Up Date on Diabetes Treatment- New Therapies

GP CME Rotorua, 2012

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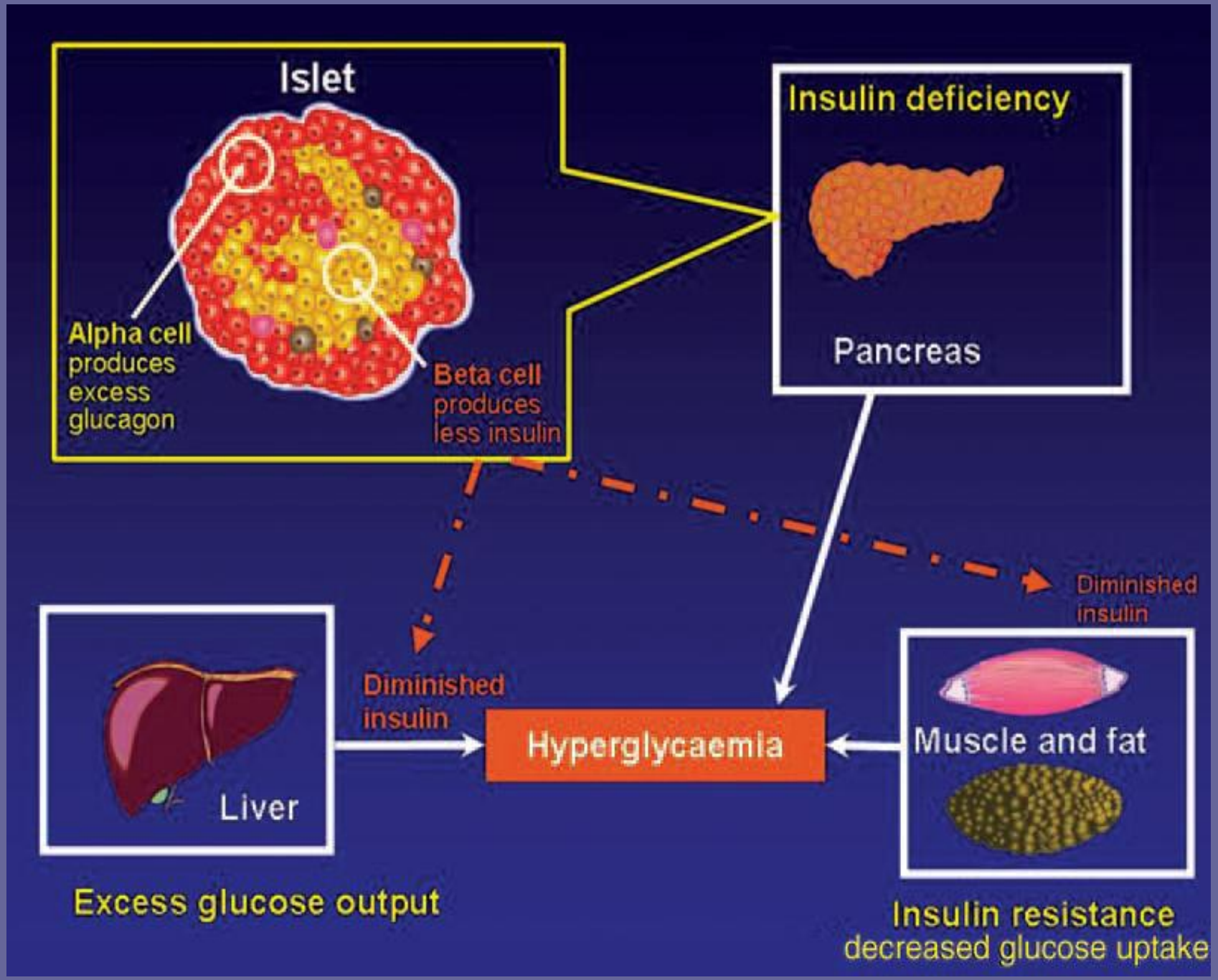
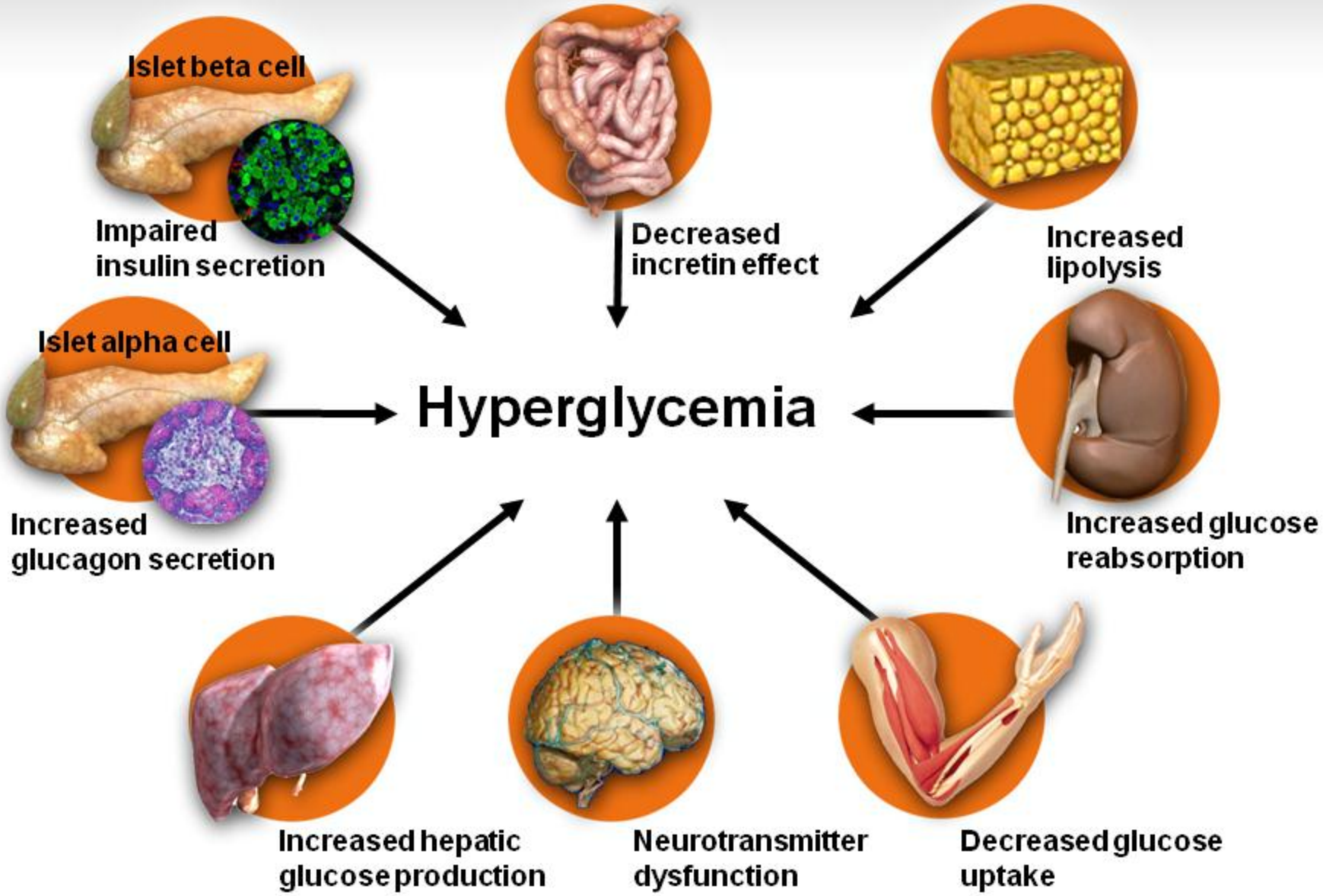
Challenges to Treatment of Type 2 Diabetes

