Incretin based treatment in Type 2 Diabetes Mellitus

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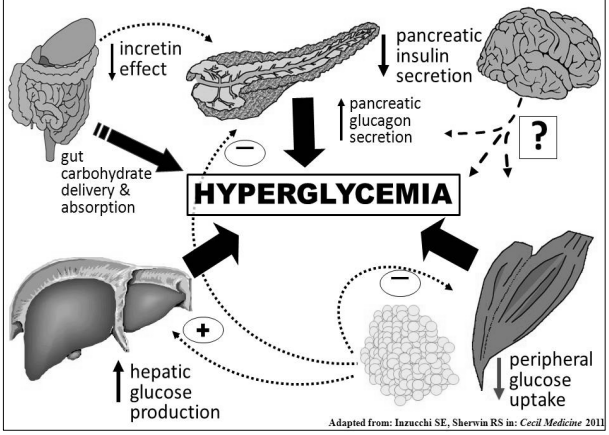
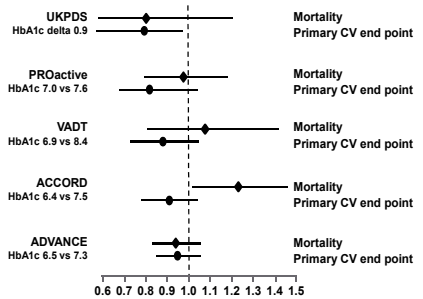
Main Pathophysiological Defects in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Intensive treatment studies



ACCORD=Action to Control Cardiovascular Risk in Diabetes trial; ADVANCE=Action in Diabetes and Vascular Disease:Preterax and Diamicron Modified Release Controlled Evaluation; CV=cardiovascular; PROactive=PROspective pioglitAzone Clinical Trial In macroVascular Events; VADT=Veterans Affairs Diabetes Trial
Ray KK *et al.* Lancet 2009;373:1765–72

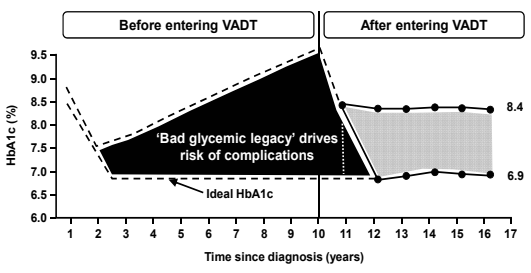
ACCORD: intensive treatment associated with increased risk of death from CV events

- Number of deaths from CV causes in intensive group versus standard group: 135 vs 94 (HR 1.35; 95% CI 1.04–1.76; *P*=0.02)
- Possible hypotheses to explain the ACCORD results:

	Intensive	Standard
HbA1c levels	6.4%	7.5%
Speed of HbA1c reduction (per 4 months)	1.4%	0.6%
Incidence of hypoglycemia†, no.	830	261*
Severe hypoglycemia‡, no.	538	179*
Weight gain >10 kg	27.8%	14.1%*
Undetected drug interaction	???	???

*P<0.001; †requiring any assistance; ‡requiring medical assistance
The ACCORD Study Group. N Engl J Med 2008;358:2545–59

Hypothetical representation of the natural history of diabetic patients in the VADT study



Modified from Del Prato S. Diabetologia 2009;52:1219–26

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvasc	CVD	Mortality
UKPDS	↓ ↓	↔ ↓	↔ ↓
DCCT / EDIC*	↓ ↓	↔ ↓	↔ ↔
ACCORD	↓	↔	↑
ADVANCE	↓	↔	↔
VADT	↓	↔	↔

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Initial Trial
Long Term Follow-up
* in T1DM

Several unmet medical needs remain

Treatment goals

- Glycemic control
- Prevention of diabetes complications

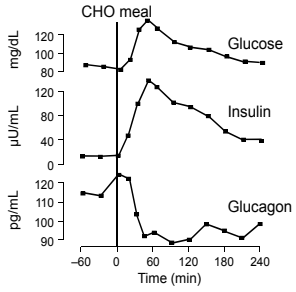
Balancing efficacy and side effects when managing type 2 diabetes

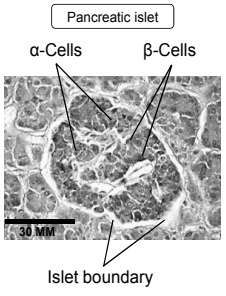
Treatment complications and challenges

- Hypoglycemia
- Weight gain
- GI side effects
- Cardiovascular risks
- Injections

