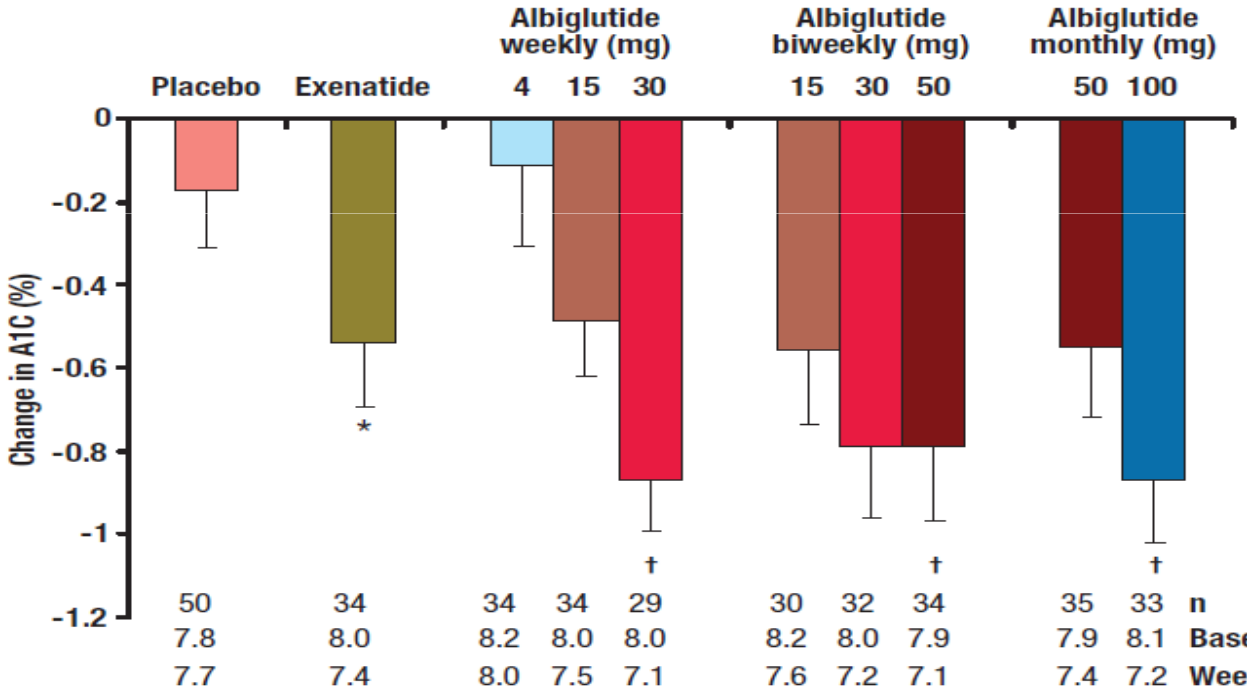
All taspoglutide doses were statistically significant ($P<0.0001$)

Nauck MA et al Diabetes Care 2009; 32:1237–43

Overview of Albiglutide

(Now in Phase III Trial)

In this 16 weeks, randomized, multicenter double-blind, parallel-group study, 356 type 2 diabetic subjects received subcutaneous placebo or albiglutide (weekly [4, 15, or 30 mg], biweekly [15, 30, or 50 mg], or monthly [50 or 100 mg]) or exenatide twice daily.

