Clinical focus on glucagon:

α-cell as a companion of β-cell

Therapeutic strategy to reduce Glucagon secretion

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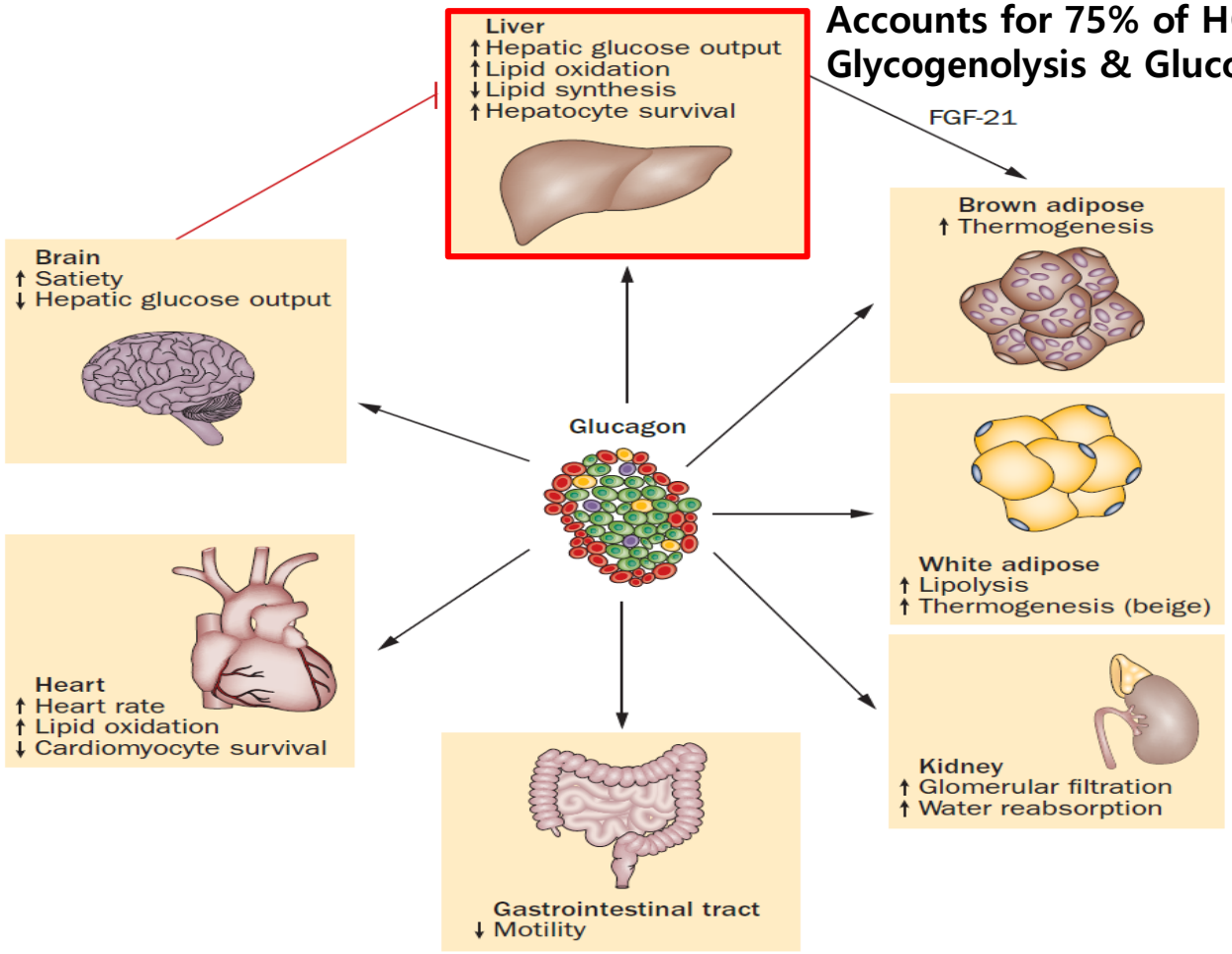
Conflict of interest disclosure

None

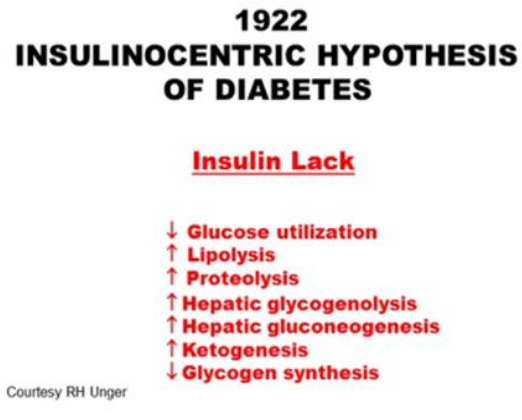
Committee of Scientific Affairs

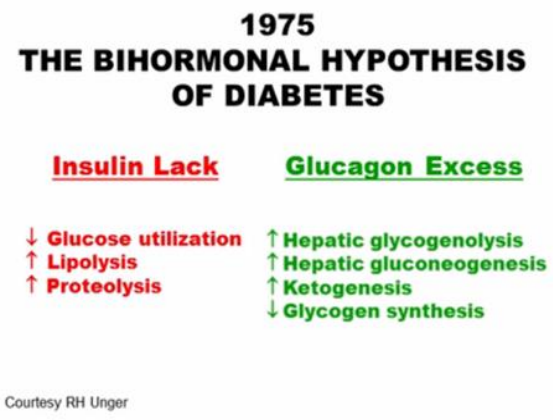
Glucagon Action

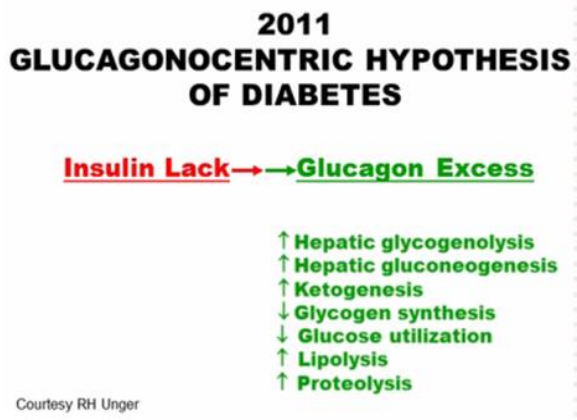


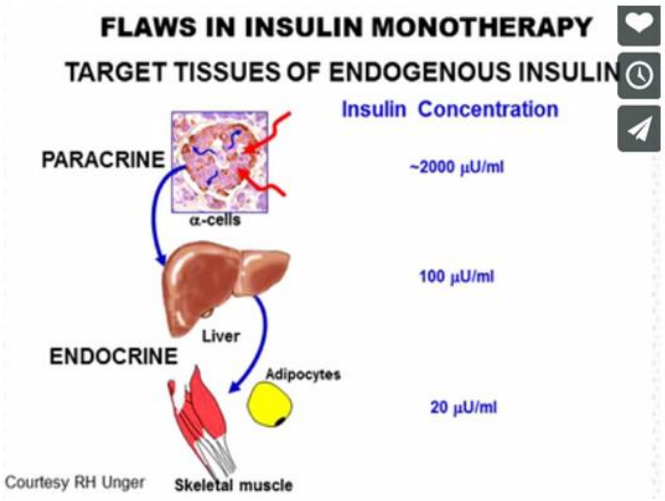
Nat Rev Endocrinol 2015;11:329–338.

2013 IDF Plenary lecture: Pierre Lefèbvre, Belgium



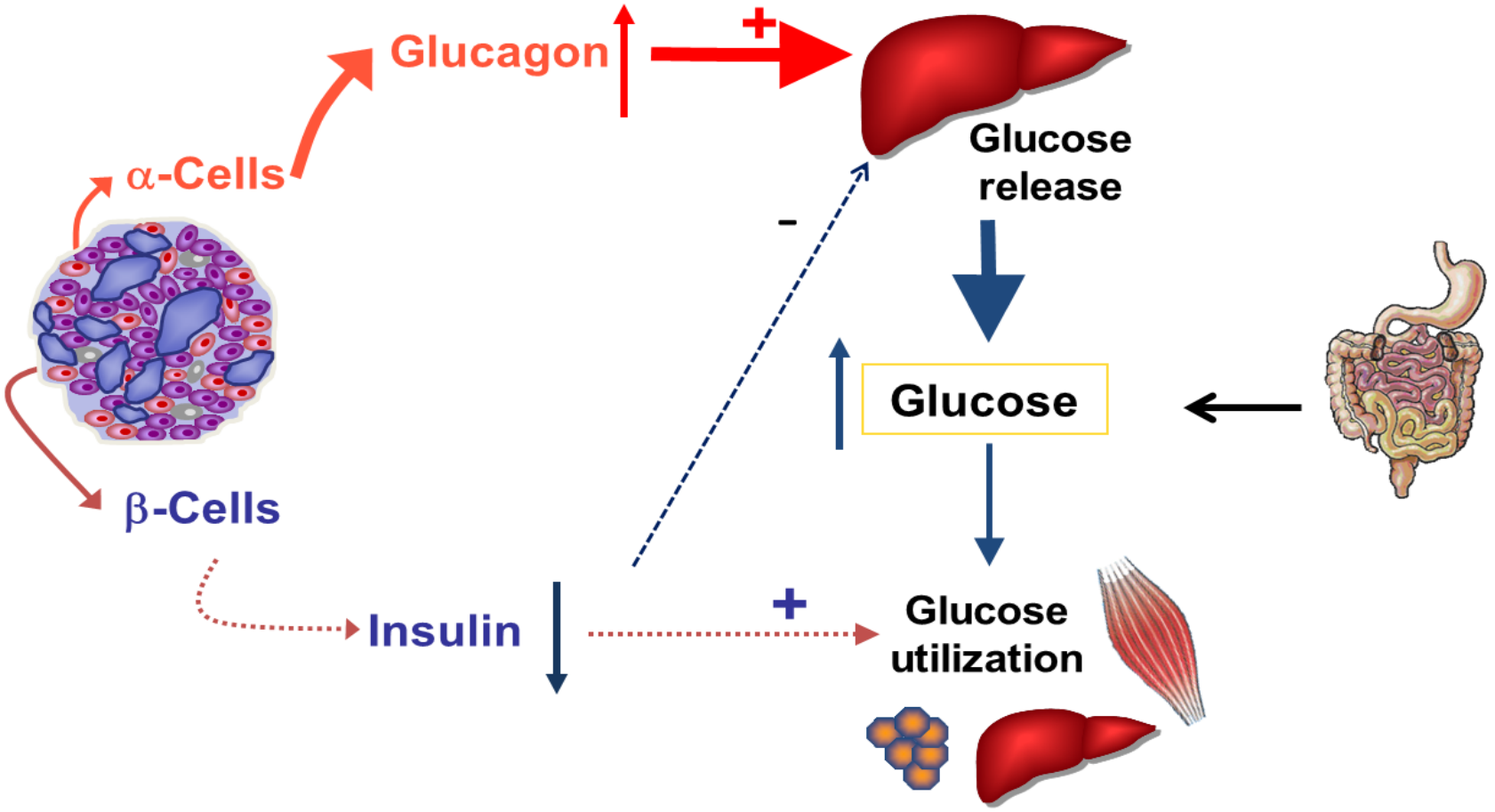






http://conference2.idf.org/MEL2013/IDF2013/0290/default.aspx

Pathophysiology of T2DM



Diabetes 2009;58:726.

Glucagon Metabolism and Pathophysiology in Diabetes

- Glucagon plays an essential role in glycemic control.

- **Excessive glucagon secretion** contributes to Hyperglycemia in T2DM.

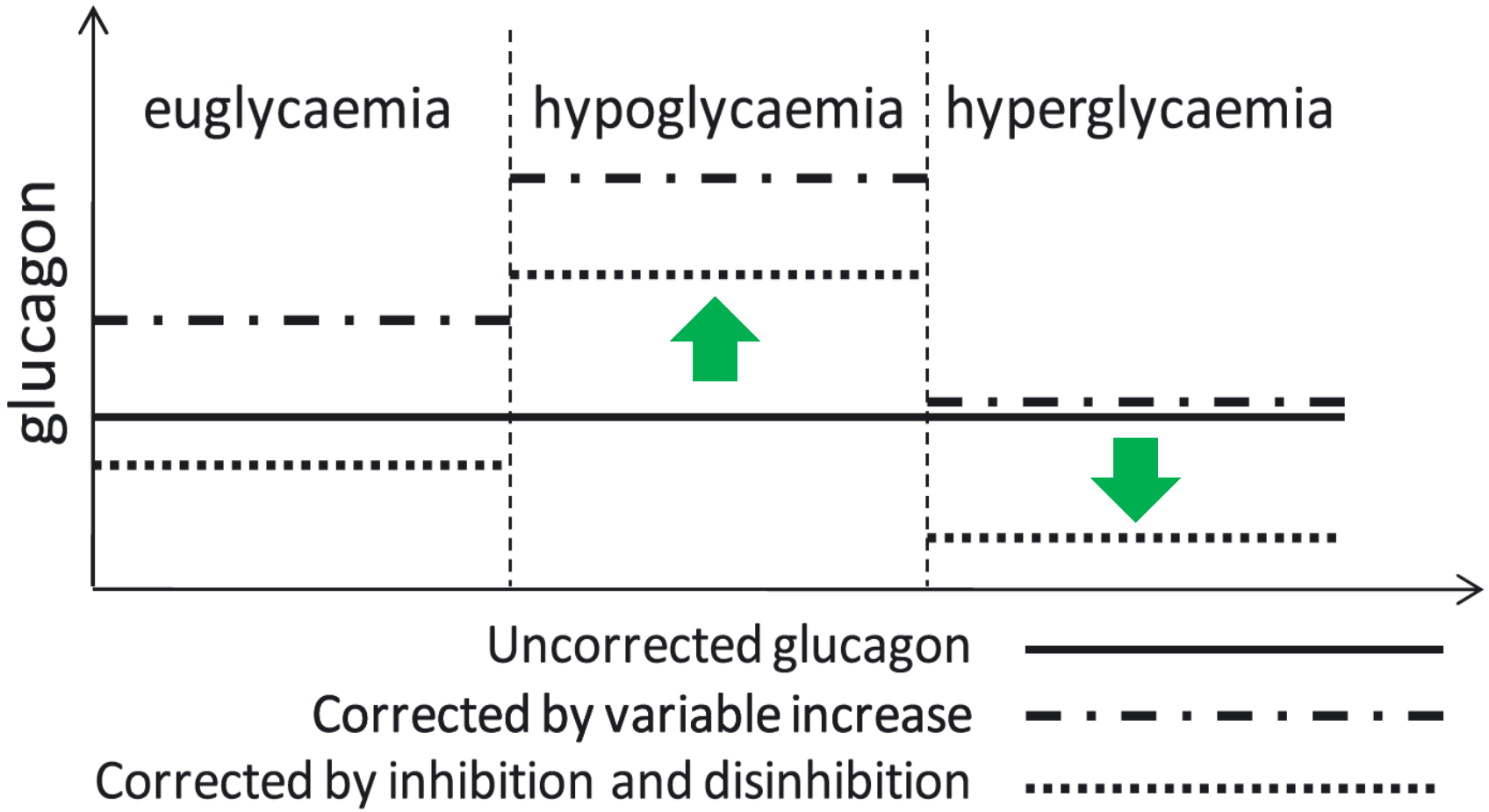
- Lowering glucagon levels will be a valuable therapeutic target in the treatment of T2DM.

Therapeutic strategy to reduce Glucagon secretion

Reduction of Glucagon for the Treatment of Diabetes

Anti-diabetes treatments
with Glucagon effects

Repair of Glucagon dynamics



Diabetes, Obesity and Metabolism 2011;13(Suppl. 1):133–143.

Regulation of alpha cells

Stimulatory Factors (↑ Glucagon)	Inhibitory Factors (↓ Glucagon)
• Hypoglycaemia	• Glucose
• Protein meal	• Carbohydrate meal
• Amino acids	• Ketones
• Stress; adrenaline (epinephrine)	• Insulin
• Sympathetic/parasympathetic nerves	• Somatostatin
• GIP	• GLP-1

Diabetoloia 2005;48:1700-1713.

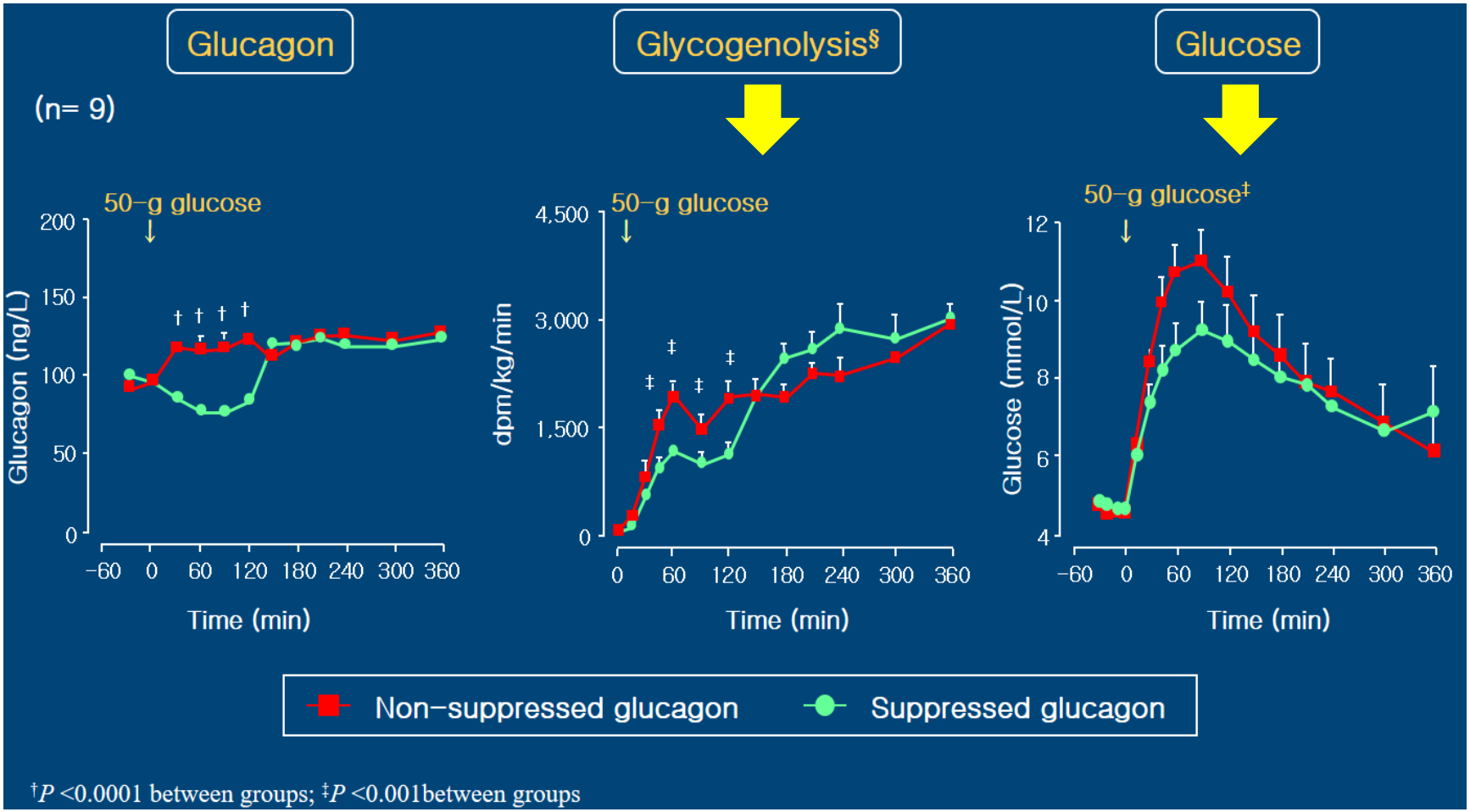
Reduction of Gcgr Signaling

The increased glucagon/insulin ratio is a key factor in the pathogenesis of hyperglycemia in T2DM;

1. Inappropriate levels of glucagon in the fasting state leads to increased HGP & fasting hyperglycemia.
2. The lack of glucagon suppression in the post-prandial state leads to post-prandial hyperglycemia

Consequently, addressing glucagon seemed an attractive treatment for T2DM by either suppression of Glucagon secretion or by blocking Gcgr.