Adapted from Hollander PA et al. Postgrad Med 2010;122(3):71–80

Reciprocal Response of Insulin and Glucagon in Postprandial Period in Persons Without Diabetes



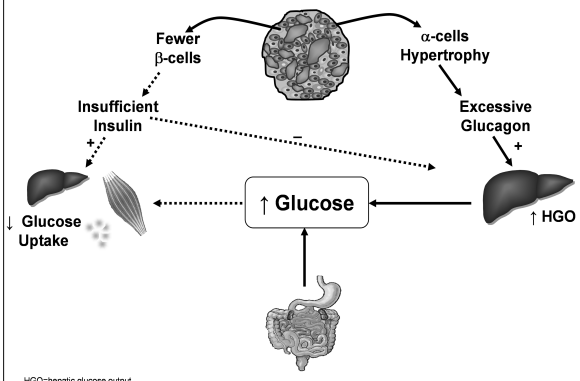


CHO = carbohydrate

Unger RH. *N Engl J Med*. 1971;285:443-449.

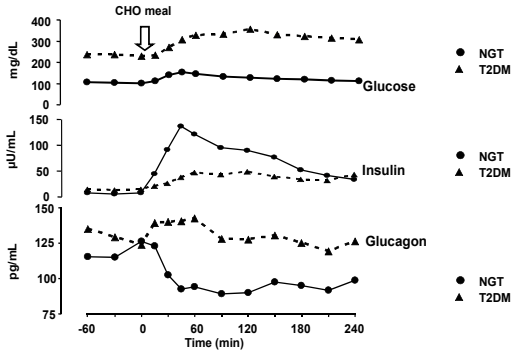
Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science.

Pancreatic Islet Dysfunction Leads to Hyperglycemia in T2DM



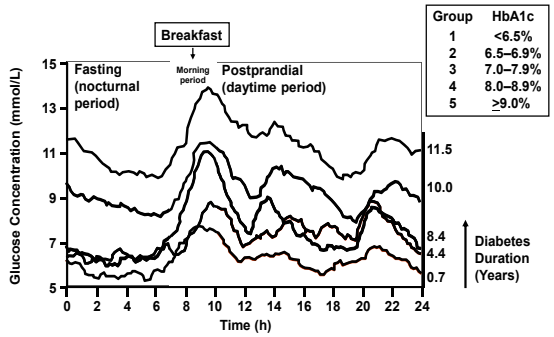
HGO=hepatic glucose output.
Adapted from Ohneda A, et al. *J Clin Endocrinol Metab*. 1978; 46: 504–510; Gomis R, et al. *Diabetes Res Clin Pract*. 1989; 6: 191–198.

Insufficient Insulin and Elevated Glucagon in T2DM (↓ Insulin / Glucagon Ratio)



CHO=carbohydrate; NGT=normal glucose tolerance; T2DM=type 2 diabetes mellitus.
Adapted from Müller WA, et al. *N Engl J Med*. 1970; 283: 109–115.

Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting with Worsening Diabetes



HbA1c=hemoglobin A1c; T2DM=type 2 diabetes mellitus.
Monnier L, et al. *Diabetes Care*. 2007; 30: 263–269.

GLP-1 & DPP-4 inhibitor

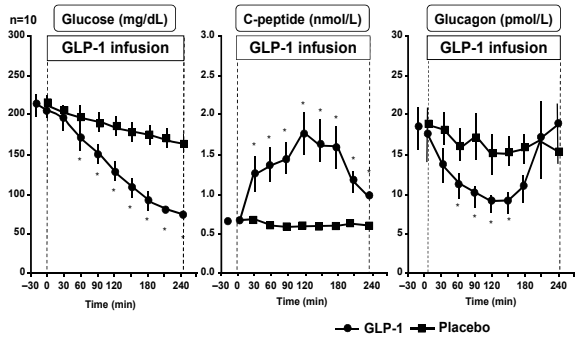
Normal GLP-1 physiology

At the beginning of each meal:

- There is a surge in GLP-1 secretion
- That improves the sensitivity of the α- and β-cells of the pancreas to glucose
- Which increases insulin secretion and decreases glucagon secretion
- Resulting in reduced PPG levels
- GLP-1 is then rapidly inactivated by DPP-4 (half-life <5 min)