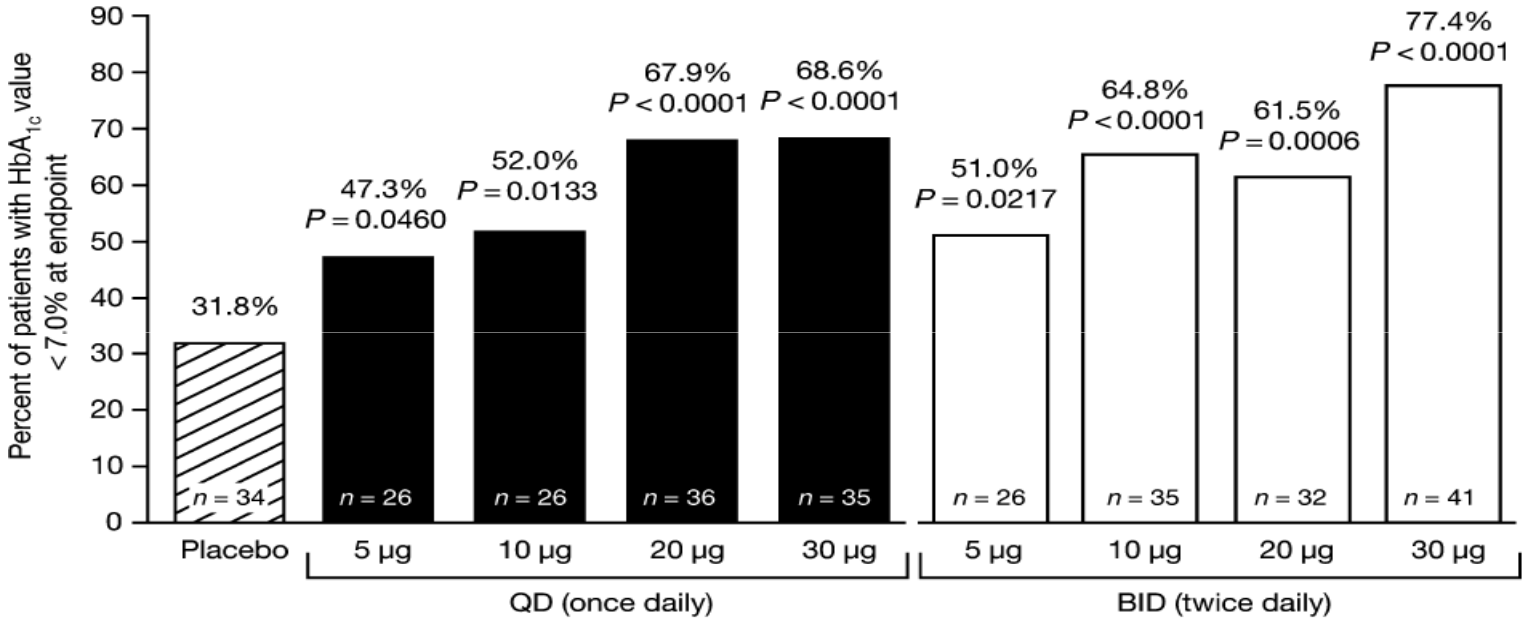


Weekly albiglutide administration significantly improved glycaemic control and elicited weight loss in type 2 diabetic patients, with a favourable safety and tolerability profile.

Rosenstock J et al. Diabetes Care 2009;32:1880–1886

Overview of Lixisenatide
(Now in Phase III Trial)

Randomized, double-blind, placebo-controlled, parallel-group, 13 week study of 542 patients with T 2 DM inadequately controlled on metformin.