Suppression of Glucagon



J Clin Endocrinol Metab. 2000;85:4053–4059.

Glucagon antagonists (2011)

Company	Compound	Status	Mode of action	Reference
Merck	MK0893	Phase II	Not disclosed	NCT00479466 NCT00631488 NCT00902161
	Imidazol	Preclinical	Glucagon antagonist	Chang et al. [74]
	Compound 1	Preclinical	Glucagon antagonist	Qureshi et al. [67]
	Spiro-urea	Preclinical	Glucagon antagonist	Shen et al. [68]
	Benzimidazol	Preclinical	Glucagon antagonist	Kim et al. [71]
	Compound 15	Preclinical	Glucagon antagonist	Jiang et al. [75]
	GRA1	Preclinical	Glucagon antagonist	Mu et al. [76]
Eli Lilly	LY2409021	Phase II	Not disclosed	NCT00871572
	GR-ASO	Preclinical	Glucagon receptor antisense oligonucleotide	Sloop et al. [58]
Boehringer Ingelheim	BI-32169	Preclinical	Glucagon antagonist	Potterat et al. and Knappe et al. [77,78]
Amgen	mAb	Preclinical	Glucagon antagonist	Yan et al. and Gu et al. [73,79]
Dainippon Sumitomo Pharma	DSR-17759	Preclinical	Glucagon antagonist	Hirata et al. [80]
Novo Nordisk	NNC25-2504	Preclinical	Glucagon antagonist	Madsen et al. [66]
	NNC25-0926	Preclinical	Glucagon antagonist	Rivera et al. [81]
	Aminothiazole	Preclinical	Glucagon antagonist	Madsen et al. [82]
Pfizer	Skyrin	Preclinical	Glucagon antagonist	Parker et al. [63]

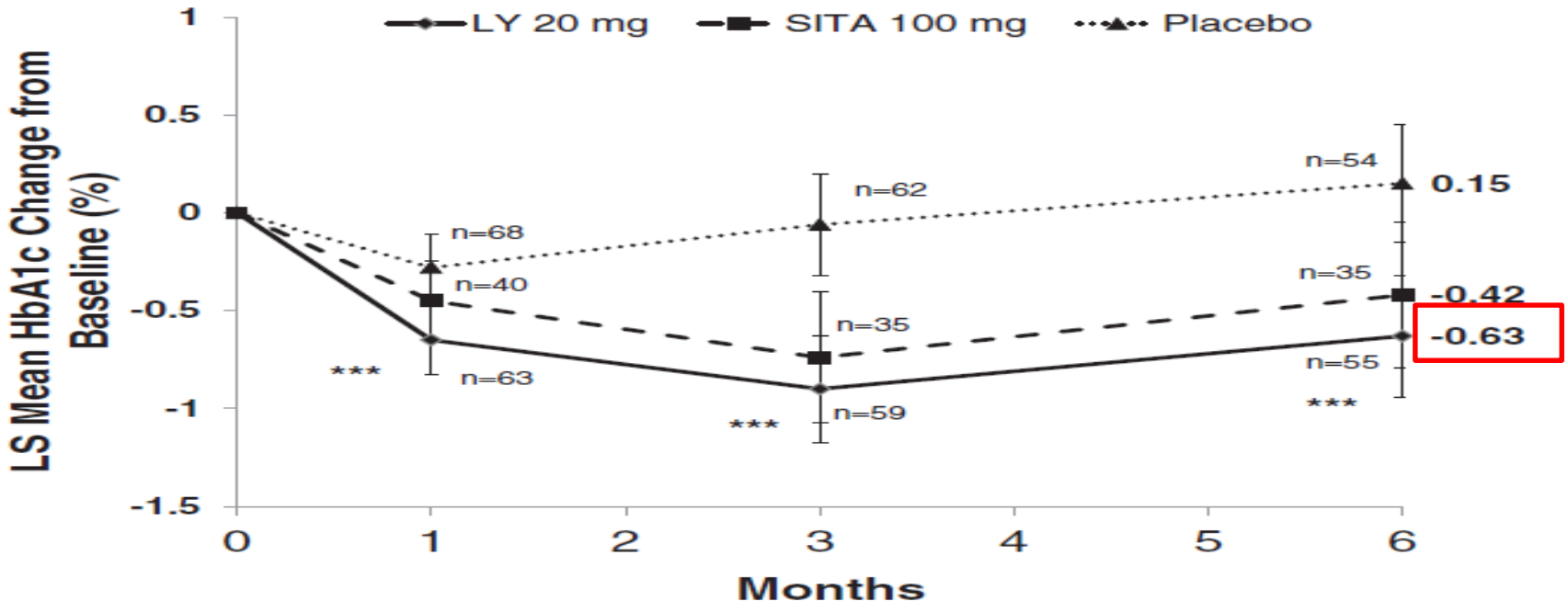
Diabetes, Obesity and Metabolism 2011;13: 965–971.

Glucagon antagonists (2015)

Drug	Mechanism of action	Study duration	Current phase	Reference
Type 1 diabetes mellitus				
LY2409021	Selective GCGR antagonist	Single dose	Phase I	NCT01640834[104]
Type 2 diabetes mellitus				
MK-0893	Selective GCGR antagonist	4–13 weeks	Phase II	NCT00631488[105]
LY2409021	Selective GCGR antagonist	6–12 months	Phase II	NCT02111096[106]
PF-06291,874	Selective GCGR antagonist	28 days	Phase II	NCT02175121[107]
Ranolazine	Inhibition of α cell Na^+ channels	14 days	Phase I	NCT01843127[108]
LGD-6,972	Selective GCGR antagonist	28 days	Phase I	NCT02250222[109]
ISIS-GCGRRx	GCGR antisense siRNA	13 weeks	Phase II	NCT01885260[110]

Nat Rev Endocrinol 2015;11:329–338.

LY2409021 in T2DM: efficacy

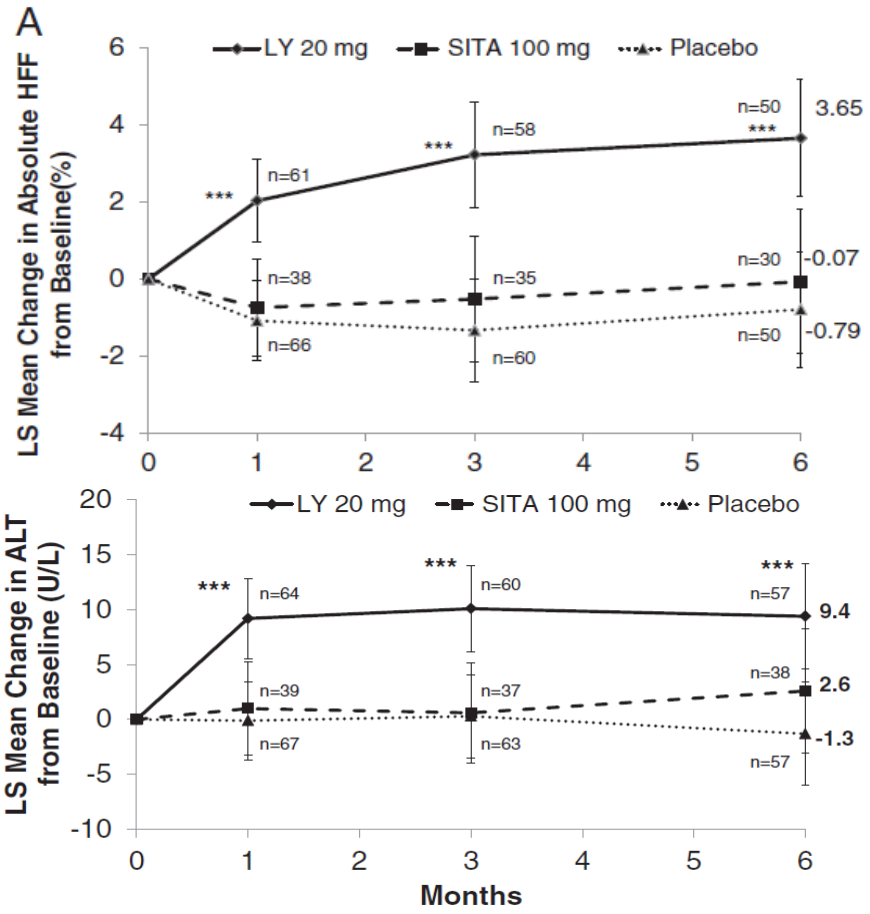


***$P<0.001$ LY vs. placebo; LY vs. sitagliptin: $P=0.048$ at Month 1

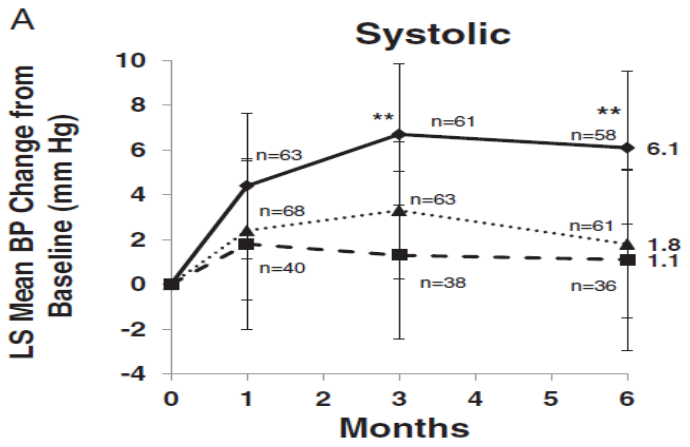
HbA1c, %	LY2409021		Sitagliptin		Placebo	
	n	mean (SD)	n	mean (SD)	n	mean (SD)
Baseline	65	8.12 (0.98)	41	8.25 (0.91)	68	8.26 (0.86)
Month 6	55	7.64 (1.23)	35	7.89 (0.85)	54	8.49 (1.47)
Month 12	16	7.00 (0.64)	7	7.93 (0.48)	11	7.45 (0.85)

Diabetes Obes Metab. 2017 Mar 31. [Epub ahead of print]

LY2409021 in T2DM: adverse events



***P<0.001 LY vs. placebo; P<0.001 LY vs. sitagliptin at Months 1 and 3, P<0.05 LY vs. sitagliptin at Month 6



** P<0.05 LY vs. placebo; p<0.05 LY vs. sitagliptin

Increase in body weight and total cholesterol.

All effects were reversible.

Diabetes Obes Metab. 2017 Mar 31. [Epub ahead of print]

Ranolazine

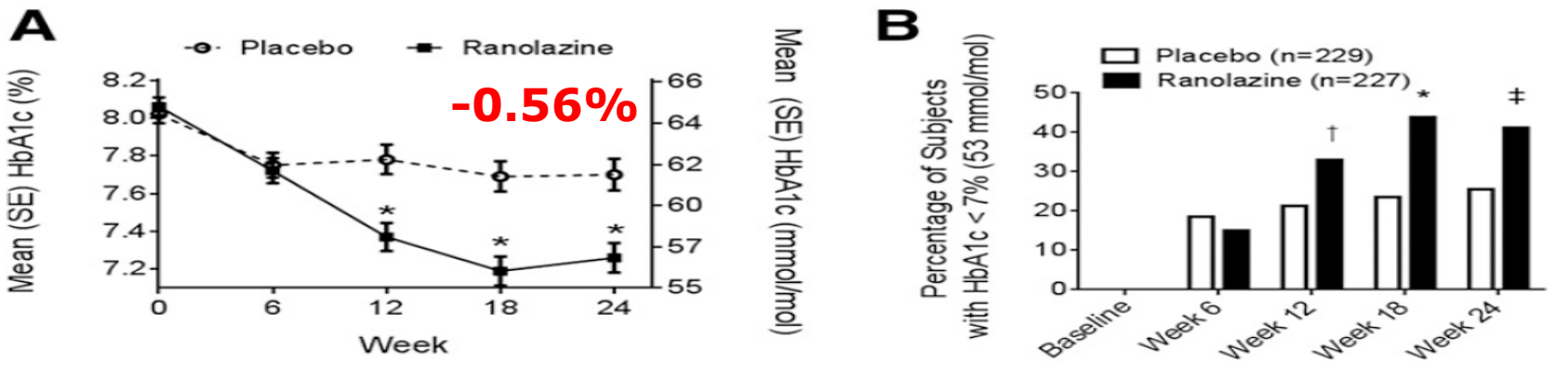
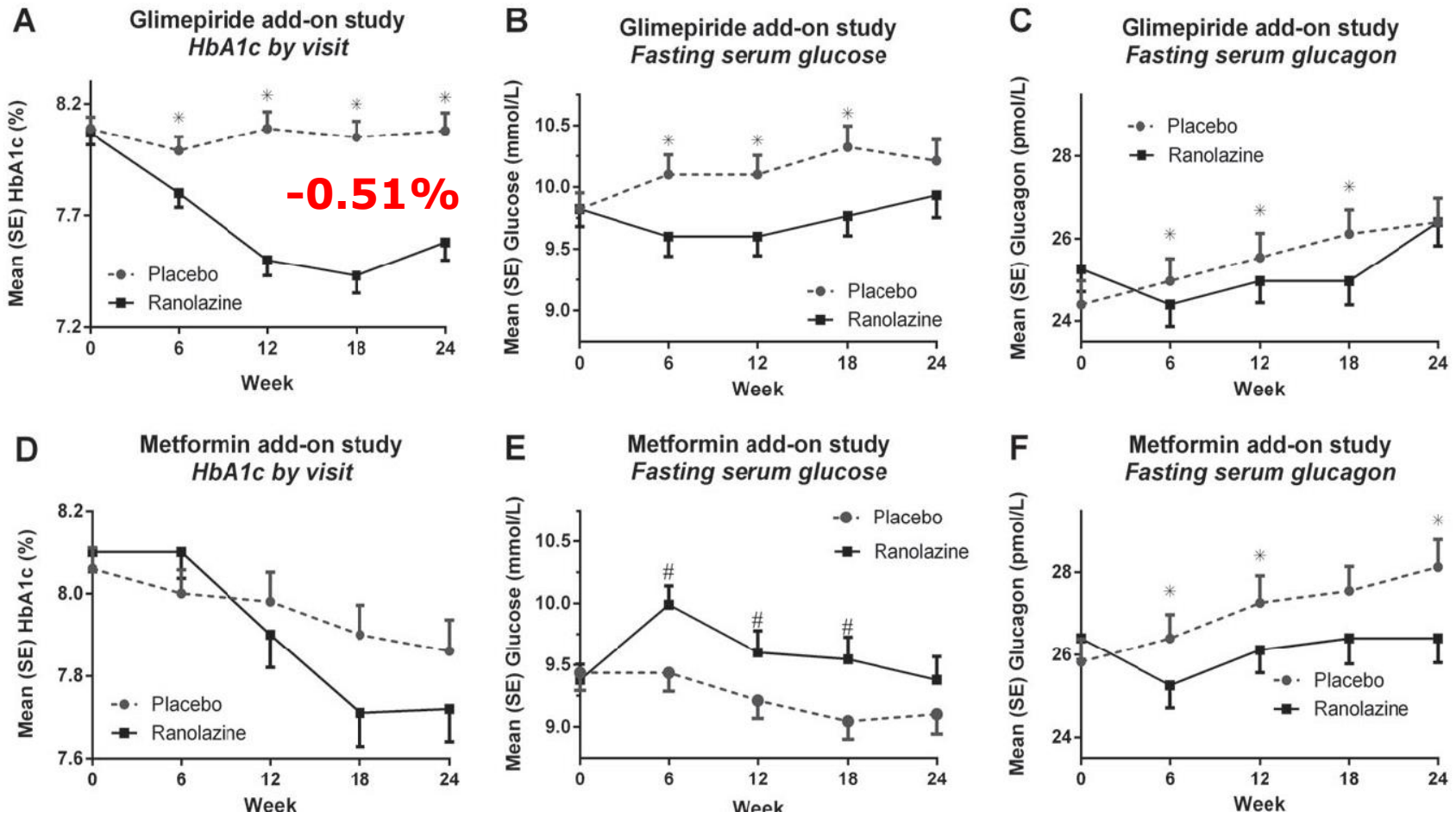


Figure 2—*A*: Effect of ranolazine on HbA_{1c} by visit. *B*: Effect of ranolazine on proportion of subjects achieving HbA_{1c} <7.0%. Placebo, $n = 229$; ranolazine, $n = 227$. *$P = 0.0046$ vs. placebo. †$P < 0.0001$ vs. placebo. ‡$P = 0.0004$ vs. placebo.