- Progressive disease[a]
- Numerous pathophysiological dysfunctions[b]
  - Insulin resistance
  - Beta-cell dysfunction
- Effective treatment requires multiple drugs used in combination to correct multiple pathophysiological defects[b]

a. Defronzo RA. *Diabetes*. 2009;58:773-795.
b. Weyer C, et al. *Diabetes Care*. 2001;24:89-94.


Islet
Alpha cell
produces
excess
glucagon
Beta cell
produces
less insulin
Insulin deficiency
Pancreas
Diminished
insulin
Diminished
insulin
Hyperglycaemia
Liver
Muscle and fat
Excess glucose output
Insulin resistance
decreased glucose uptake

Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58:773-795.

Current Antihyperglycemic Agents

- Sulfonylureas
  - Glyburide
  - Glipizide/glibenclamide
  - Glimepiride
- Biguanides
  - Metformin
- Thiazolidinediones
  - Pioglitazone
- Alpha-glucosidase inhibitors
  - Acarbose

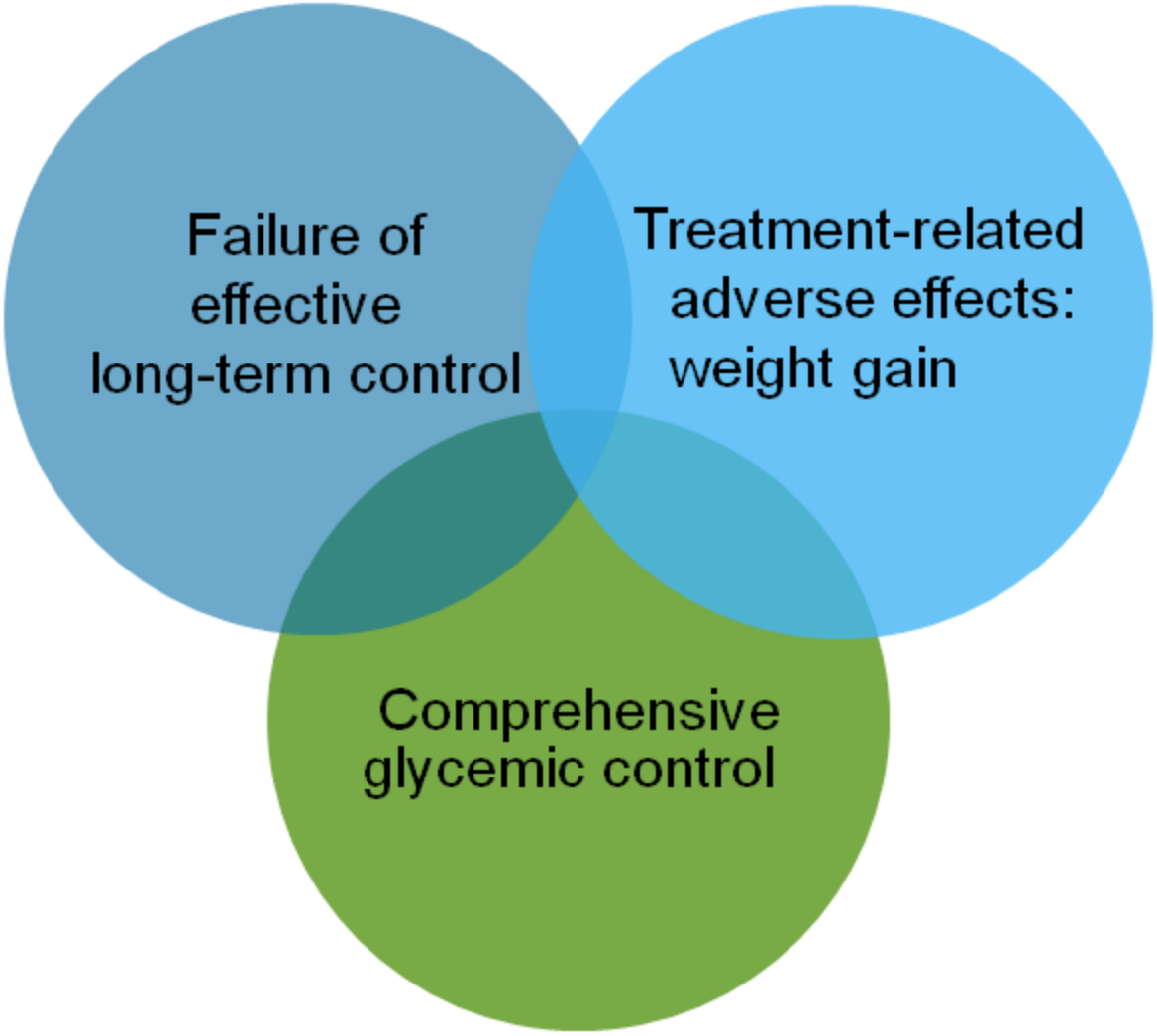
Kimmel B, Inzucchi SE. *Clin Diab*. 2005;23:64-76.