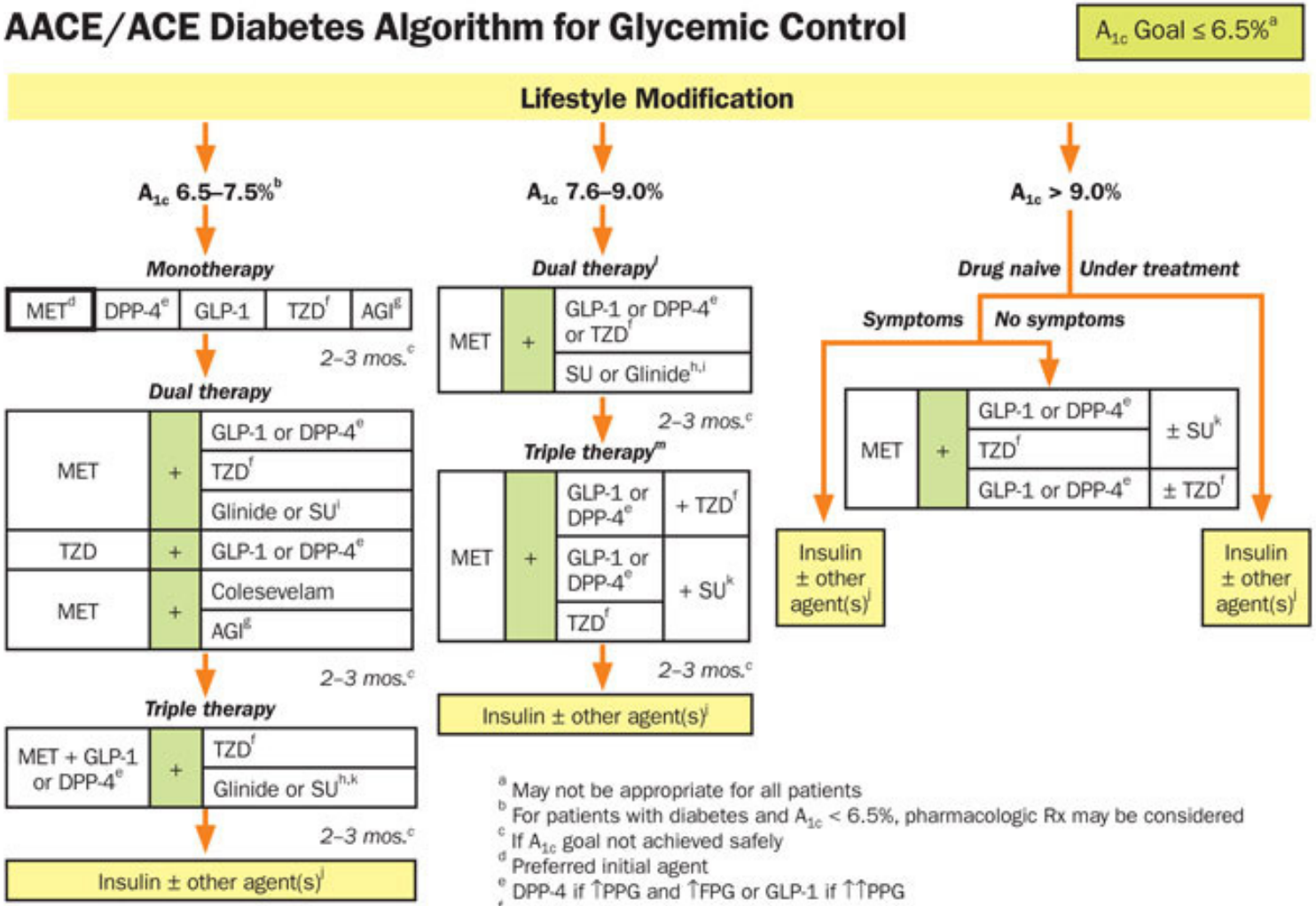


- Lixisenatide significantly improved glycaemic control in patients with Type 2 diabetes on metformin.
- In GETGOAL-L-Asia, a phase 3, 24 week trial, treatment with lixisenatide led to superior reductions in A1c relative to placebo (-0.77% vs. 0.11%, p<0.001) in an Asian population inadequately controlled on basal insulin therapy with or without a sulfonylurea.

Ratner RE et al. Diabet. Med.2010; 27: 1024–32.
Yutaka Seino,Paper Presented at ADA 2011

Current Status of Incretin Based Therapy

AACE/ACE Diabetes Algorithm for Glycemic Control



Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AGI, alpha-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; MET, metformin; PPG, postprandial glucose; SU, sulfonylurea; TZD, thiazolidinedione.