Safety data		
Treatment assignment (*n*)	Placebo (*n* = 232)	Ranolazine (*n* = 232)
AEs		
Subjects with any AE, *n* (%)	89 (38.4%)	97 (41.8%)
Hyperglycemia, *n* (%)	23 (9.9%)	19 (8.2%)
Constipation, *n* (%)	10 (4.3%)	12 (5.2%)
Nausea, *n* (%)	2 (0.9%)	9 (3.9%)
Dizziness, *n* (%)	2 (0.9%)	6 (2.6%)
AEs related to study drug		
Subjects with any related AE, *n* (%)	9 (3.9%)	21 (9.1%)
Constipation, *n* (%)	3 (1.3%)	5 (2.2%)
Headache, *n* (%)	2 (0.9%)	6 (2.6%)
Dizziness, *n* (%)	1 (0.4%)	5 (2.2%)
SAEs, *n* (%)	7 (3.0%)	6 (2.6%)
AE leading to premature study drug discontinuation, *n* (%)	8 (3.4%)	12 (5.2%)
Deaths during study, *n* (%)	0	1 (0.4%)

Diabetes Care. 2015 Jul;38(7):1189-96.

Ranolazine on SU or Metf



Diabetes Obes Metab. 2016 May;18(5):463-74.

Ranolazine on SU or Metf

Adverse Events	Glimepiride add-on study		Metformin add-on study	
	Placebo N = 216	Ranolazine N = 215	Placebo N = 222	Ranolazine N = 220
Number of patients with any AE, n (%)	104 (48)	102 (47)	96 (43)	99 (45)
Mild	60 (28)	57 (27)	63 (28)	57 (26)
Moderate	39 (18)	40 (19)	31 (14)	37 (17)
Severe	5 (2.3)	5 (2.3)	2 (0.9)	5 (2.3)
Number of AEs occurring with >2% frequency† n (%)				
Nausea	7 (3.2)	11 (5.1)	9 (4.1)	7 (3.2)
Constipation	1 (0.5)	4 (1.9)	0	7 (3.2)
Dizziness	5 (2.3)	5 (2.3)	4 (1.8)	4 (1.8)
Headache	4 (1.9)	4 (1.9)	5 (2.3)	2 (0.9)
Respiratory tract infection, viral	8 (3.7)	4 (1.9)	2 (0.9)	0
Upper respiratory tract infection	3 (1.4)	2 (0.9)	5 (2.3)	2 (0.9)
Bronchitis	1 (0.5)	5 (2.3)	2 (0.9)	3 (1.4)
Influenza	4 (1.9)	3 (1.4)	7 (3.2)	2 (0.9)
Nasopharyngitis	6 (2.8)	4 (1.9)	5 (2.3)	5 (2.3)
Urinary tract infection	0	1 (0.5)	1 (0.5)	5 (2.3)
Pyrexia	1 (0.5)	0	1 (0.5)	5 (2.3)
Arthralgia	1 (0.5)	0	5 (2.3)	1 (0.5)
Hypertension	1 (0.5)	2 (0.9)	3 (1.4)	5 (2.3)
Number of patients with any MACE/MACE+ AEs, n (%)	3 (1.4)	0	1 (0.5)	0
Myocardial infarction	1 (0.5)	0	1 (0.5)	0
Urgent revascularization procedure	1 (0.5)	0	1 (0.5)	0
Ischaemic stroke	1 (0.5)	0	0	0
Cardiovascular death (pulmonary embolism)	1 (0.5)	0	0	0
Number of glycaemic AEs, n (%)				
Hypoglycaemia‡	10 (4.6)	13 (6)	2 (0.9)	4 (1.8)
Severe hypoglycaemia	0	0	0	0
Hypoglycaemia related to study drug	4 (1.9)	4 (1.9)	0	0
Hyperglycaemia	32 (14.8)	21 (9.8)	14 (6.3)	18 (8.2)
Hyperglycaemia requiring rescue therapy	6 (2.8)	2 (0.9)	5 (2.3)	6 (2.7)
Hyperglycaemia related to study drug	1 (0.5)	1 (0.5)	1 (0.5)	2 (0.9)
Number of AEs leading to study drug discontinuation§ n (%)	12 (5.6)	9 (4.2)	5 (2.3)	8 (3.6)
Number of patients with any AE related to study drug§ n (%)	14 (6.5)	18 (8.4)	10 (4.5)	18 (8.2)
Number of patients with any serious AE† n (%)	4 (1.9)	4 (1.9)	2 (0.9)	3 (1.4)
Related to study drug	0	0	0	1 (0.5)
Deaths, n (%)	1 (0.5)	0	0	0

Diabetes Obes Metab. 2016 May;18(5):463-74.

Glucagon modulating therapies

Table 2
Glucagon Modulating Therapies in Preclinical and Early Phase Development

Agent	Effect on alpha cells	Effect on glucagon levels	Effect on glucagon signaling	Other effects
Antisense oligonucleotide technology targeted against the glucagon receptor	Alpha cell hypertrophy and hyperplasia in preclinical studies	Increase	Reduce expression of the glucagon receptor	Increase in GLP-1 levels in preclinical studies; injection site reactions in clinical studies
Monoclonal antibodies against glucagon or the glucagon receptor	Alpha cell hyperplasia noted in some preclinical studies	Increase	Inhibit binding of glucagon to the glucagon receptor	Increase in GLP-1 levels in preclinical studies
Ranolazine	Found to block voltage-gated sodium channels in rat alpha cells to decrease glucagon secretion	Decrease	N/A	Increased rate of nausea and dizziness compared with placebo
Small-molecule glucagon receptor antagonists	Alpha cell hyperplasia noted in some preclinical studies	Increase	Bind the glucagon receptor and inhibit glucagon signaling	Increased LDL cholesterol, liver transaminases, body weight, blood pressure in human trials

Abbreviations: GLP-1 = glucagon-like peptide 1; LDL = low-density lipoprotein N/A = not available.

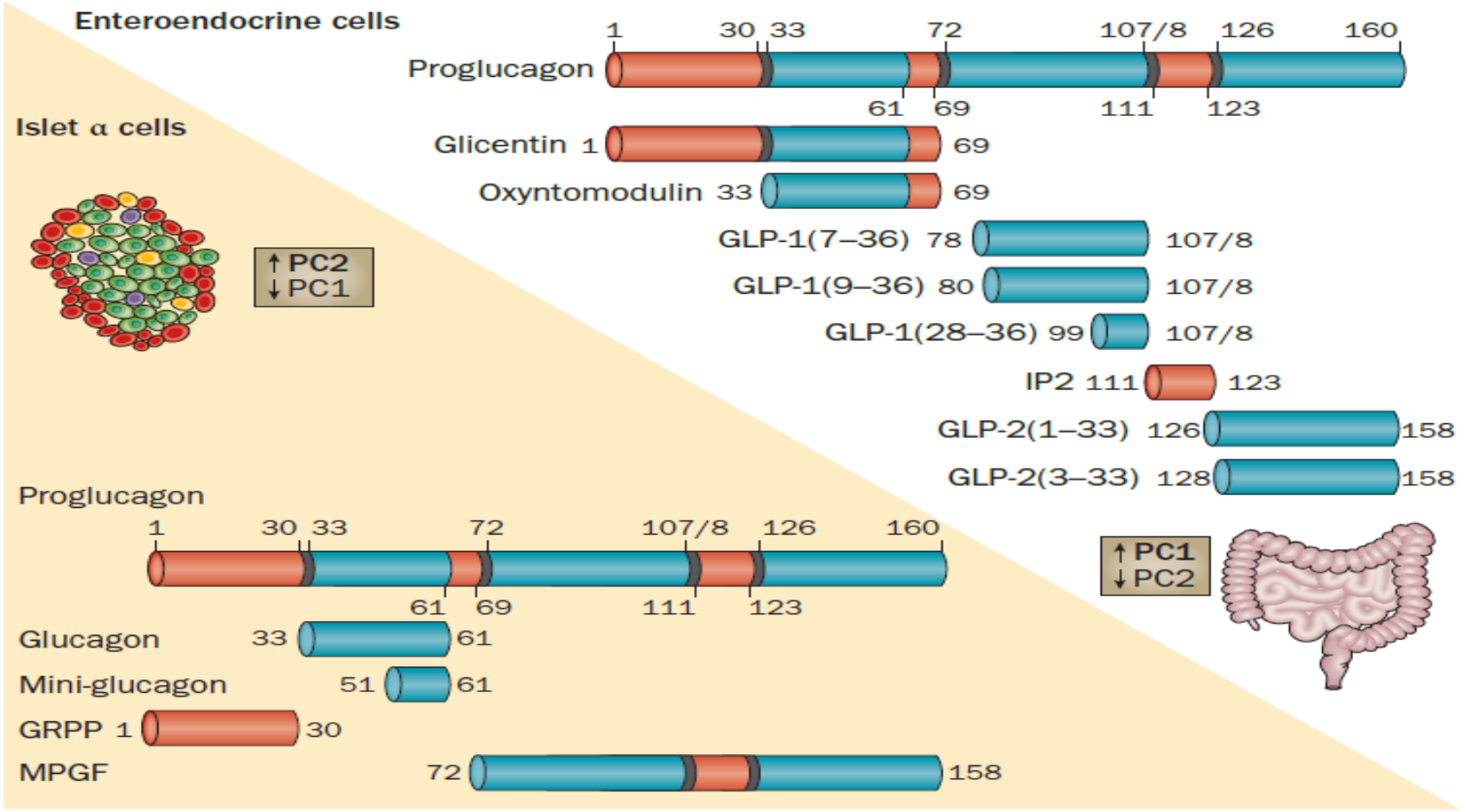
Endocr Pract 2016;22(5):617.

Potential adverse effects

- Germline disruption of Gcgr in mice leads to hyperglucagonaemia, which largely arises from hyperplastic α cells with **dysregulated synthesis and secretion of proglucagon-derived peptides** (including glucagon).
- **An increase in total pancreatic mass** has been observed in rodents with interrupted GCGR signalling.
- Disruption of GCGR signalling in mice resulted in impaired hepatic lipid oxidation, which predisposed these animals to **hepatic steatosis and liver injury**.
- Mechanism-based adverse events, such as **cardiovascular effects**, are mediated by glucagon receptor signalling and should be considered when developing therapeutic strategies directed at enhancing or attenuating glucagon action.

Nat Rev Endocrinol 2015;11:329–338.

Proglucagon-derived peptides



Nat Rev Endocrinol 2015;11:329–338.

Summary (Gcg modulators)

- The inhibition of glucagon receptor signaling represents a possible option for the treatment of diabetes.
- Monoclonal glucagon antibodies, Glucagon receptor antagonists, and molecules targeting the expression of Gcgr have all been tested as potential treatments for T2DM.

- However, research on those agents encountered a number of major obstacles, most notably a **limited efficacy, the risk of iatrogenic hypoglycemia, and other safety issues related to lack of specificity of glucagon blockade, immunogenity and liver toxicity.**
- Further investigation into the safety of these agents is required.

Therapeutic strategy to reduce Glucagon secretion

Reduction of Glucagon for the Treatment of Diabetes

Anti-diabetes treatments with Glucagon effects

Therapy with Glucagon effects

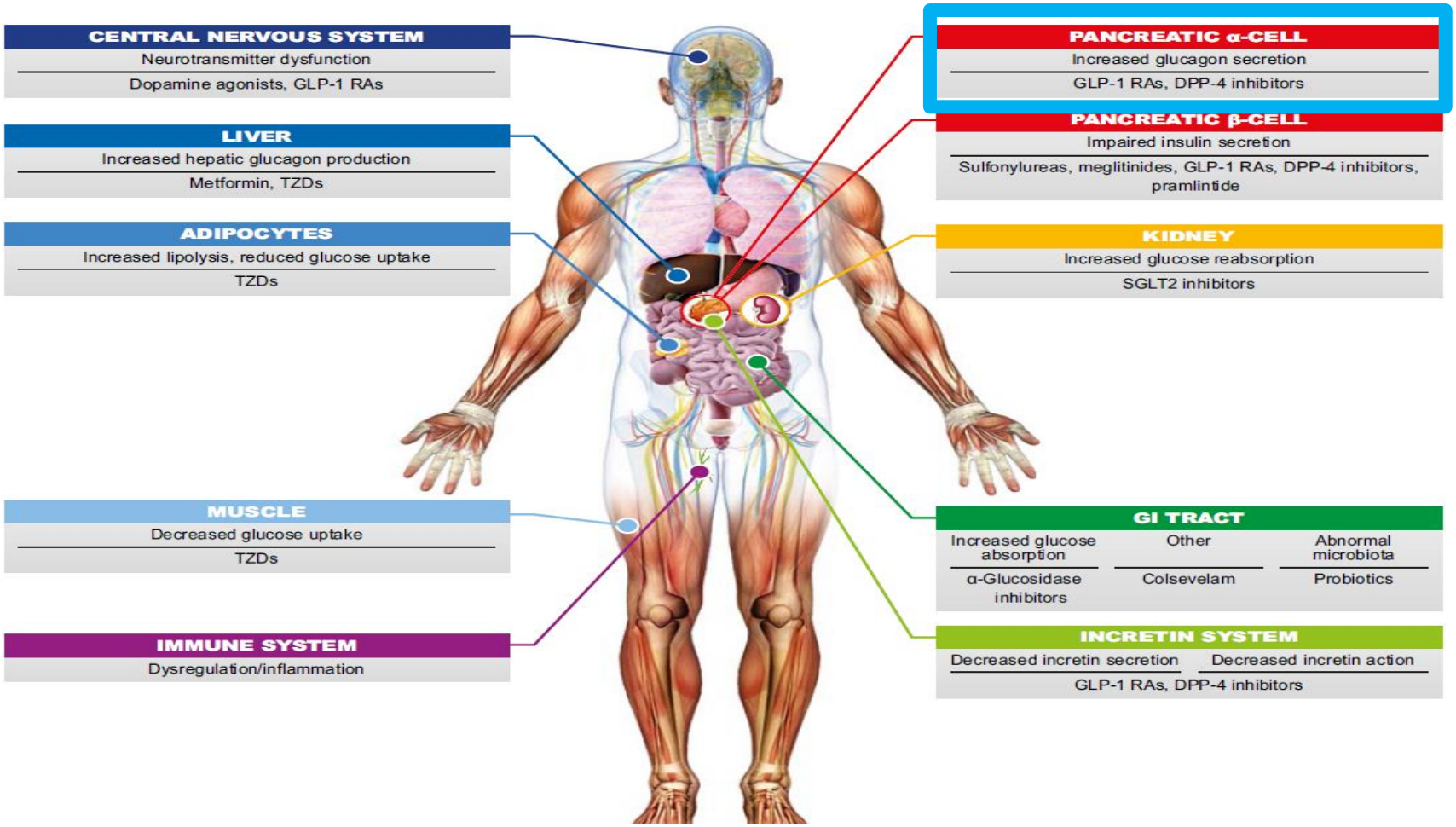
Table 1
Current Diabetes Therapies With Glucagon Effects

Agent	Effect on alpha cells/glucagon
Insulin	Suppresses glucagon secretion from the alpha cells
Metformin	May inhibit glucagon signaling in hepatocytes by increasing levels of AMP and thereby inhibiting the conversion of ATP to cAMP by adenylate cyclase
Sulfonylureas	Unclear, may vary between agents
Pramlintide	Decreases postprandial glucagon secretion from alpha cells
GLP-1 receptor agonists	Decrease glucagon secretion from alpha cells
DPP-4 inhibitors	Decrease glucagon secretion from alpha cells by increasing circulating endogenous GLP-1
SGLT-2 inhibitors	May increase glucagon secretion by inhibiting SGLT-2 Na-glucose cotransporter on alpha cells

Abbreviations: AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter 2.

Endocr Pract 2016;22(5):612-621.

Pathophysiology based Tx



Endocrine Practice 2017. 10.4158/EP161725.RA

GLP-1 RA Treatment

- Short-acting GLP-1 RA (exenatide and lixisenatide)

lower mainly post-prandial glucose, partly by inhibiting gastric empting: conversely **Long-acting molecules** of the class (albiglutide, dulaglutide, exenatide LAR, liraglutide) target predominantly fasting plasma glucose through their **Insulinotropic and Glucagonostatic actions**.

- GLP-1RA: the α-cell do not show GLP-1 receptors

: Insulin synthesis and secretion in a glucose-dependent manner and glucagon levels, this latter effect could be exerted through **somatostatin or neural regulation**.

Cardiovasc Diabetol 2016;15:!23.