Limitations of Traditional Treatment Options for Type 2 Diabetes

- Hypoglycemia[a]
- Weight gain[b]
- Lack of durability[c]
- Minimal or no effect on cardiovascular risk[d]

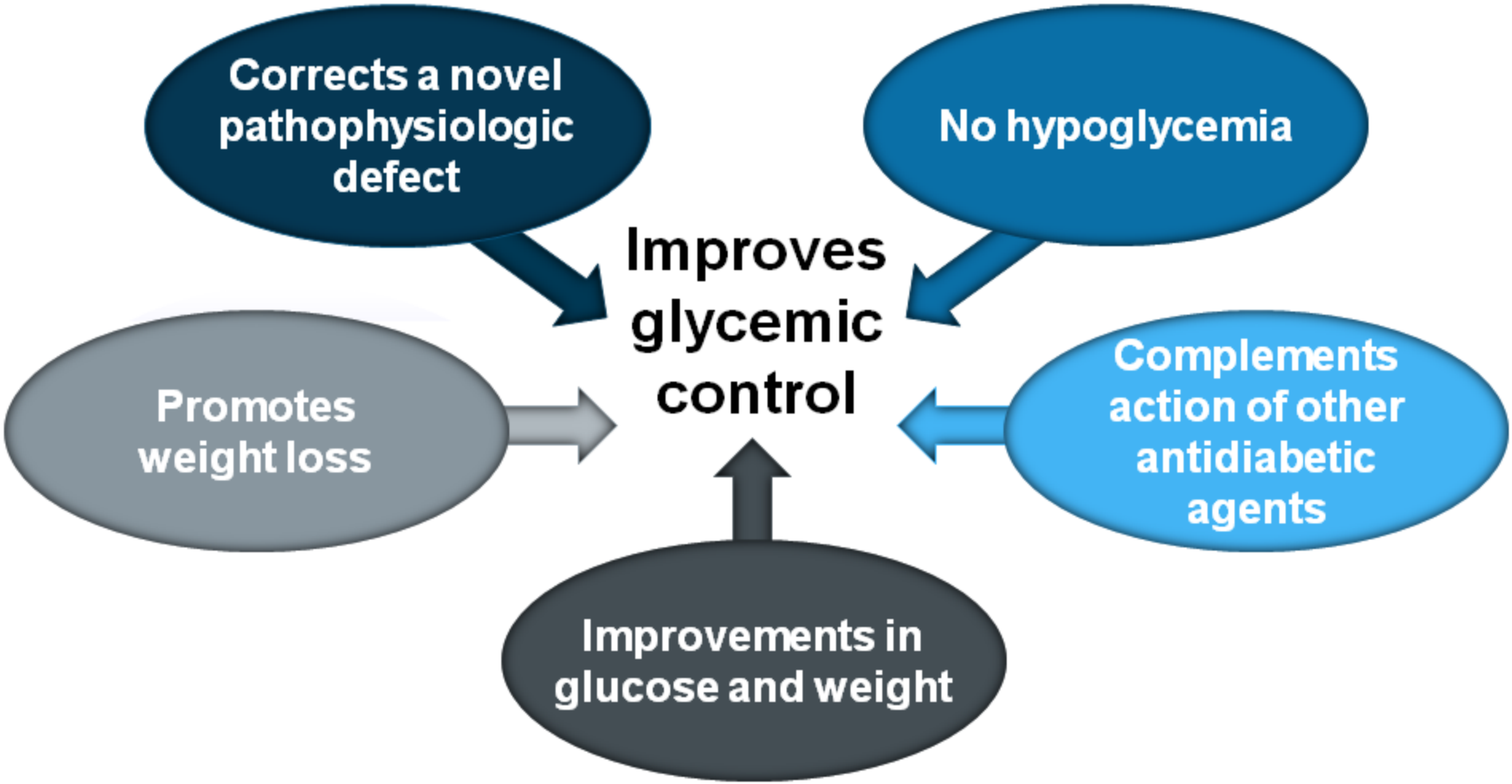
a. DeFronzo RA. *Ann Intern Med*. 1999;131:281-303.
b. Mitri J, et al. *Expert Opin Drug Saf*. 2009;8:573-584.
c. Cook MN, et al. *Diabetes Care*. 2005;28:995-1000.
d. DeSouza C, et al. *Nat Rev Drug Discov*. 2009;8:361-367.