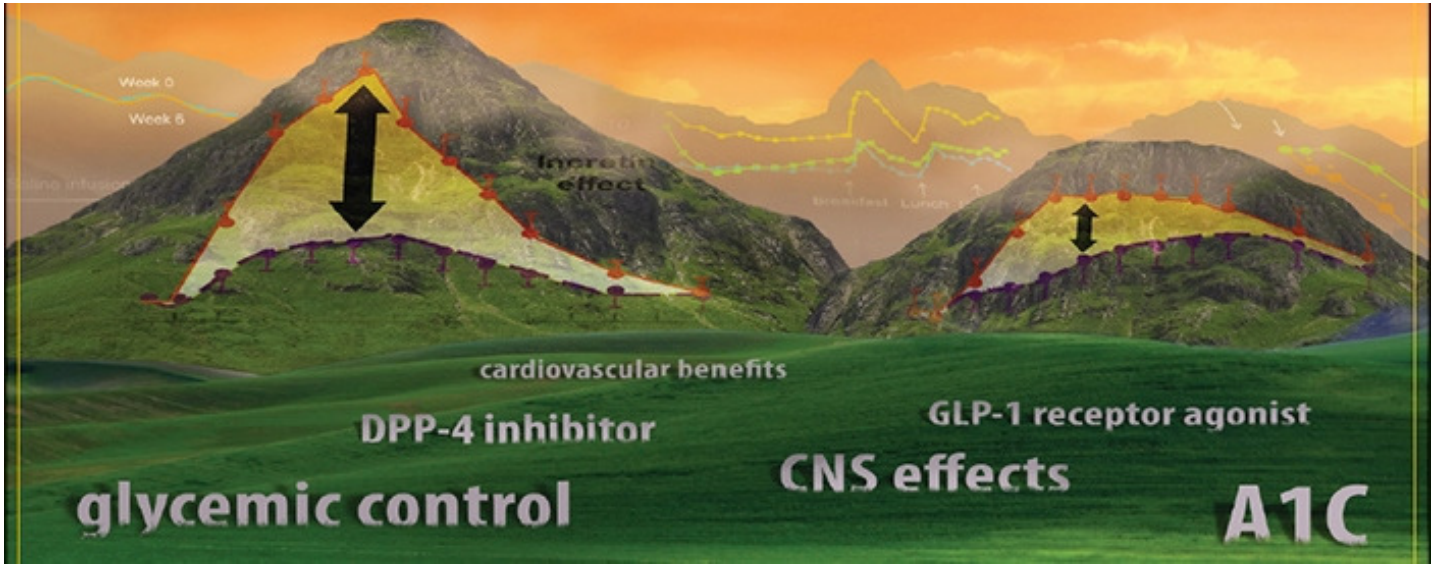
[a] May not be appropriate for all patients
[b] For patients with diabetes and A_{1c} < 6.5%, pharmacologic Rx may be considered
[c] If A_{1c} goal not achieved safely
[d] Preferred initial agent
[e] DPP-4 if ↑PPG and ↑FPG or GLP-1 if ↑↑PPG
[f] TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
[g] AGI if ↑PPG
[h] Glinide if ↑PPG or SU if ↑FPG
[i] Low-dose secretagogue recommended
[j] a) Discontinue insulin secretagogue with multidose insulin; b) Can use pramlintide with prandial insulin
[k] Decrease secretagogue by 50% when added to GLP-1 or DPP-4
[l] If A_{1c} < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
[m] If A_{1c} > 8.5%, in patients on dual therapy, insulin should be considered

Rodbard HW, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control [published correction appears in *Endocr Pract.* 2009;15(7):768-770]. *Endocr Pract.* 2009;15(6):540-559. Reprinted with permission from American Association of Clinical Endocrinologists.