Paradoxical increase in postchallenge glucagonemia

Table 2. Comparison of Placebo and Liraglutide Groups With Respect to Baseline-Adjusted Fasting Glucagon and Baseline-Adjusted $iAUC_{glucagon}$ in Response to OGTTs at 12, 24, 36, and 48 Weeks

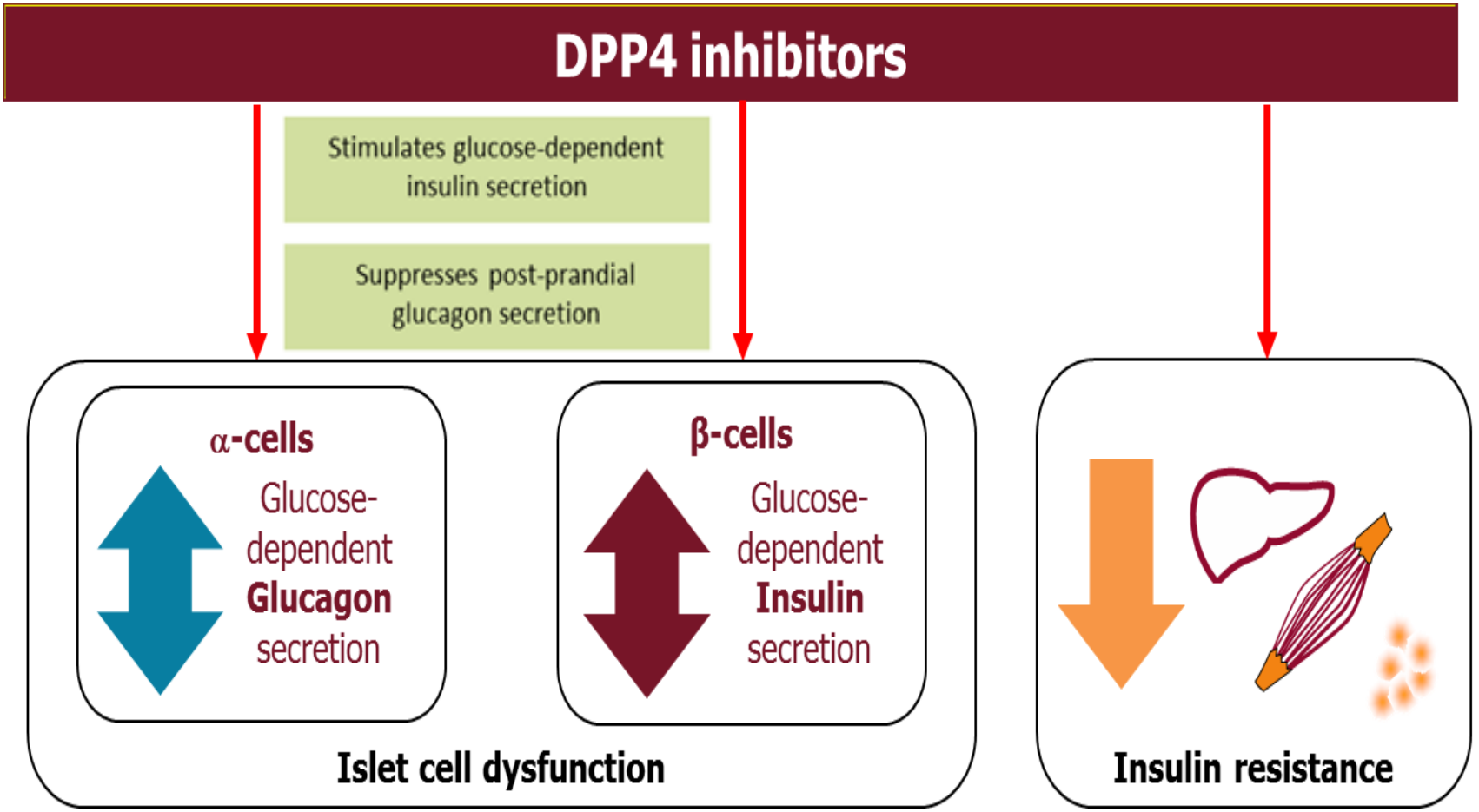
	Placebo	Liraglutide	*P*
Fasting glucagon, pg/mL			
12 wk	97.1 ± 6.5	76.2 ± 6.2	.03
24 wk	88.8 ± 5.9	78.8 ± 5.5	.22
36 wk	85.4 ± 5.4	78.8 ± 4.9	.37
48 wk	111.5 ± 9.9	89.8 ± 9.5	.12
$iAUC_{glucagon}$, pg/mL · 2 h			
12 wk	65.4 ± 36.4	170.2 ± 34.9	.04
24 wk	90.7 ± 29.7	122.9 ± 28.4	.44
36 wk	55.7 ± 30.4	162.2 ± 27.9	.01
48 wk	45.7 ± 27.0	155.5 ± 26.5	.006

Data are means ± SE.

The real effects of GLP-1RA on glucagon probably remains to be further elucidated

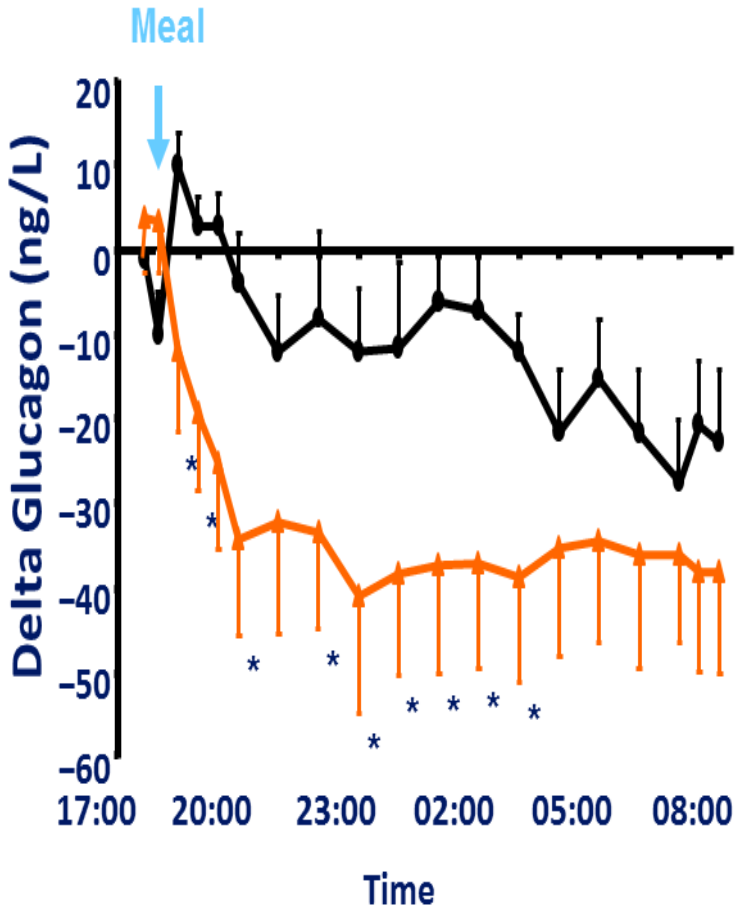
J Clin Endocrinol Metab. 2015;100:3702–9.

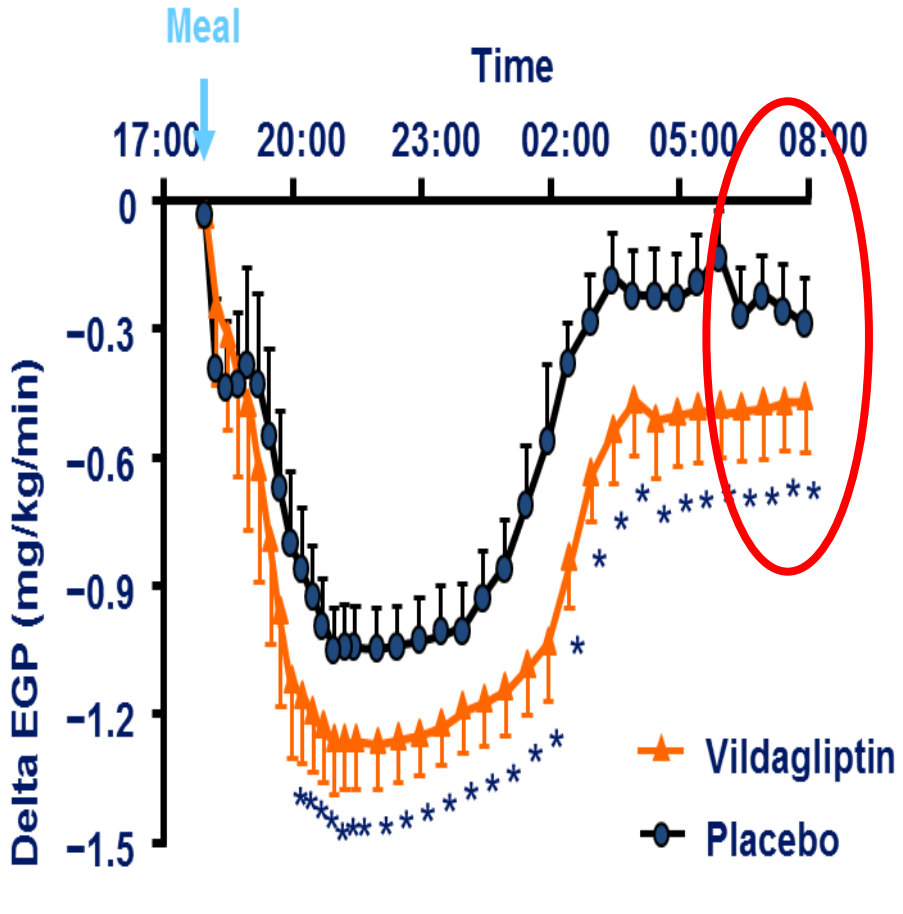
DPP4i addresses Key defects



Diabetes Obes Metab 2011;13:775–830.
Expert Opin Invest Drugs 2003;12:87.
Curr Diab Rep 2003;3:365.

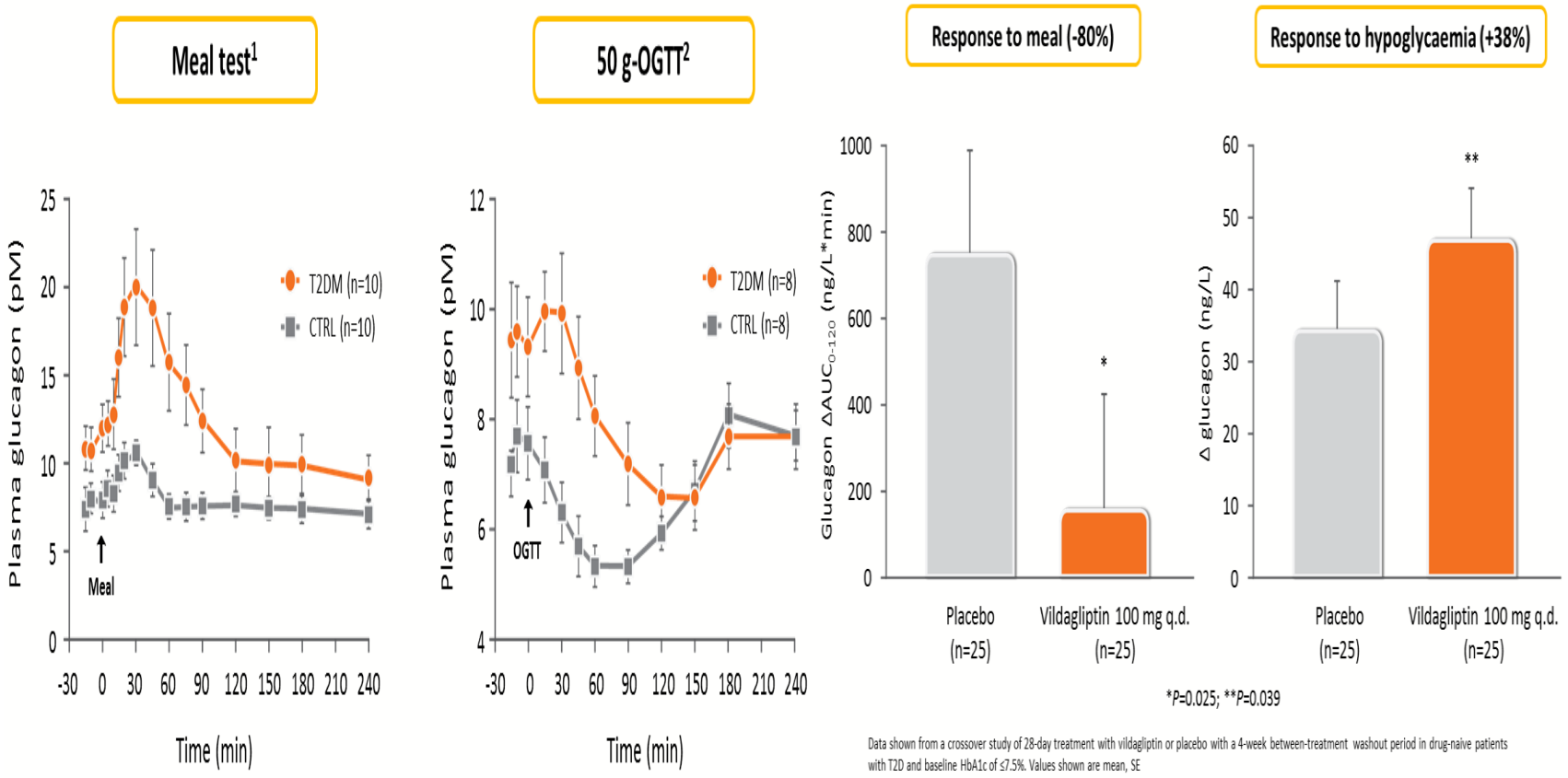
DPP4i reduces Gcg and HGP





. J Clin Endocrinol Metab 2007;92:1249.

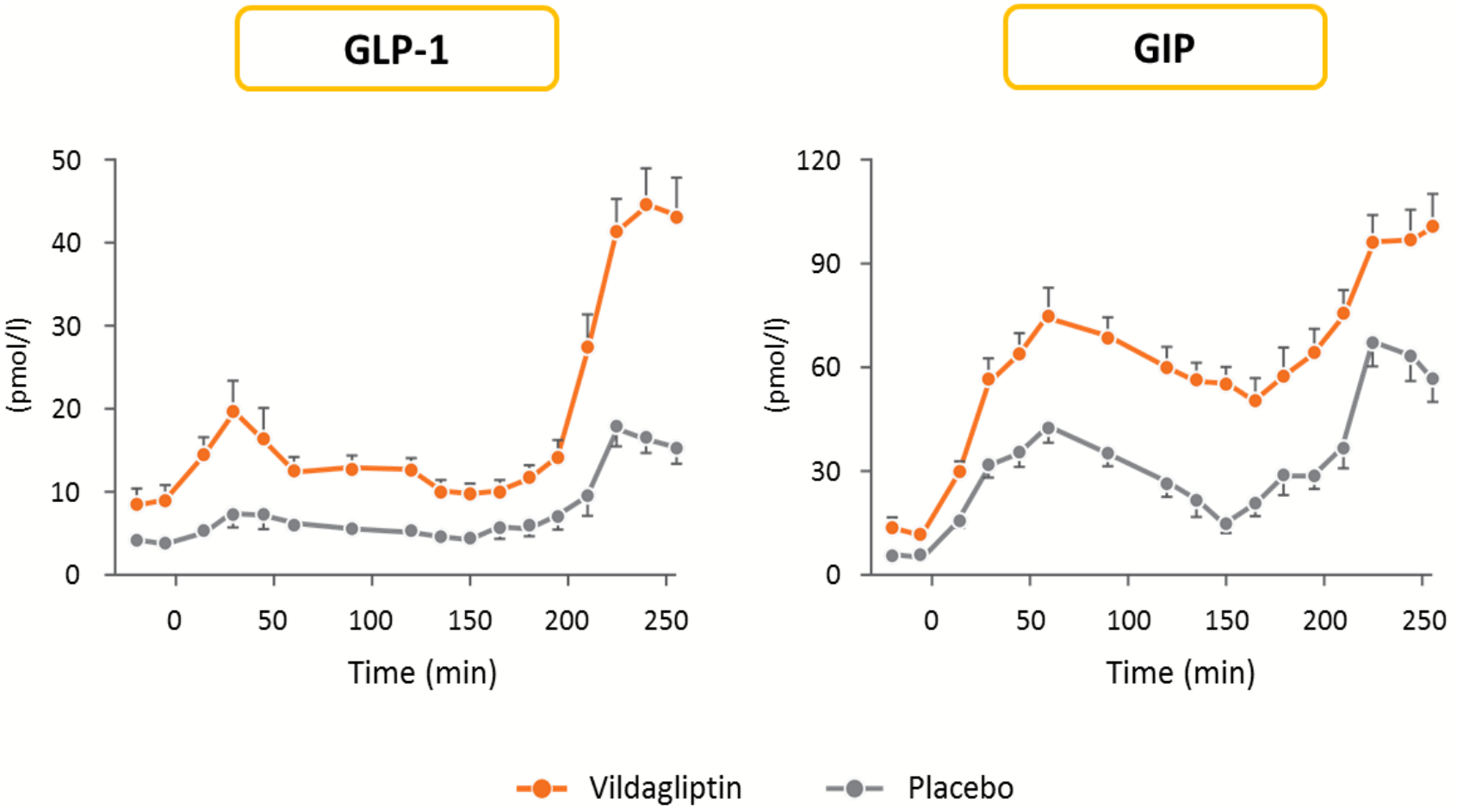
Vildagliptin regulates Glucagon



Data shown from a crossover study of 28-day treatment with vildagliptin or placebo with a 4-week between-treatment washout period in drug-naive patients with T2D and baseline HbA1c of ≤7.5%. Values shown are mean, SE

J Clin Endocrinol Metab 2009;94:1236..

Vildagliptin increases Incretins



Diabetes Obes Metab 2014 Sep;16(9):812-8.