PPG=postprandial blood glucose
Ahrén B, et al. Diabetes Care 2003;26:2860–4
Nauck MA, et al. Diabetologia 1993;36:741–4

GLP-1 restores insulin and glucagon responses in a glucose-sensitive manner in patients with T2DM



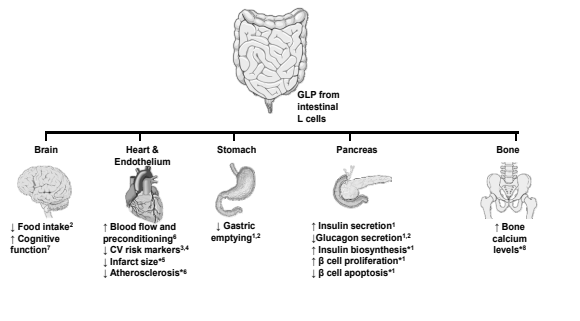
*P<0.05
Nauck MA, et al. Diabetologia 1993;36:741–4

GLP-1 Demonstrates Multiple Metabolic Effects in Patients with T2DM

- GLP-1 decreases PPG and FPG by:
  - improving α- and β-cell sensitivity to glucose
  - delaying gastric emptying
  - reducing appetite and food intake

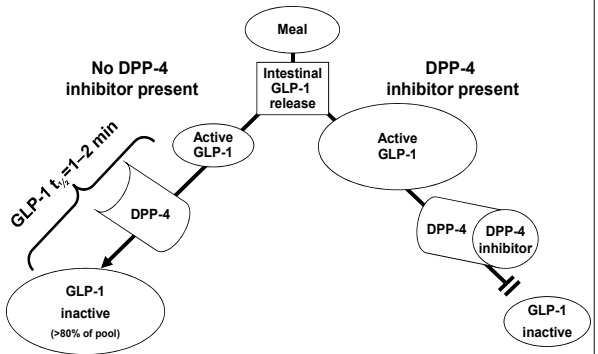
FPG=fasting plasma glucose; GLP-1=glucagon-like peptide-1; PPG=postprandial glucose; T2DM=type 2 diabetes mellitus.
Zander M, et al. *Lancet*. 2002; 359: 824–830; Nauck MA, et al. *Diabetologia*. 1993; 36: 741–744.

Potential pathophysiological targets of GLP-based therapies



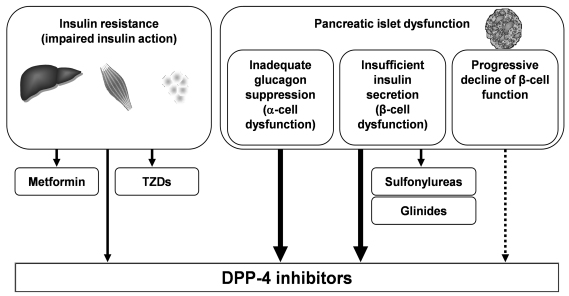
ED=endothelial dysfunction. *Pre-clinical data
1. Solomon. N Engl J Med 2003;348:457-459; 2. Kelly et al. Ann Intern Med 2009;151:394-403; 3. Ray et al. Lancet 2009;373:1765-1772; 4. Sowers et al. Hypertension 2001;37:1053-1059; 5. Stratton et al. BMJ 2000;321:405-412; 6. UKPDS Group Lancet 1998;352:837-853; 7. Wild et al. Diabetes Care 2004;27:1047-1053; 8. Holman et al. N Engl J Med 2008;359:1577-1589;

Inhibition of DPP-4 increases active GLP-1



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.
Adapted from Rothenberg P, et al. *Diabetes*. 2000; 49 (Suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. *Diabetes*. 1995; 44: 1126–1131.

DPP-4 inhibitors influence both insulin resistance and pancreatic islet dysfunction



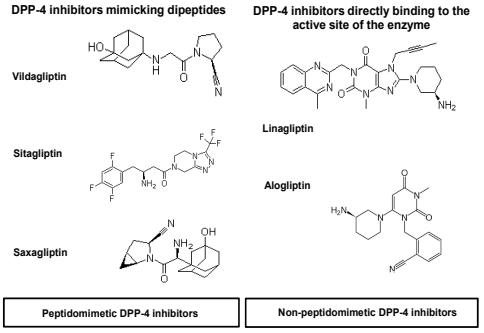
Weight of red arrows reflects the degree to which DPP-4 inhibitors influence the disease mechanisms.
DPP-4=dipeptidyl peptidase-4; TZD=thiazolidinedione.
Adapted from DeFronzo RA. *Br J Diabetes Vasc Dis.* 2003; 3(suppl 1): S24–S40.