Need for New Treatment Approaches



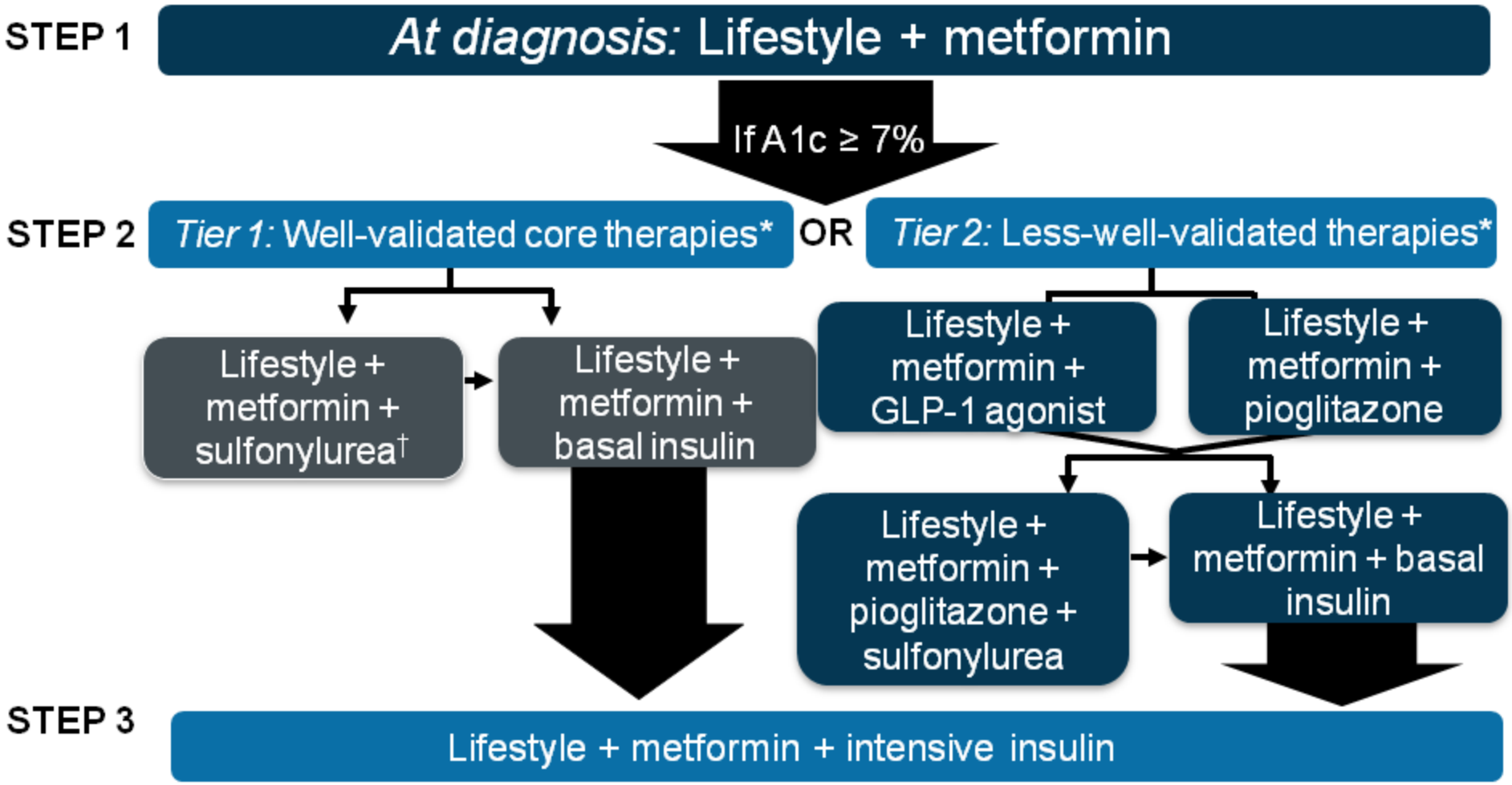
Reasner CA, Göke B. *Br J Diab Vasc Dis*. 2002;2:290-295.