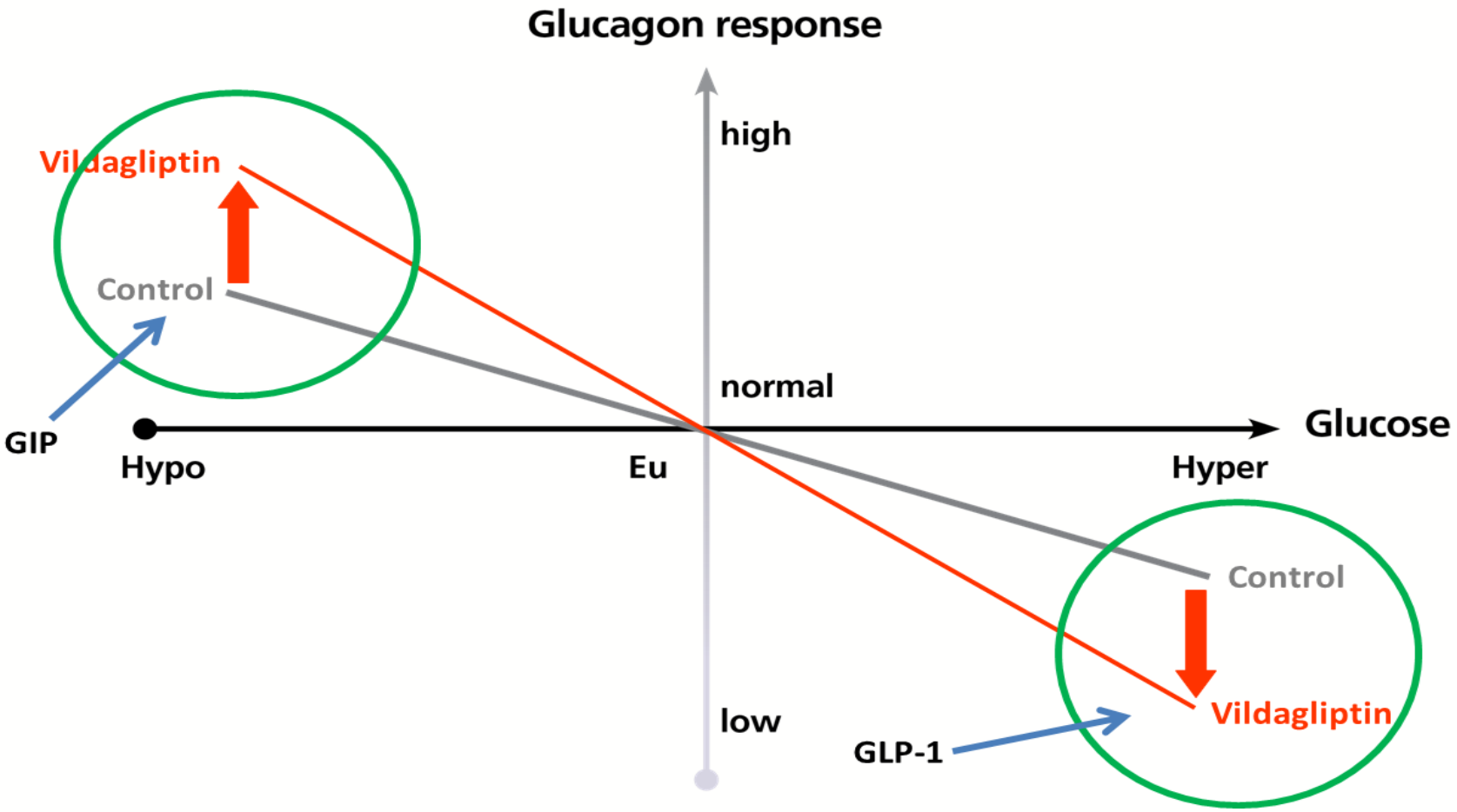
Target for T2DM therapy

	β-cell glucose sensitivity	α-cell glucose sensitivity	
	Glucose-dependent ↑ ↓ in insulin secretion	Glucagon at high glucose	↑ Glucagon at low glucose
GLP-1	✓	✓	
GIP	(✓)		✓

DPP-4 inhibition increases both GLP-1 and GIP, and therefore has the desired effect on islet function

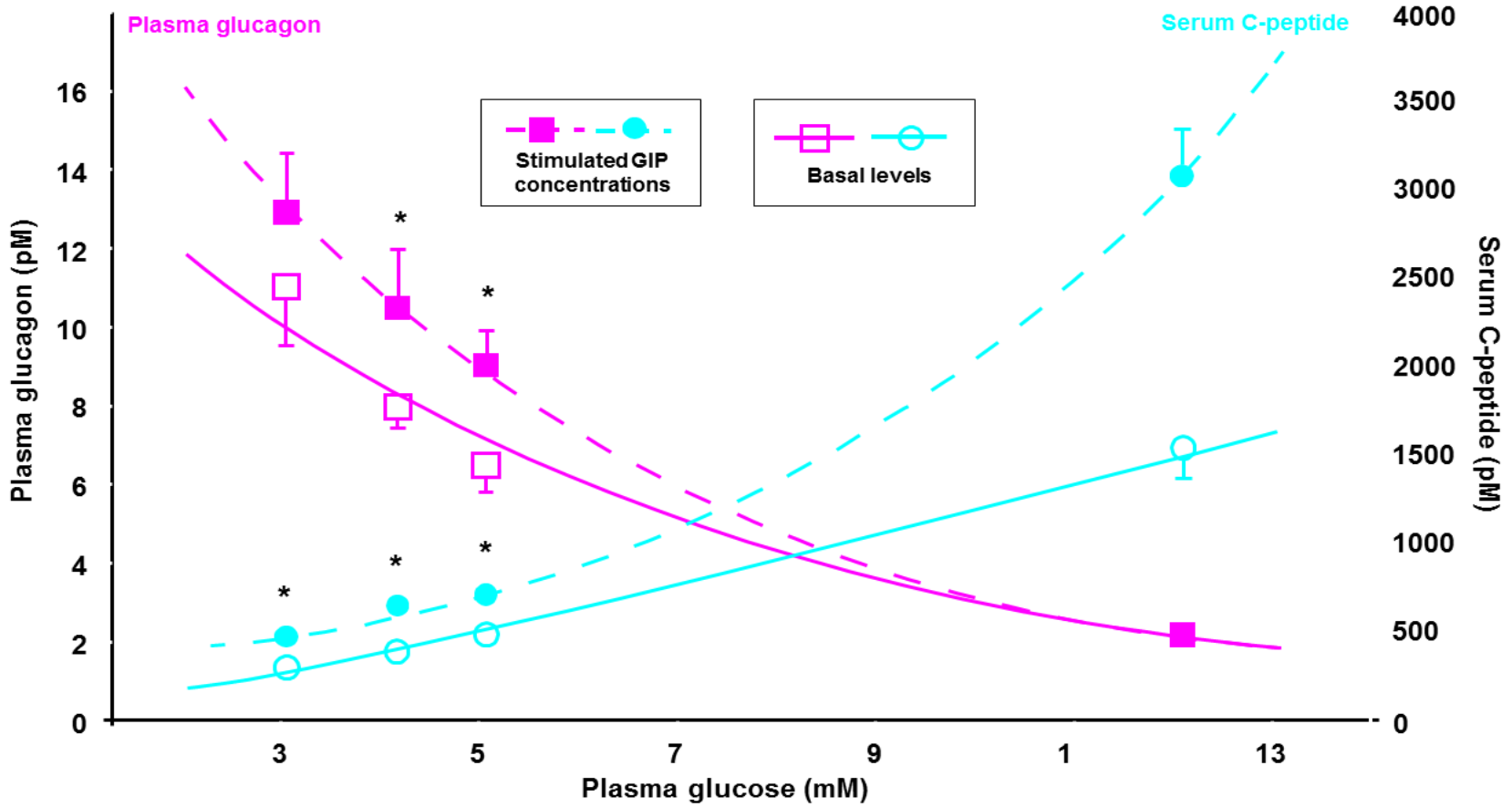
Diabetes Obesity Metab 2011;13:775–83.

Vildagliptin regulates Glucagon



J Clin Endocrinol Metab. 2009;94:1236.

GIP improves sensitivity to Alpha & Beta cells to glucose



Data are means ± SEM. *Significant ($P < 0.05$) differences according to paired *t* tests

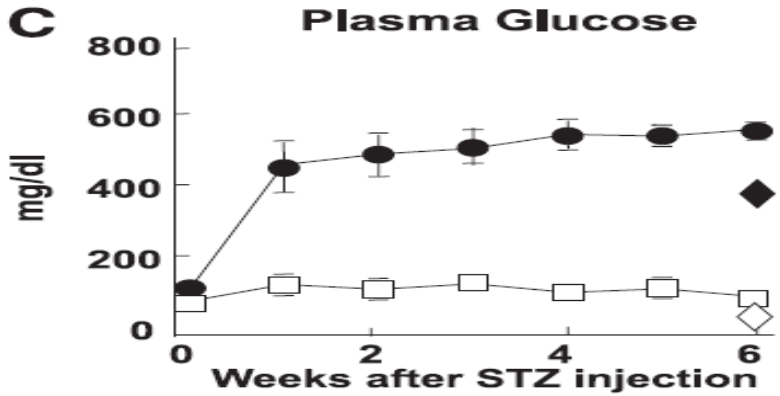
Diabetes 2011;60:3103–9

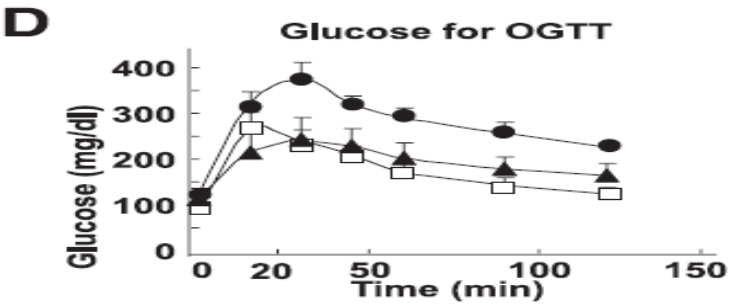
Glucagon is Important (T1DM)

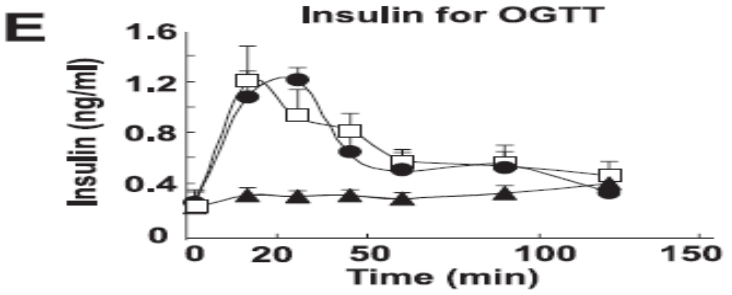
ORIGINAL ARTICLE

Glucagon Receptor Knockout Prevents Insulin-Deficient Type 1 Diabetes in Mice

Young Lee,[1] May-Yun Wang,[1] Xiu Quan Du,[2] Maureen J. Charron,[2] and Roger H. Unger[1,3]





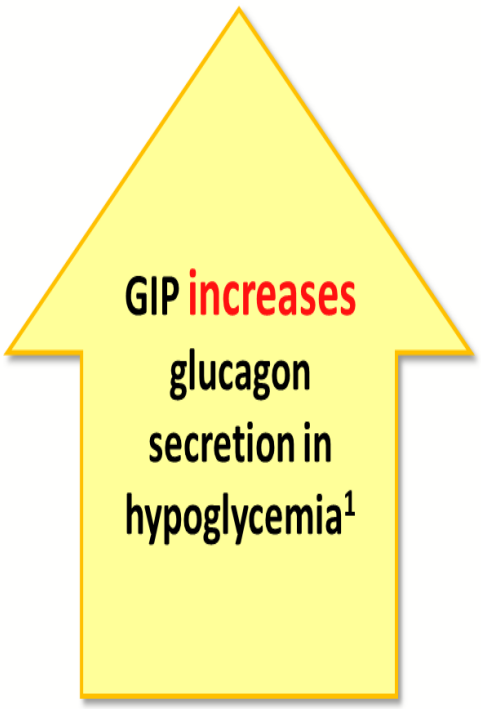


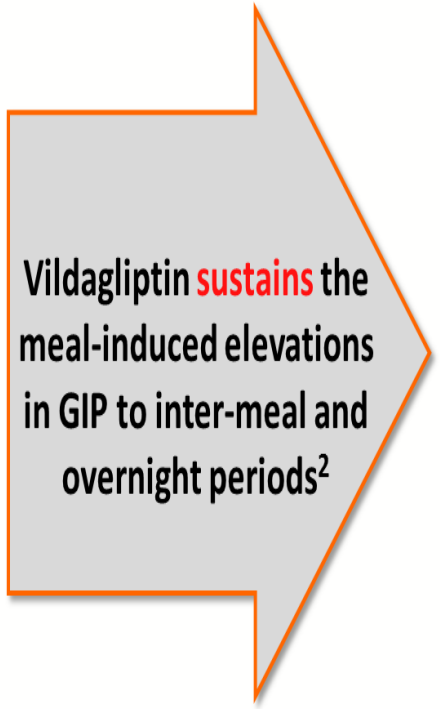
Diabetes 2011;60(2):391–397.

Vildagliptin on Glucagon

ß-cells stop secrete insulin

Augmented glucagon secretion through GIP

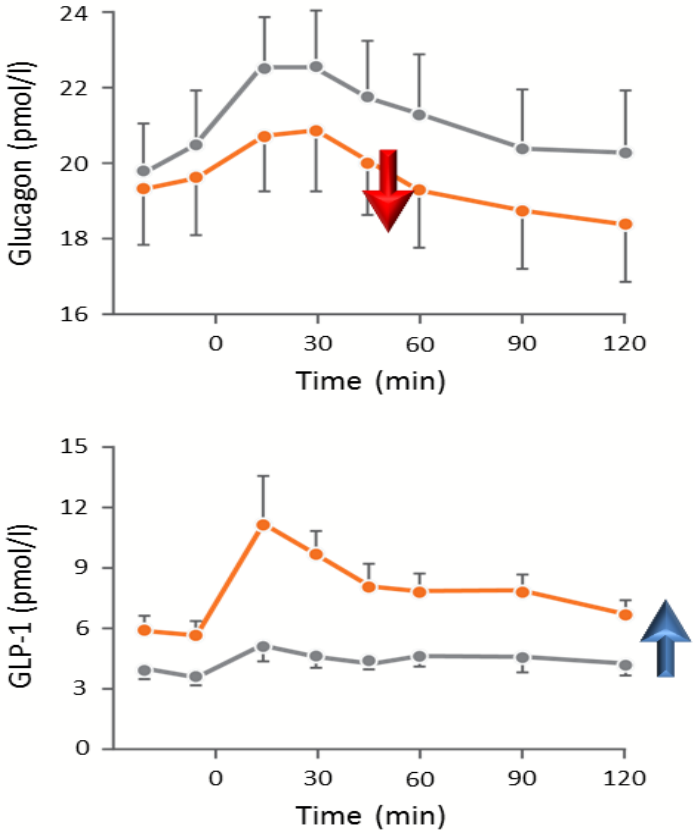




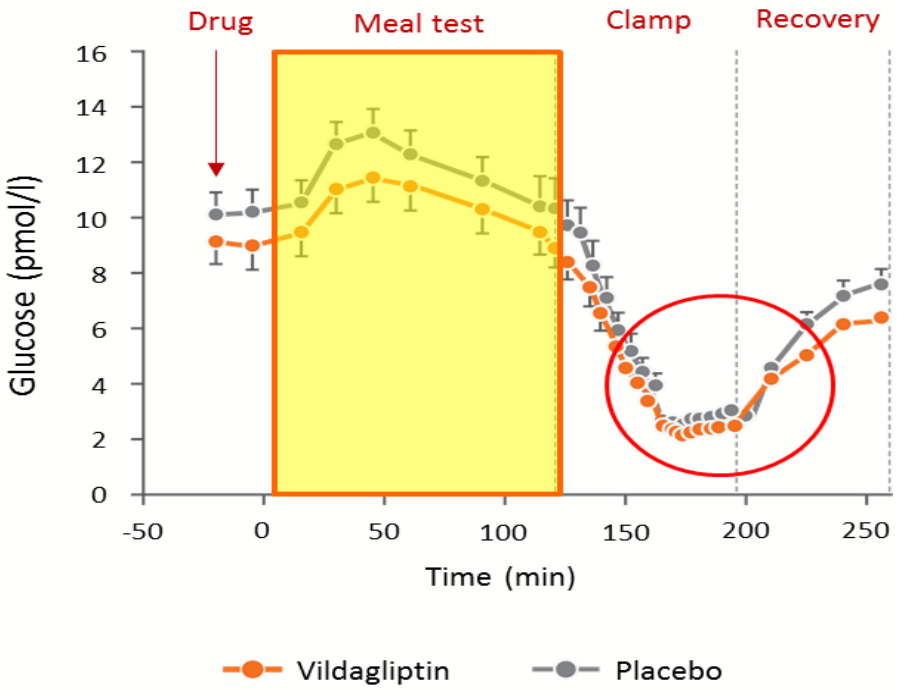
May explain no relevant increase in hypoglycemia with vildagliptin in the face of reduced glucose levels

Diabetes 2011;60:3103-3109.
Diabetes Obes Metab 2011;13:775-783.

Vildagliptin regulates Glucagon (T1DM)



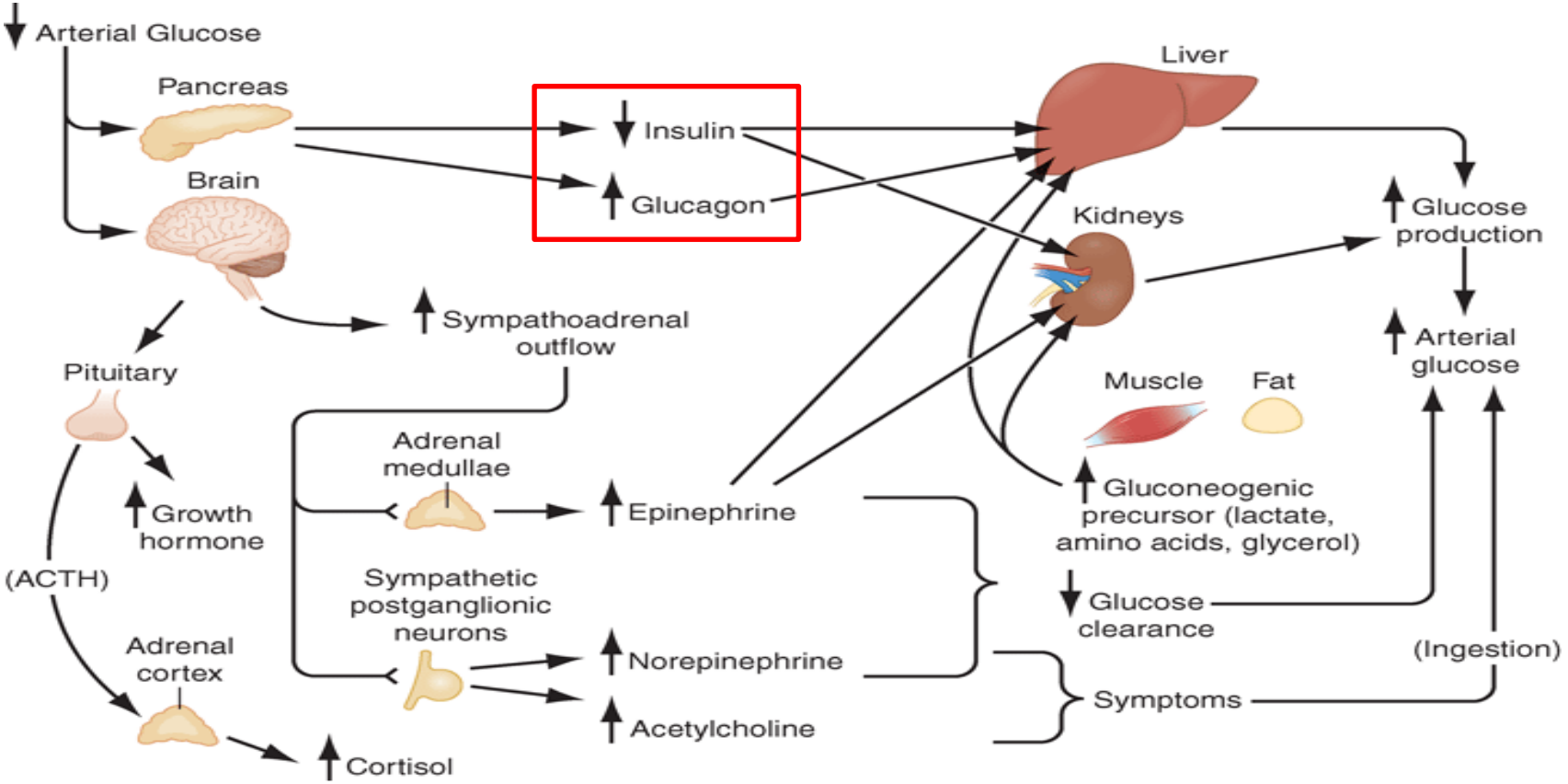
Plasm levels of glucagon and GLP-1 during standard breakfast meal tests after 28d of treatment with vildagliptin or placebo in subjects (n=28) with T1D. Means ± SEM are shown.