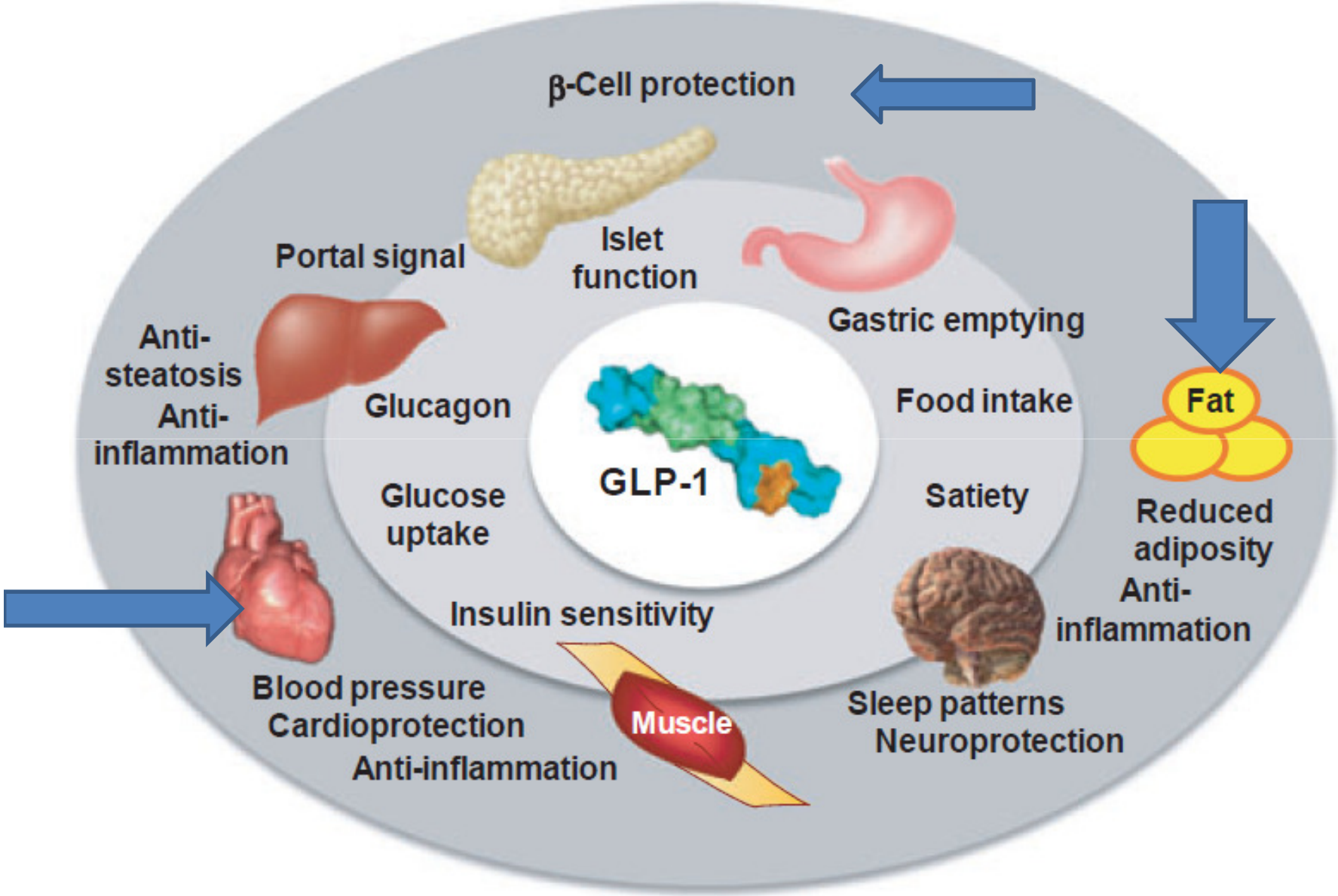
Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Hypo-Glycemia	Weight Change	CVD Risk Factors	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	2	Kidney, liver
Insulin, Long-acting	1.5 - 2.5	Yes	Gain	TG	1, Injected	None
Insulin, Rapid-acting	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Sulfonylureas	1.5	Yes	Gain	None	1	Essentially none
Thiazolidinediones	0.5 - 1.4	No	Gain	Variable	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	Essentially none
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	Essentially none
Alpha-glucosidase Inhibitors	0.5 - 0.8	No	Neutral	Minimal	3	Essentially none
Amylin-mimetics	0.5 - 1.0	No	Loss	With weight loss	3, Injected	None
GLP-1R Agonist	0.5 - 1.0	No	Loss	With weight loss	2, Injected	Kidney
DPP-4 Inhibitor	0.6 - 0.8	No	Neutral	None	1	None
Bile acid sequestrant	0.5	No	Neutral	LDL	1-2	Severe TGs
Bromocriptine	0.7	No	Neutral	Minimal	1	Essentially none