Individualizing Therapy: Factors to Consider



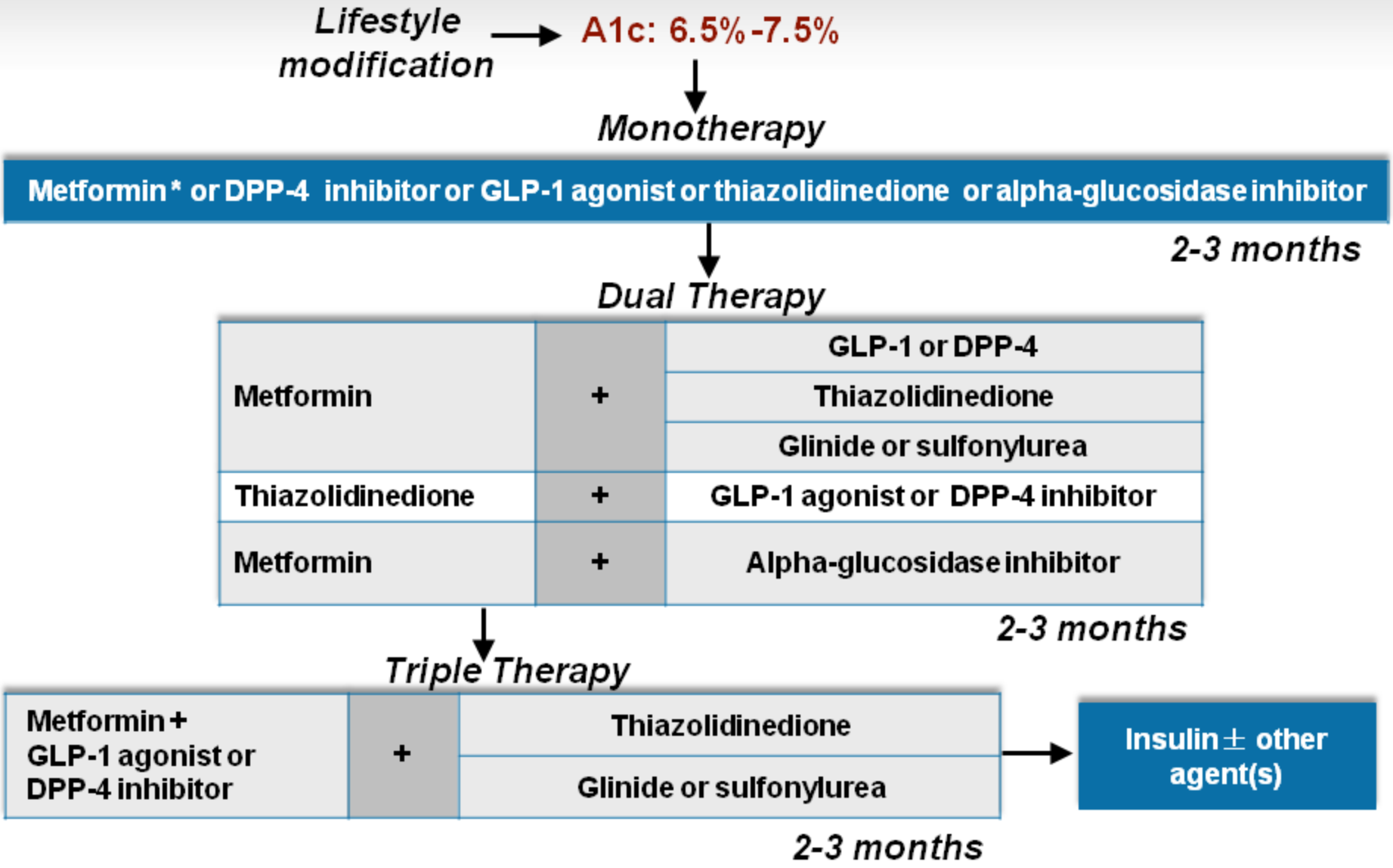
DeFronzo RA. *Diabetes*. 2009;58:773-795.

ADA/EASD Consensus Algorithm



*Validation based on clinical trials and clinical judgment.
†Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.
Adapted from Nathan DM, et al. *Diabetes Care*. 2009;32:193-203.

AACE/ACE Diabetes Algorithm



*Preferred initial agent

Rodbard HW. *Endocr Pract*. 2009;15:540-559.

Evolving Treatment Paradigm

- Beyond glucose control
- Consider impact on weight, hypoglycemia, and cardiovascular risk factors

Brunton S. *Postgrad Med*. 2009;121:68-81.