Current DPP-4 Inhibitors in Korea

- Sitagliptin: Launch in Dec 2008, marketed by MSD and Daewoong
- Vildagliptin: Launch in Feb 2009, marketed by Novartis and Handok
- Saxagliptin: Launch in Nov 2011, marketed by AZ and BMS
- Linagliptin: Launch in Jun 2012, marketed by BI, Lilly & Yuhan
- Gemigliptin: Launch in Dec 2012, marketed by LG and Sanofi
- Alogliptin: Will be launched in 2014, promoted by Taketa & Jeil

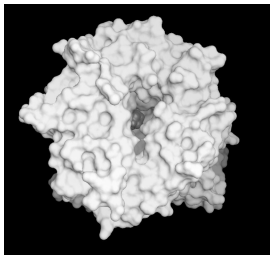
Similarities and differences of DPP-4 inhibitors: chemistry

- Despite the common mechanism of action, DPP-4 inhibitors show marked structural heterogeneity

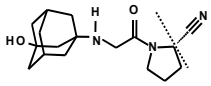


Adapted from Deacon CF. *Diabetes Obes Metab.* 2011;13:7–18.

Vildagliptin



X-ray crystallographic structure of vildagliptin (green) bound to the active site (yellow) of human DPP-4



- Highly selective DPP-4 substrate that effectively blocks other substrates from using the enzyme
- Has a high affinity for the human enzyme

"Gli": WHO suffix for antidiabetic agents
"DA, P": Dipeptidyl Amino Peptidase
"Tin": Enzyme inhibitor
"Vil": contribution from inventor Edwin Vilhauer

Vildagliptin

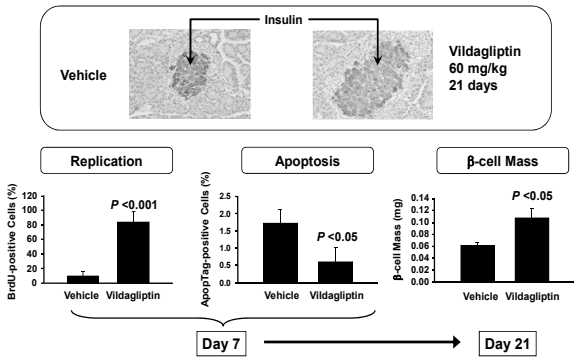
DPP-4=dipeptidyl peptidase-4

Vildagliptin

- Extends the meal-induced increase in GLP-1 levels into the inter-meal and overnight periods by blocking GLP-1 inactivation by DPP-4, leading to increased glucose-sensitive insulin secretion and decreased glucagon levels during meals resulting in:
  - Reduced PPG
  - Reduced FPG (secondary to reduced PPG)
- Increased glucose-sensitive insulin secretion and decreased glucagon levels during the overnight period results in:
  - Reduced FPG (secondary to reduced overnight HGP)

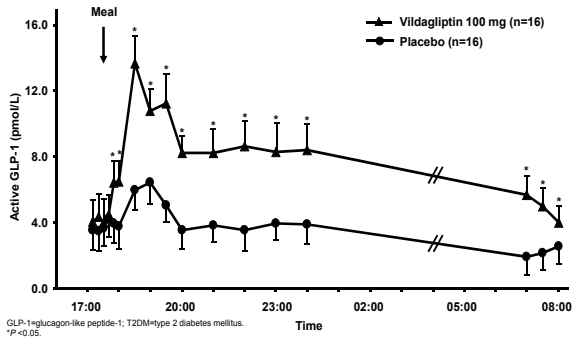
DDP-4=dipeptidyl peptidase-4; FPG=fasting plasma glucose; HGP=hepatic glucose production; PPG=post-prandial glucose
Ahrén B, et al. Diabetes Obes Metab 2011;13:775–83

Effect of Vildagliptin on β-cell Mass in a Neonatal Rat Pancreatic Growth Model



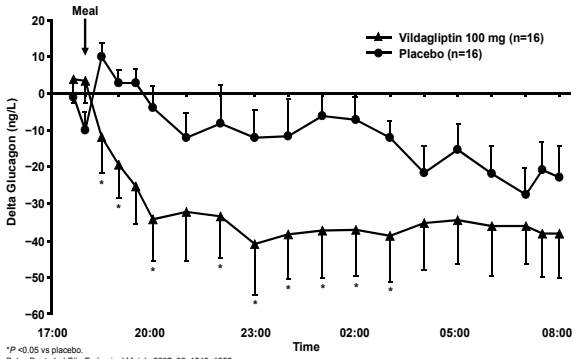
Duttaroy A, et al. *Diabetes.* 2005; 54 (Suppl 1): A141. Abstract 572-P and poster presented at ADA.