Blood glucose levels before, during and after standard breakfast meal tests followed by a hypoglycemic clamp and recovery from hypoglycaemia after 28d of treatment with vildagliptin or placebo in subjects (n=28) with T1D. Means ± SEM are shown.

J Clin Endocrinol Metab. 2012;97(10).

Glucose Counter-regulation



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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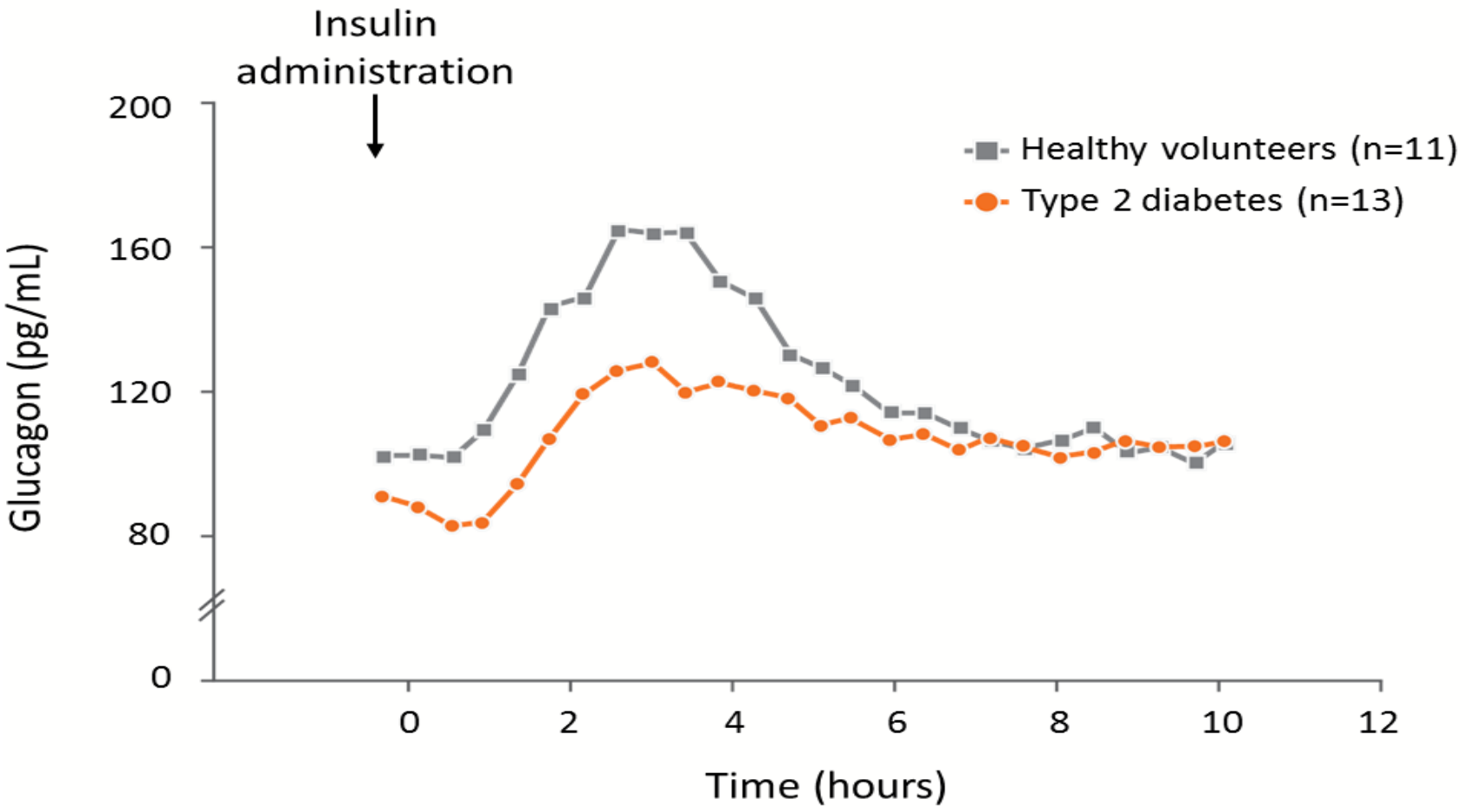
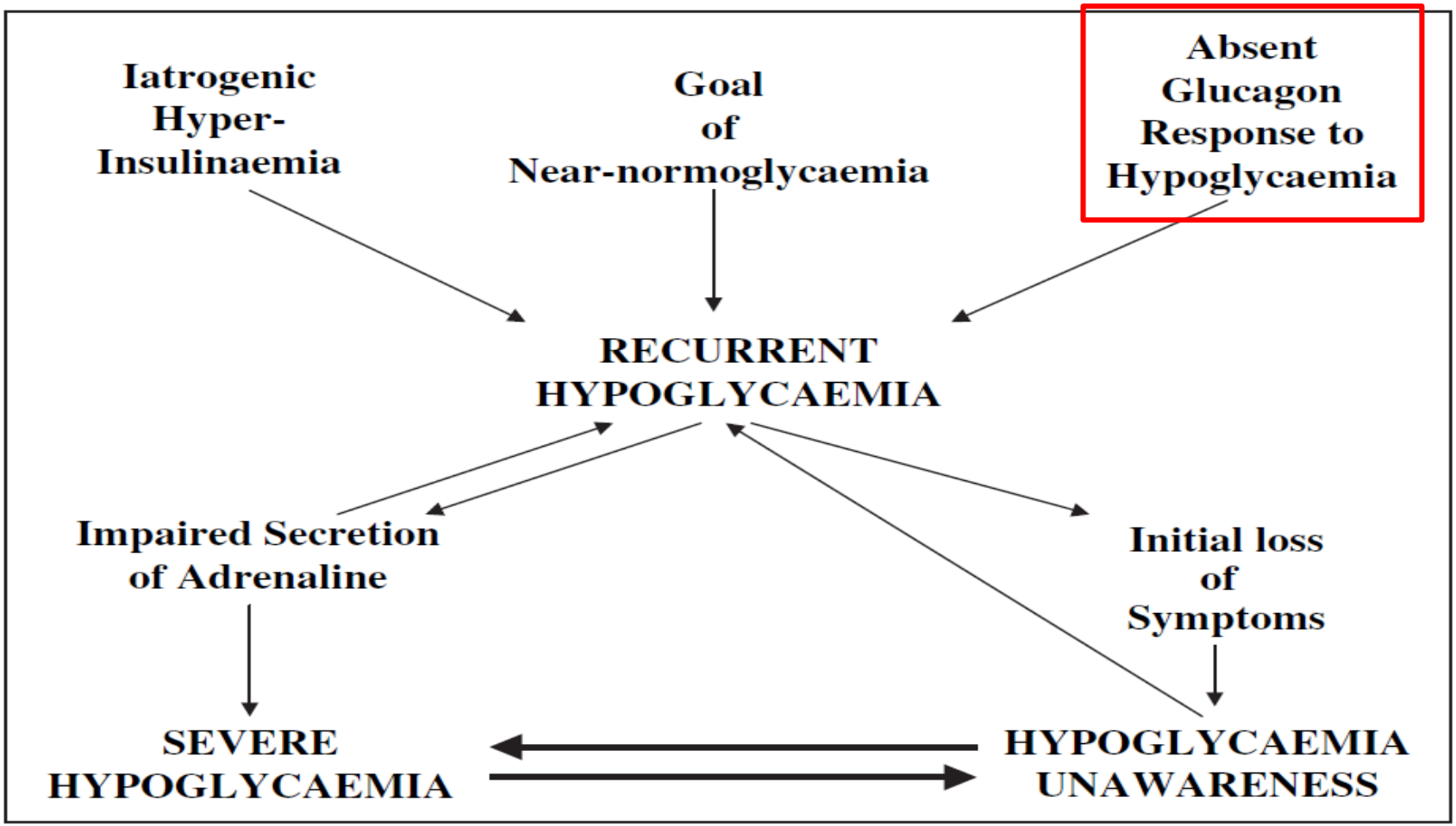
Impaired Glucagon counter-regulation in T2DM



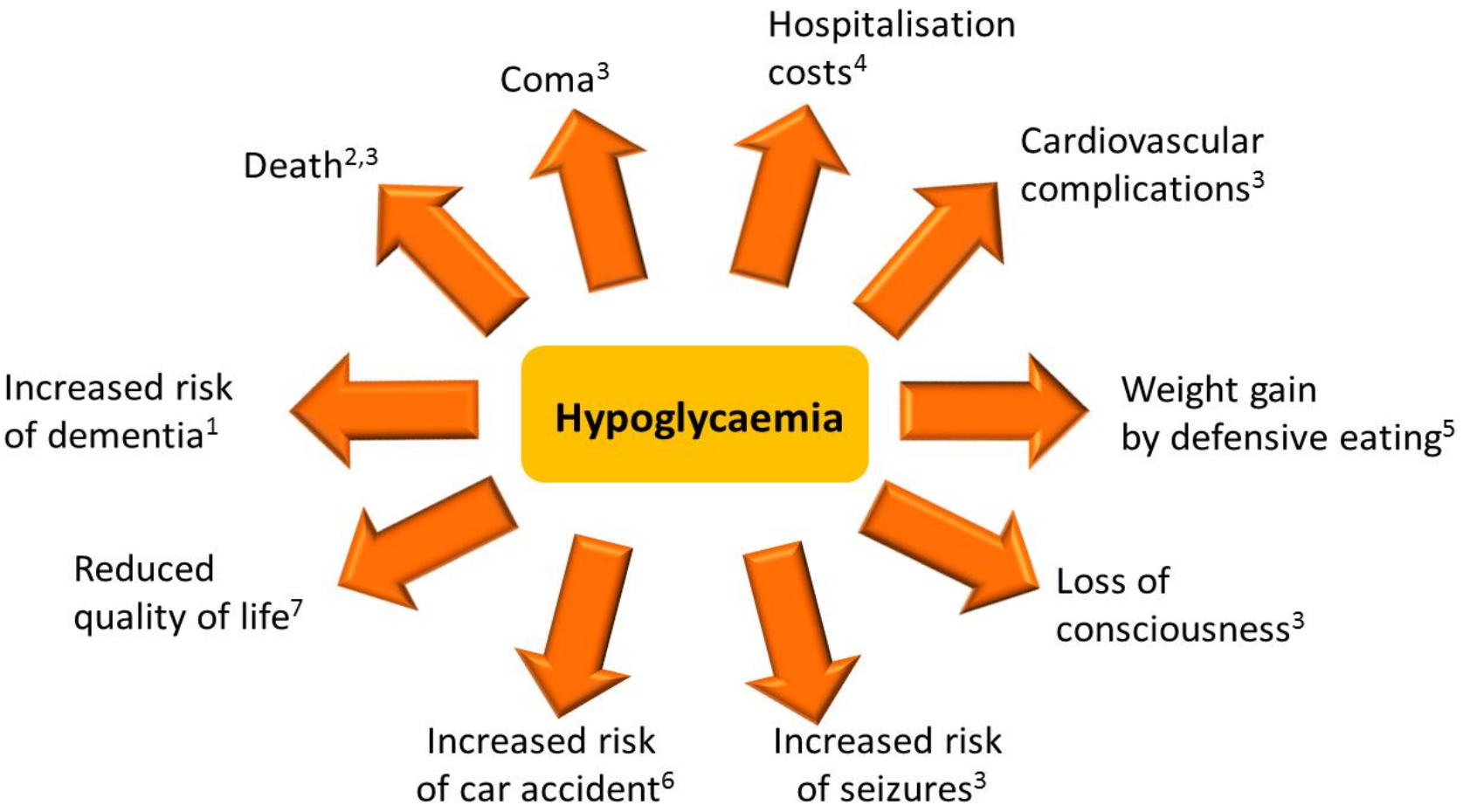
J Clin Invest 1984;73:1532.

Hypoglycemia unawareness



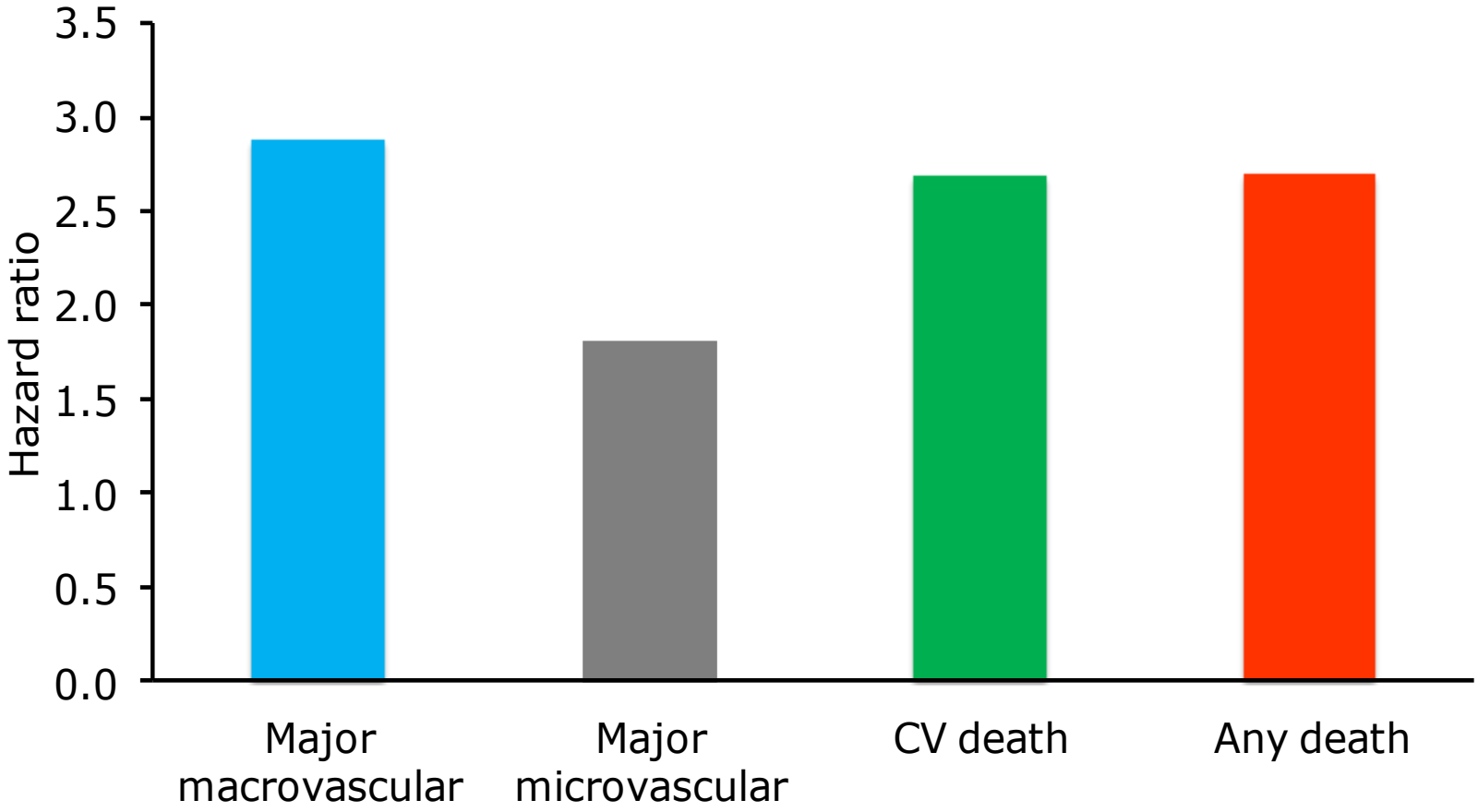
Nutrition, Metabolism & Cardiovascular Diseases 2006;16:S28eS34.