Figure 1—*Relative comparison of properties exhibited by different classes of agents approved for the treatment of type 2 diabetes. CVD, cardiovascular disease; TG, triglycerides; CHF, congestive heart failure. A1C reduction depends on starting A1C.*



INCRETINS THERAPY BEYOND GLYCEMIA


β-Cell protection
Islet function
Portal signal
Gastric emptying
Anti-steatosis
Anti-inflammation
Glucagon
Food intake
GLP-1
Fat
Glucose uptake
Satiety
Reduced adiposity
Anti-inflammation
Insulin sensitivity
Blood pressure
Cardioprotection
Anti-inflammation
Muscle
Sleep patterns
Neuroprotection

CV Protection

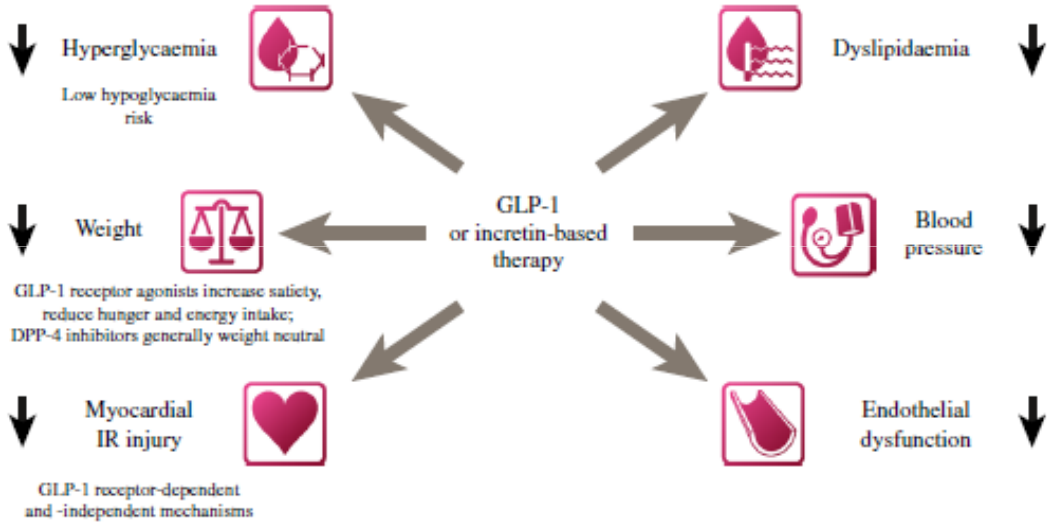


Figure 1 Mechanisms underlying the putative cardiovascular effects of incretin-based therapies. ANP, atrial natriuretic peptide, IR, ischaemia-reperfusion.