Acute Effects of Vildagliptin on GLP-1 Levels in Patients with T2DM



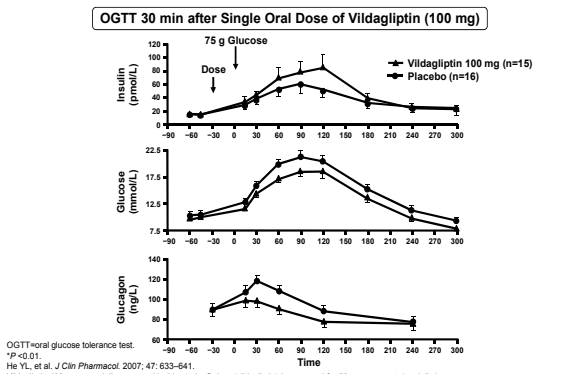
GLP-1=glucagon-like peptide-1; T2DM=type 2 diabetes mellitus.
*P <0.05.
Balas B, et al. *J Clin Endocrinol Metab.* 2007; 92: 1249–1255.
Vildagliptin 100 mg once daily was used in this study. Galvus (vildagliptin) is approved for 50 mg once or twice daily in combination with metformin or a TZD, and Galvus (vildagliptin) 50 mg once daily in combination with a sulfonylurea.

Acute Effects of Vildagliptin on Glucagon Levels in Patients with T2DM



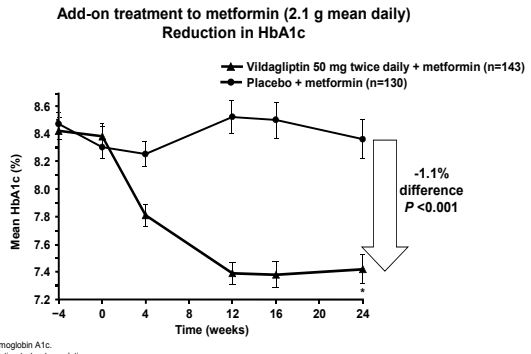
*P <0.05 vs placebo.
Balas B, et al. *J Clin Endocrinol Metab.* 2007; 92: 1249–1255.
Vildagliptin 100 mg once daily was used in this study. Galvus (vildagliptin) is approved for 50 mg once or twice daily in combination with metformin or a TZD, and Galvus (vildagliptin) 50 mg once daily in combination with a sulfonylurea.

Acute Effects of Vildagliptin on Insulin, Glucose and Glucagon Levels in Patients with T2DM



OGTT=oral glucose tolerance test.
*P <0.01.
He YL, et al. *J Clin Pharmacol.* 2007; 47: 633–641.
Vildagliptin 100 mg once daily was used in this study. Galvus (vildagliptin) is approved for 50 mg once or twice daily in combination with metformin or a TZD, and Galvus (vildagliptin) 50 mg once daily in combination with a sulfonylurea.

Vildagliptin plus metformin: powerful 1.1% reduction in HbA1c at 24 weeks



HbA1c=haemoglobin A1c.
Primary intention-to-treat population.
Only data using the marketed regimen of vildagliptin are shown.
Bosi E, et al. *Diabetes Care.* 2007; 30: 890–895.

Advantages with incretin therapy

Improves glycemic control

- Monotherapy
- Combination with metformin, SU, TZD or insulin

Well tolerated therapy

- Low risk for hypoglycemia
- Weight reduction (DPP-4 inhibitors weight neutral)
- Low risk for adverse events
- No deterioration o kidney function

Can be used early since it targets the pathophysiology of type 2 diabetes

Specially for

- Elderly patients, patients with renal impairment, overweight patients, when aiming at avoiding hypoglycemia

User friendly

- Simple dosing without dose titration
- No glucose monitoring
- Minimal fear for hypoglycemia

Ahrén B J Eur Diabetes Nursing 10:31, 2013