The consequences of Hypoglycemia



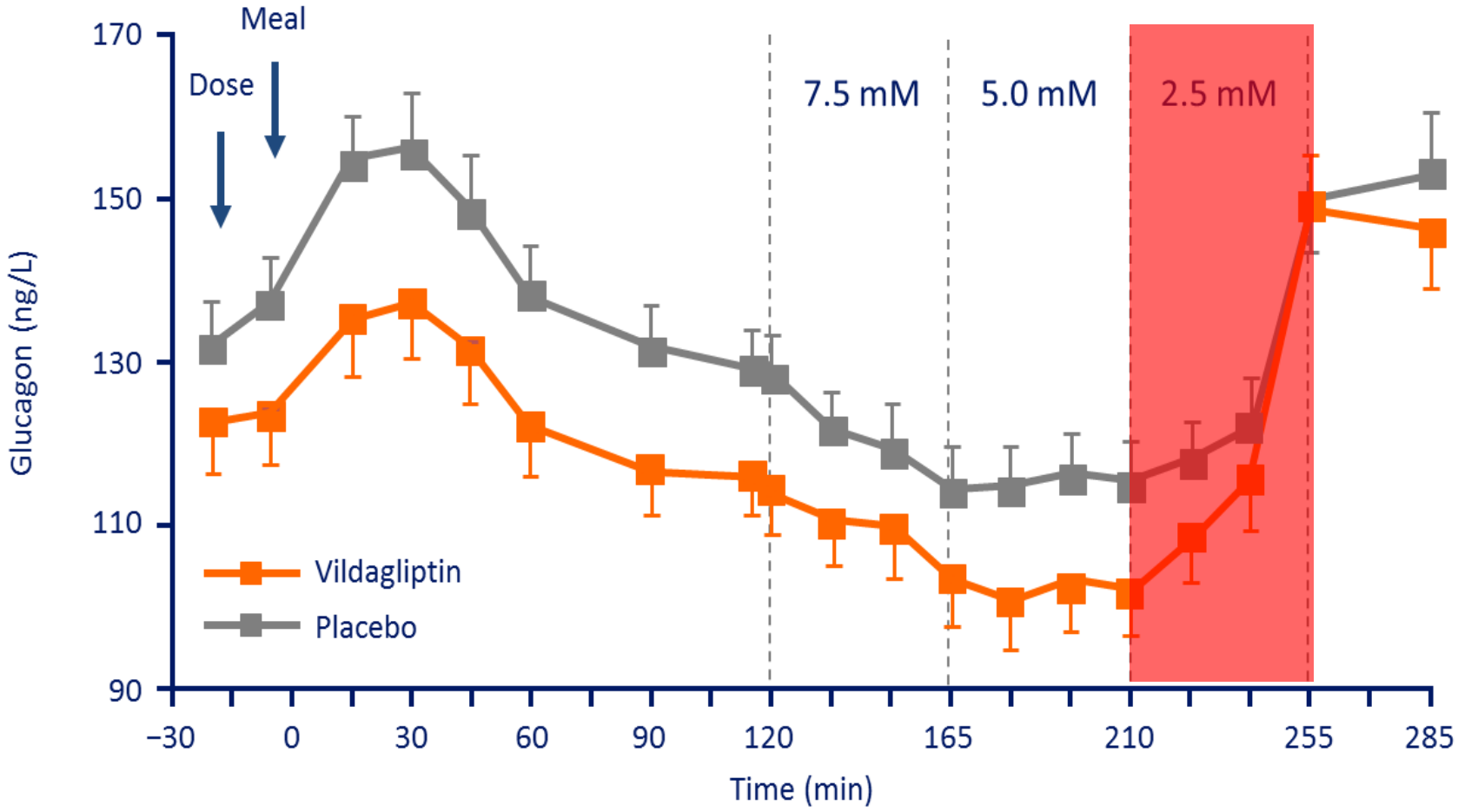
JAMA. 2009; 301: 1565–1572; Br Med J. 2010; 340: b4909;
Curr Med Res Opin. 2010; 26: 1333–1342; Value Health. 2006; 9: 193–198;
Vasc Health Risk Manag. 2010; 6: 541–548; Can J Diabetes. 2003; 27: 128–140; Diabetes Obes Metab. 2010; 12: 431–436.

Severe Hypoglycemia and CVD



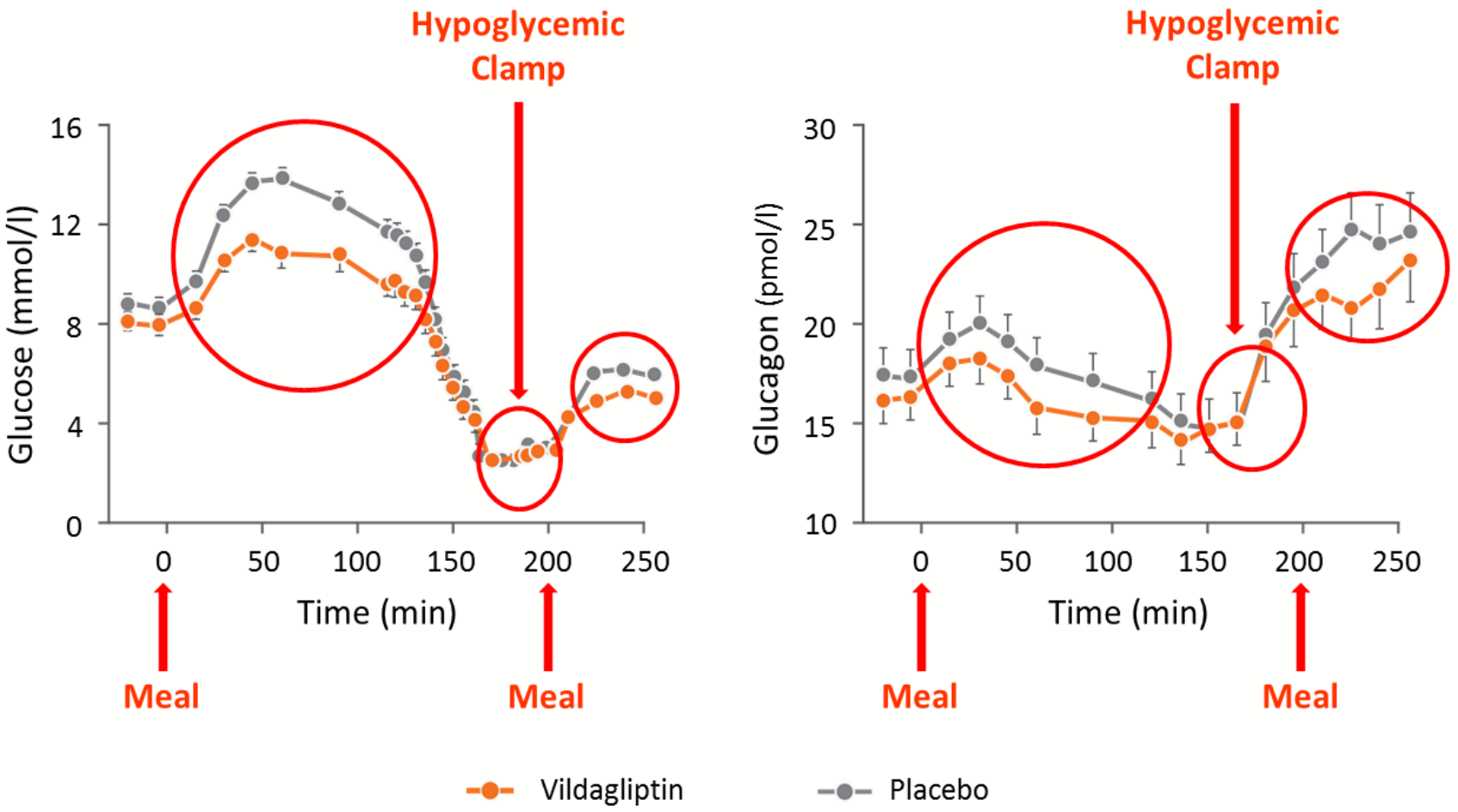
Int J Clin Pract 2005;59:1345–55.

Vildagliptin augments counter-regulation



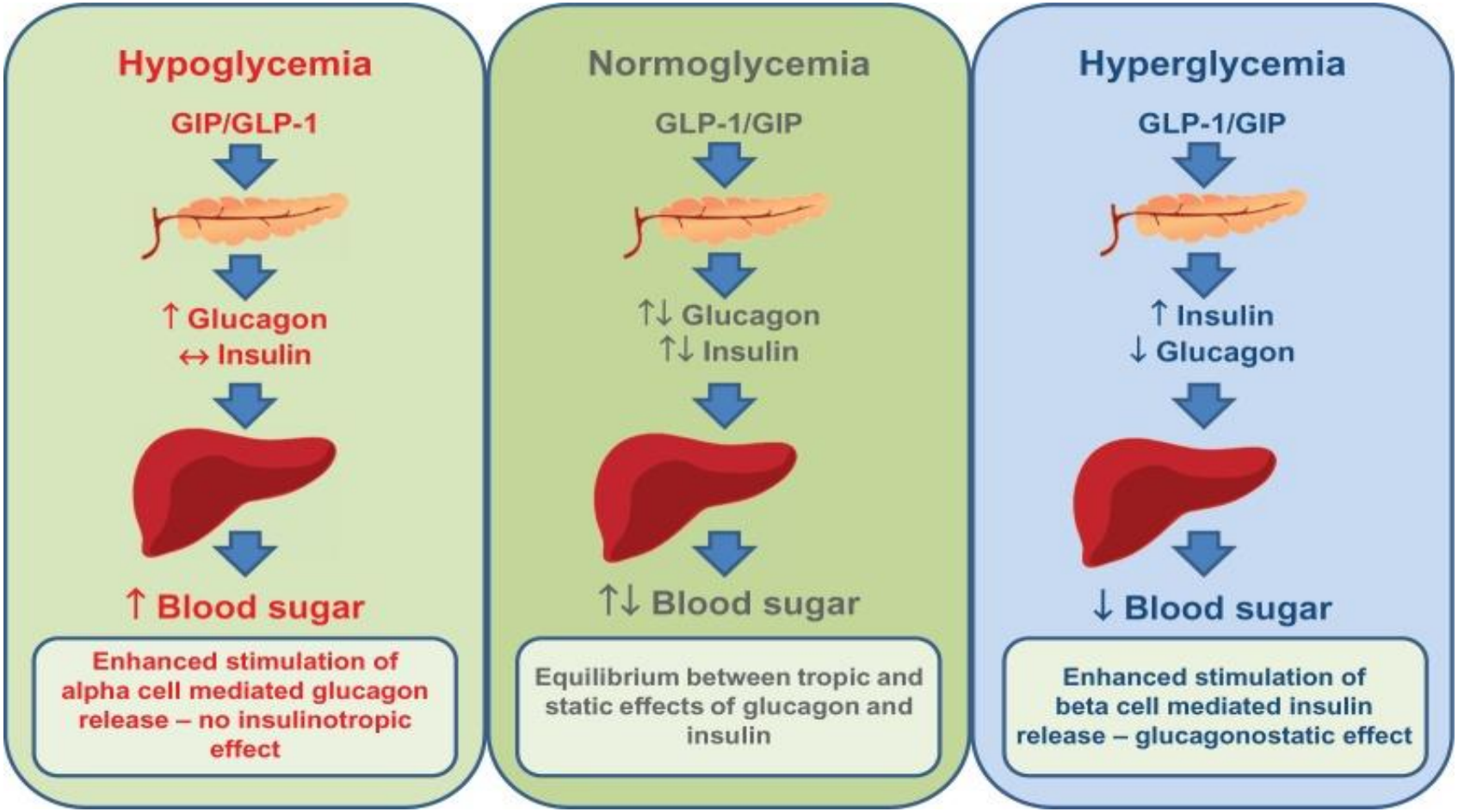
J Clin Endocrinol Metab 2009;94:1236.

Glucagon Dynamics with DPP4i in Insulin-treated T2DM patients



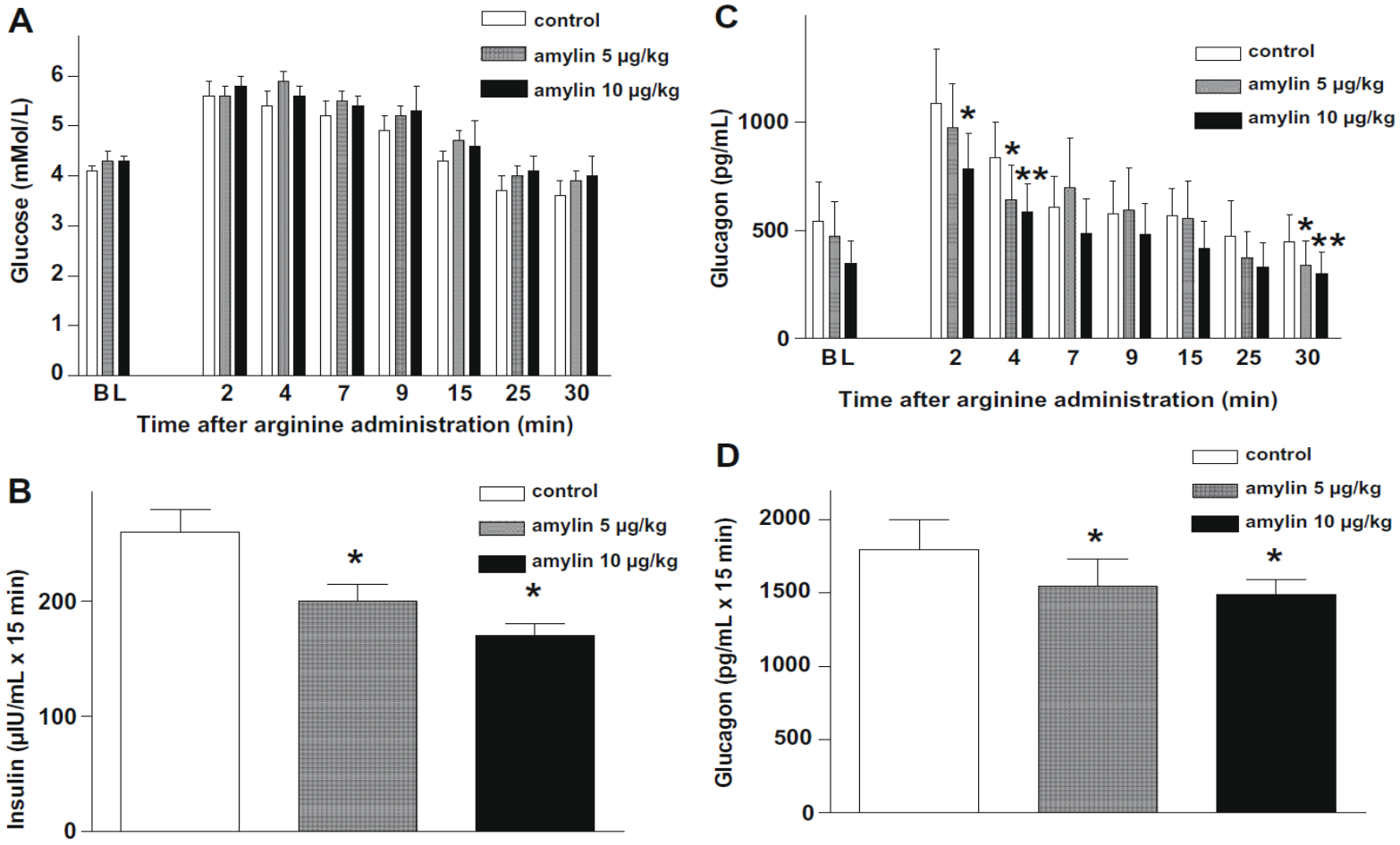
Diabetes Obes Metab. 2014.

Mode of action of Incretins according to Glycemic state



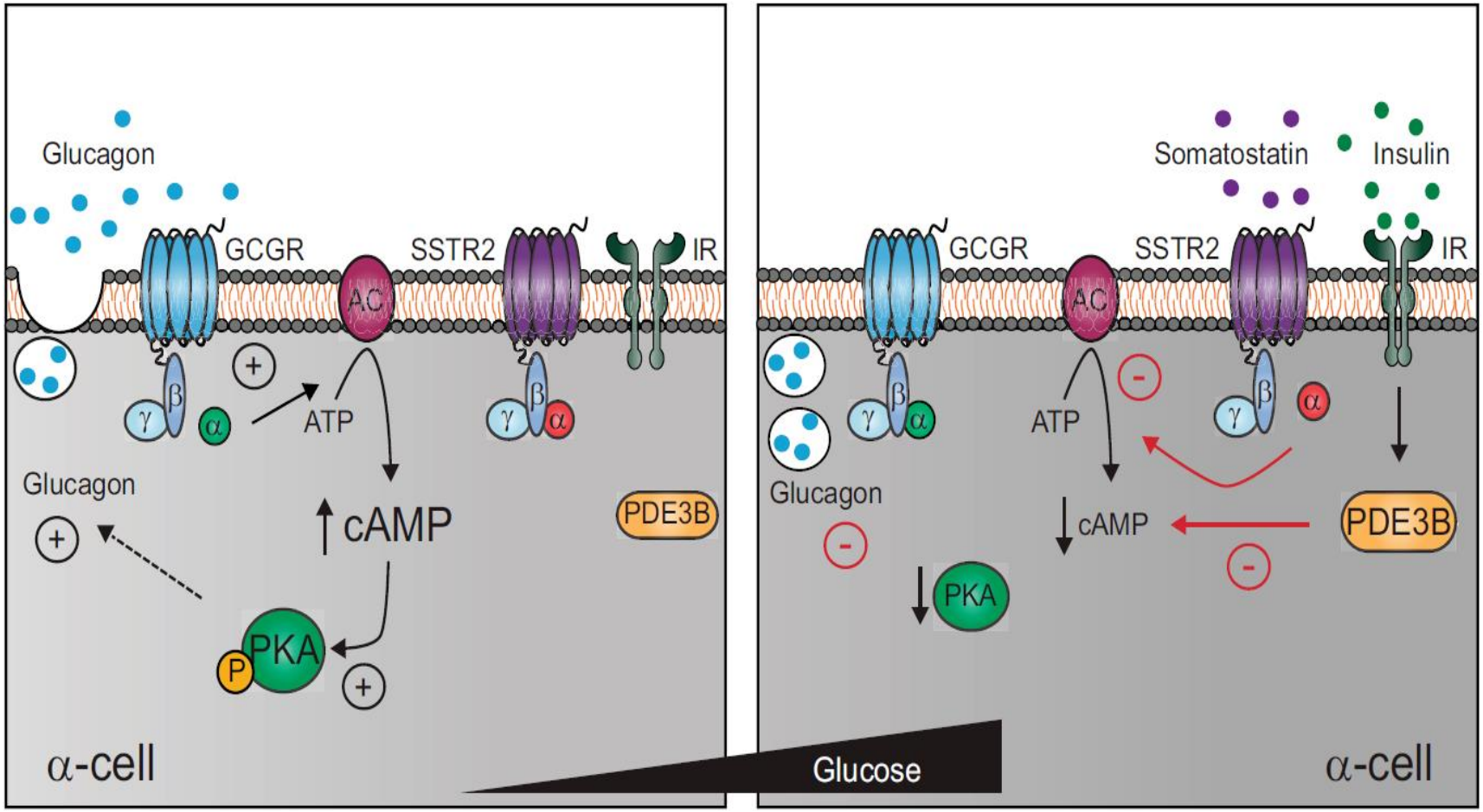
Vasc Health Risk Manag. 2013;9:681–694.

Amylin reduces glucagon concentrations



The Veterinary Journal 184 (2010) 236–240.