Osteoporosis

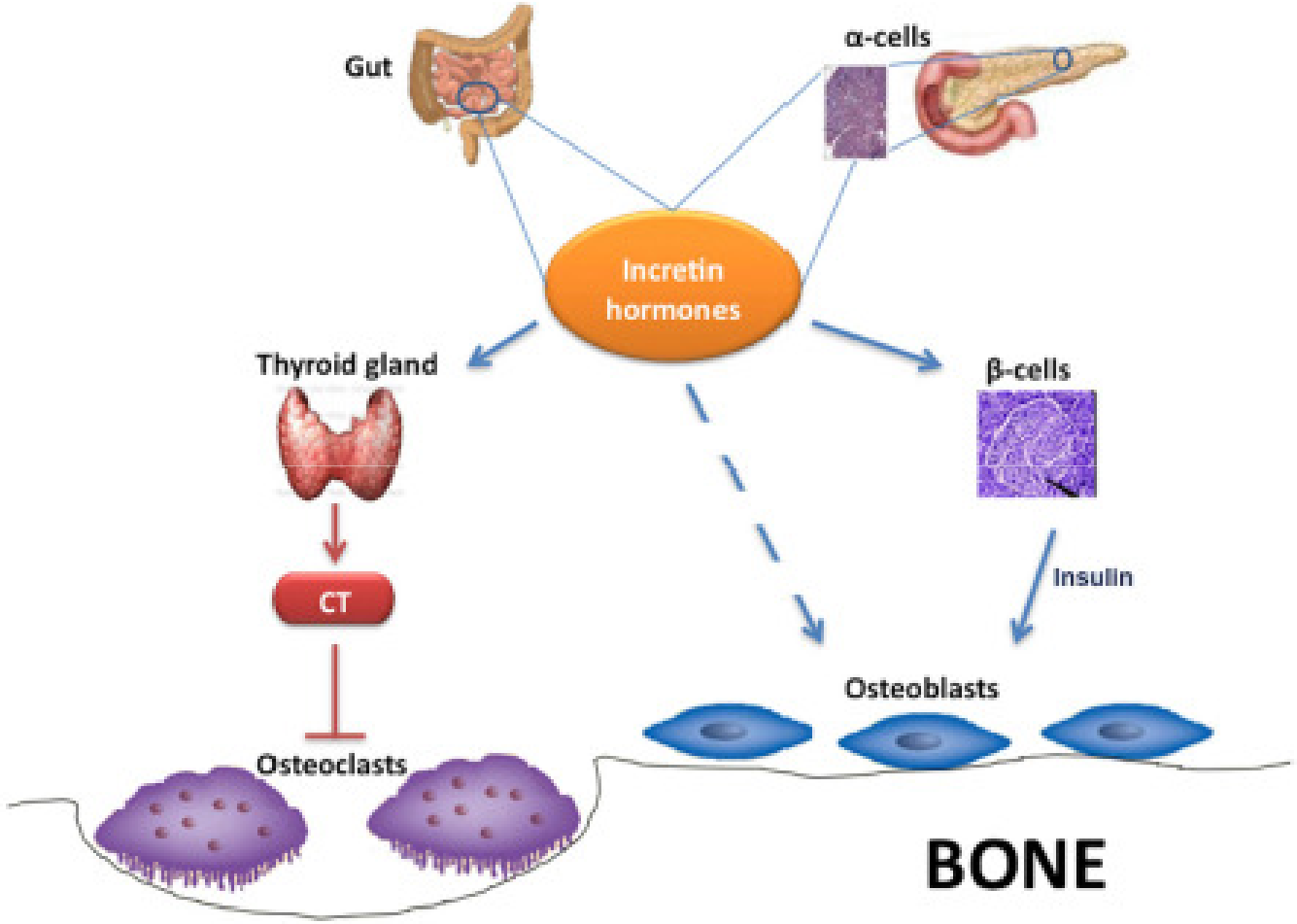


FIGURE 2 | Effects of incretin hormones on bone metabolism. Incretin hormones are secreted by intestinal L-cells and, in minor amounts, by pancreatic α-cells. Incretin hormones can stimulate osteoblastogenesis indirectly via increased insulin secretion as well as through a direct action on osteoblasts. Moreover, incretin hormones can inhibit osteoclastogenesis by stimulating calcitonin production. CT, calcitonin.

Key Points To Remember

- The GLP-1 receptor agonists and DPP-4 inhibitors achieve clinically meaningful reductions in HbA1c & improvements in β-cell functions with a low risk of hypoglycaemia.
- GLP-1 analogues have been associated with weight loss as an additional clinical benefit.
- The results achieved with long-acting GLP-1 receptor agonists appear to be superior to those achieved with short-acting GLP-1 receptor agonists.
- Meal-independent dosing (with exception of exenatide) & simple administration & dosage adjustment also make the incretin based therapies an attractive options for treatment of type 2 diabetes.
- Incretin therapy beyond glycemia : Cardiovascular protection needs further research & long term safety data needed

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Today's physiology is Tomorrow's medicine



Starling

Questions?





Thank you