Somatostatin and Glucagon



Am J Physiol Endocrinol Metab 2015;308:E130–E143.

DPP4i and SGLT2i: Different Mechanisms

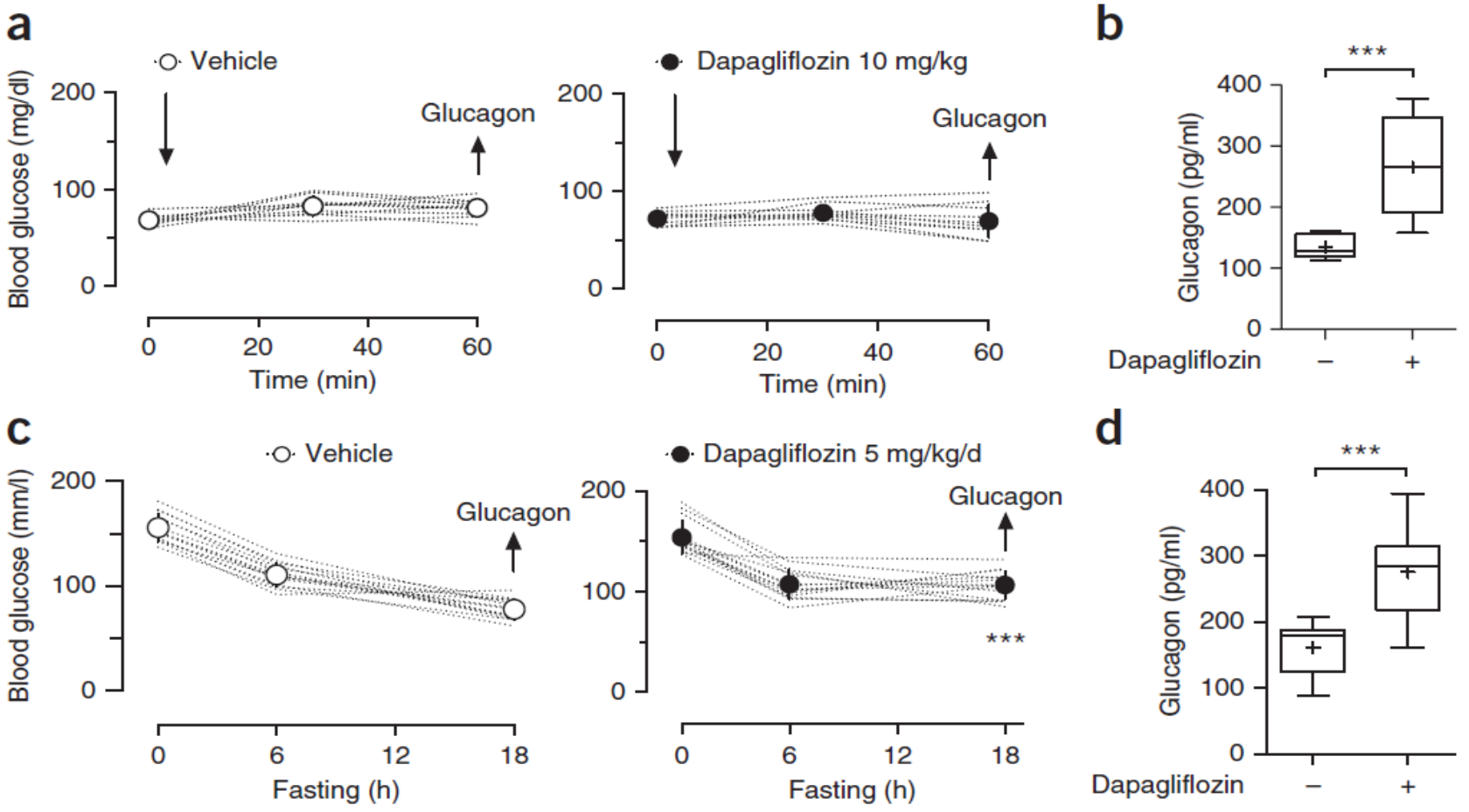
Table 1. Complementary pathways and select physiologic effects of SGLT2 inhibitors and DPP-4 inhibitors [9–12].

Mediating pathways	SGLT2i	DPP4i
Glucose-dependent insulin secretion		✓
Glucose-dependent decrease in glucagon secretion		✓
Increased glucagon secretion	✓	
Increased glucosuria	✓	
Increased β-cell sensitivity/function	✓	✓
Decreased glucotoxicity	✓	
Inhibit degradation of incretin hormones (GLP-1, GIP)		✓
Anti-inflammatory effects		✓
Physiologic effects	**SGLT2i**	**DPP4i**
HbA1c reduction	✓	✓
FPG reduction	✓	✓
Weight loss	✓	
Blood pressure reduction	✓	

FPG: fasting plasma glucose; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide; HbA1c: glycated hemoglobin; DPP4i: DPP-4 inhibitor; SGLT2i: SGLT2 inhibitor; ✓: clinical evidence available.

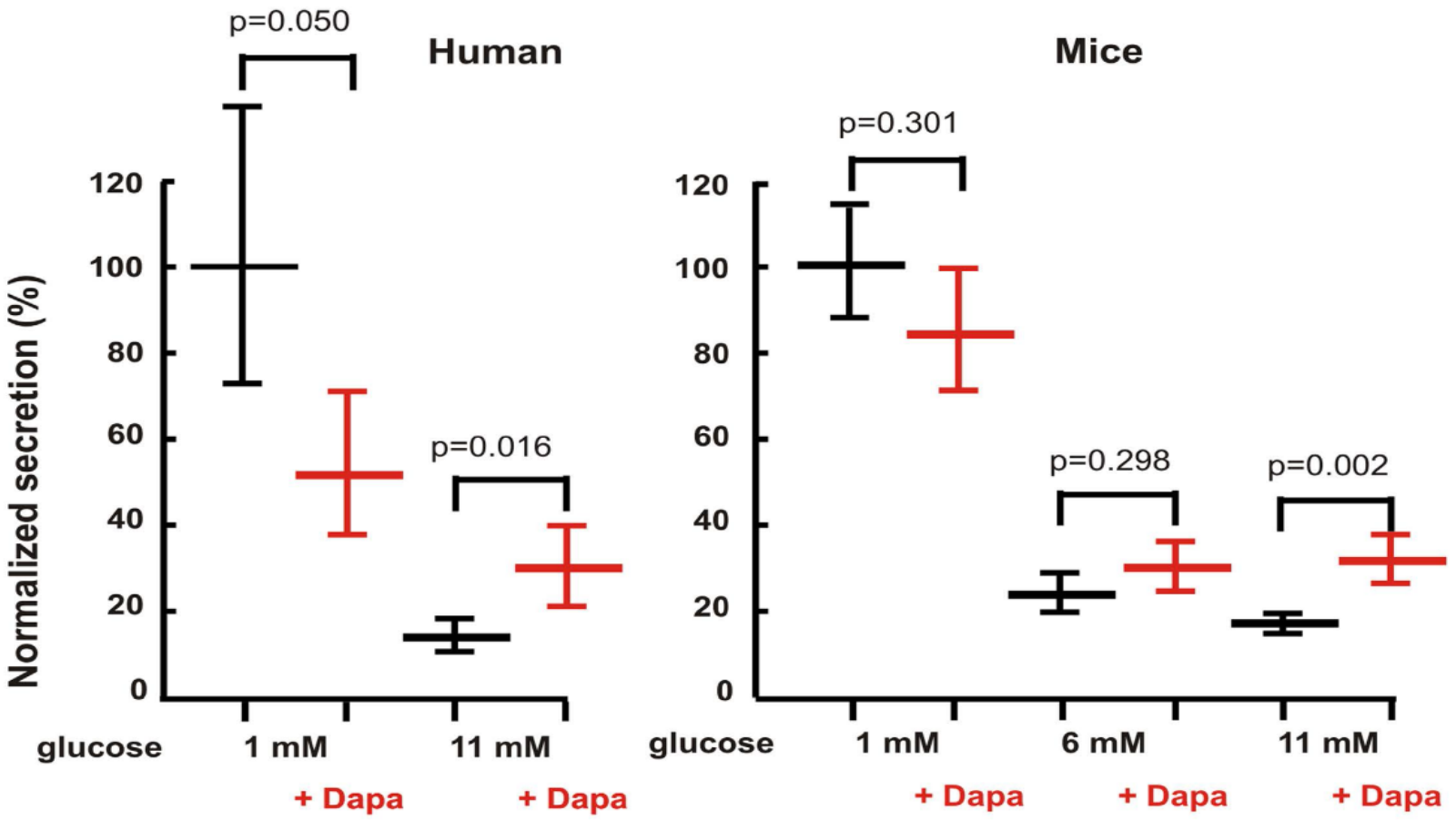
POSTGRADUATE MEDICINE 2017;129(4):409–420.

Dapagliflozin triggers Glucagon secretion



Nature Medicine 2015;21(5):512.

Dapagliflozin stimulates Glucagon secretion at high glucose



Scientific Reports 2016;6:31214.

Glucagon and CV outcome trial

- Hospitalization for HF in T2DM

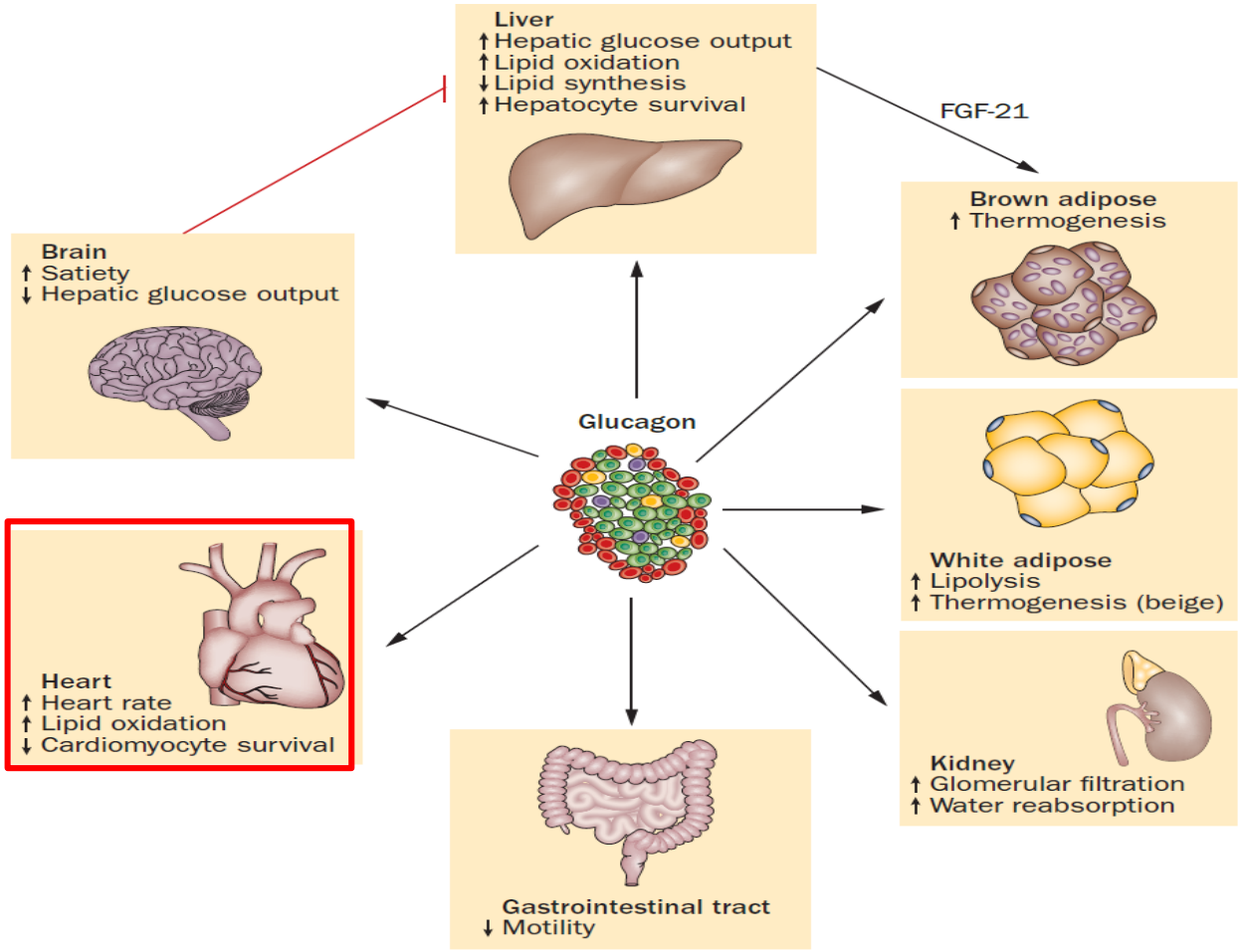
- Unfavorable with Saxagliptin in SAVOR-TIMI 53
- Favorable with Empagliflozin in EMPA-REG
  Liraglutide in LEADER

might be explained, by their impact on glucagon levels:
DPP-4i reduce, but Liraglutide & SGLT-2i increase Glucagon.

However, a possible involvement of glucagon in the results on the mortality of EMPA-REG & LEADER trials cannot be either claimed or excluded.

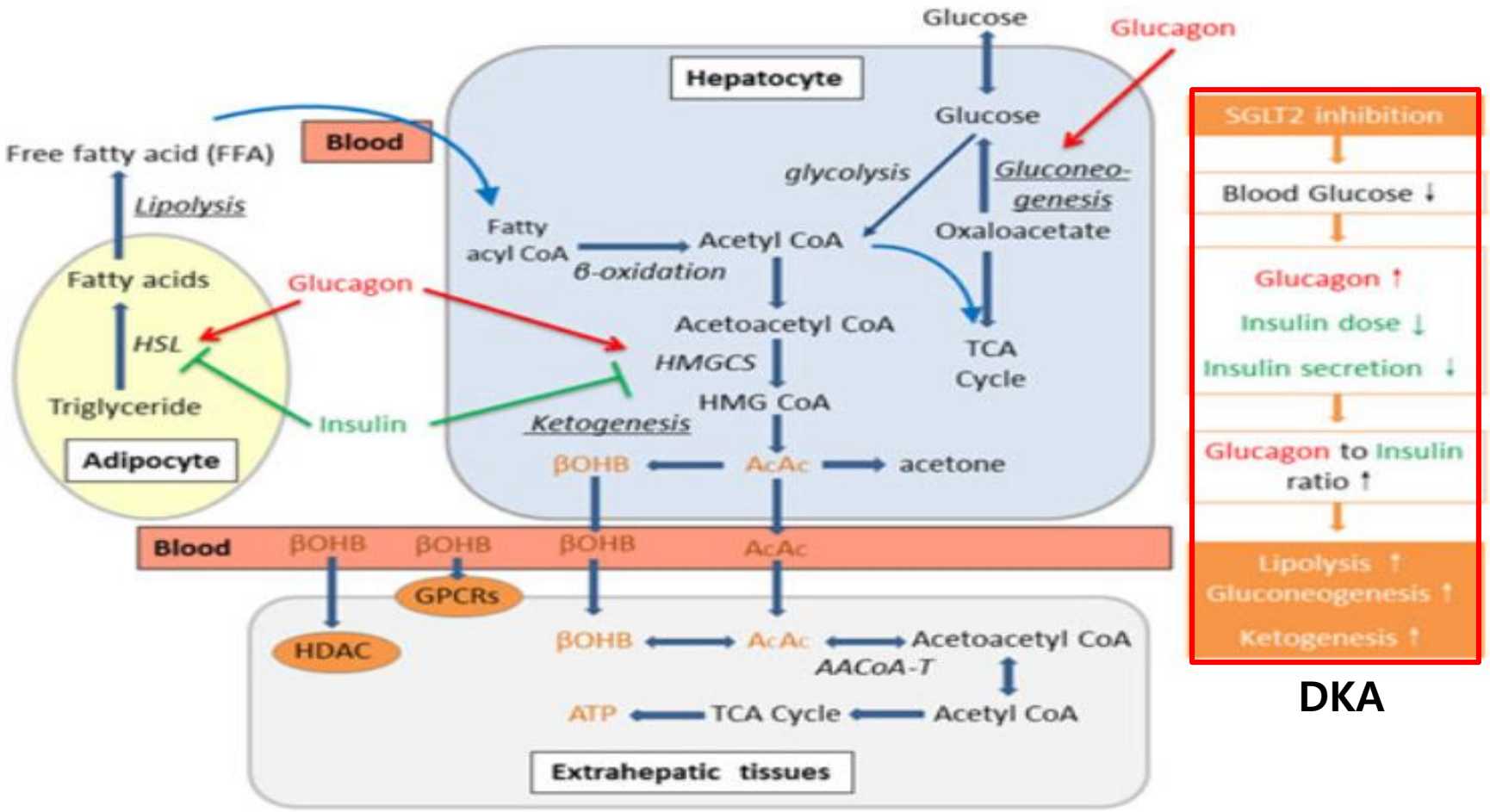
Cardiovasc Diabetol 2016;15:123.

Glucagon Action



Nat Rev Endocrinol 2015;11:329–338.

SGLT2i and Glucagon control



Summary (Diabetes therapy)

- Antagonizing glucagon action as a therapy for diabetes may improve glucose and insulin levels but in addition may have several unintended consequences.
- The physiological processes regulated by glucagon and its receptor are much broader than expected.
- Glucagon might be very important for the heart and cardiovascular system in T2DM.

- **Glucagon modulator and GLP-1 combination** has a significant greater efficacy than GLP-1 RA monotherapy on body weight, body composition, glucose and lipid metabolism, including the reversal of hepatic steatosis, making this combination therapy an attractive and promising treatment for obesity and MetS.

Conclusions

- Therapeutic strategies to safely achieve euglycemia in patients with DM now encompass **bi-hormonal approaches** to simultaneously deliver insulin and glucagon (in patients with T1DM) or reduce excess glucagon action (in patients with T1DM or T2DM).
- Recent efforts resurrected glucagon as a key hormone in the pathophysiology of DM. **New studies target abnormal glucagon regulation and action** that is keys for improving DM treatment.
- Manipulation of the glucagon axis is a promising addition to traditional diabetes insulin therapy.
- The progress is promising, but pleiotropic actions of glucagon should also be considered.

Special Thanks to

- Bo Ahrén (Lund University, Sweden)