Novel Therapeutic Approach—Restoring the Loss of Incretin Effect in Diabetes

INCRETINS

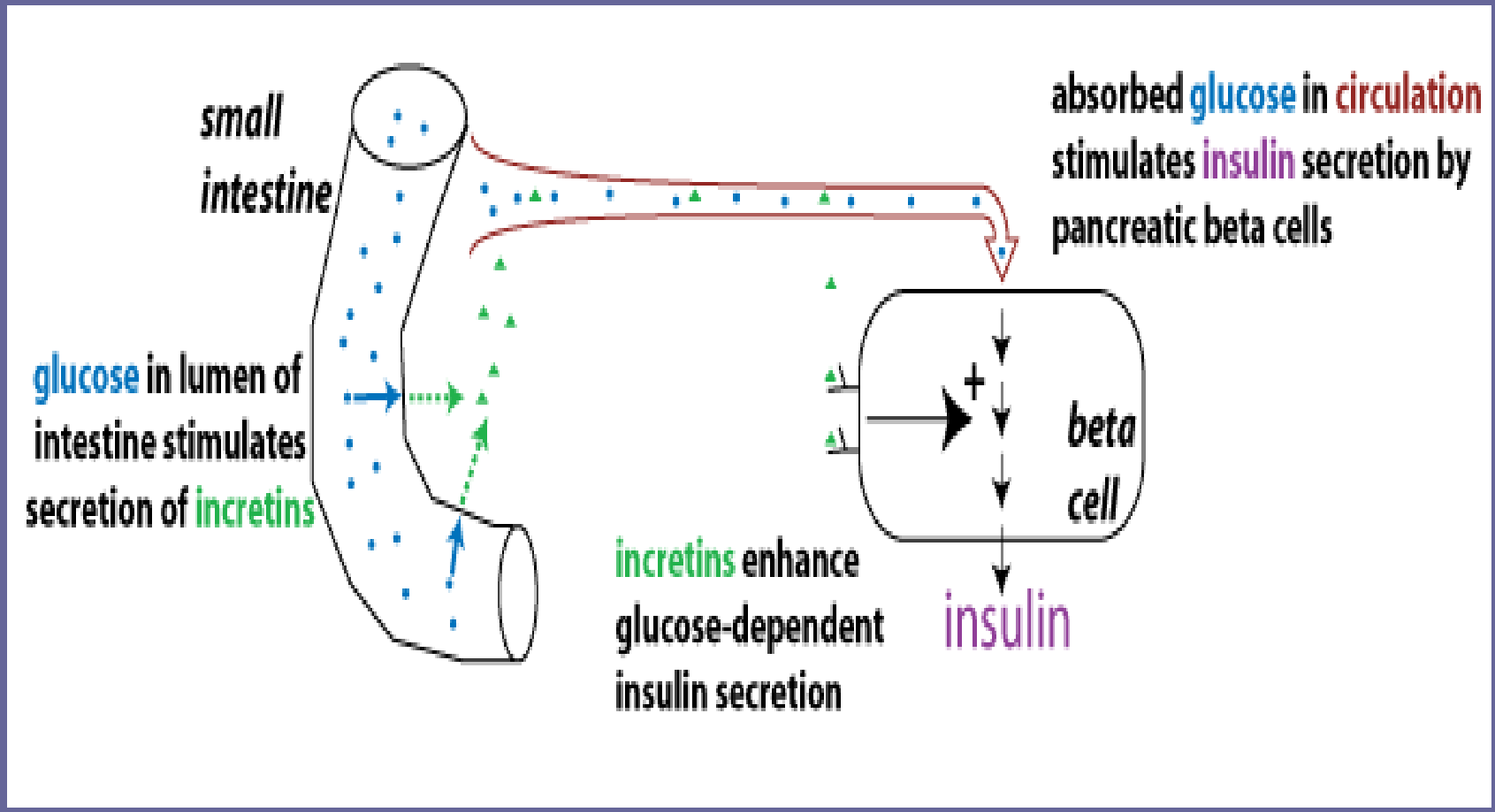
- The **incretins** are gut hormones that work to **increase insulin secretion**
- Two main incretin hormones in humans.
  - **GIP** (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide)
  - **GLP-1** (glucagon-like peptide-1).

Definition of Incretins

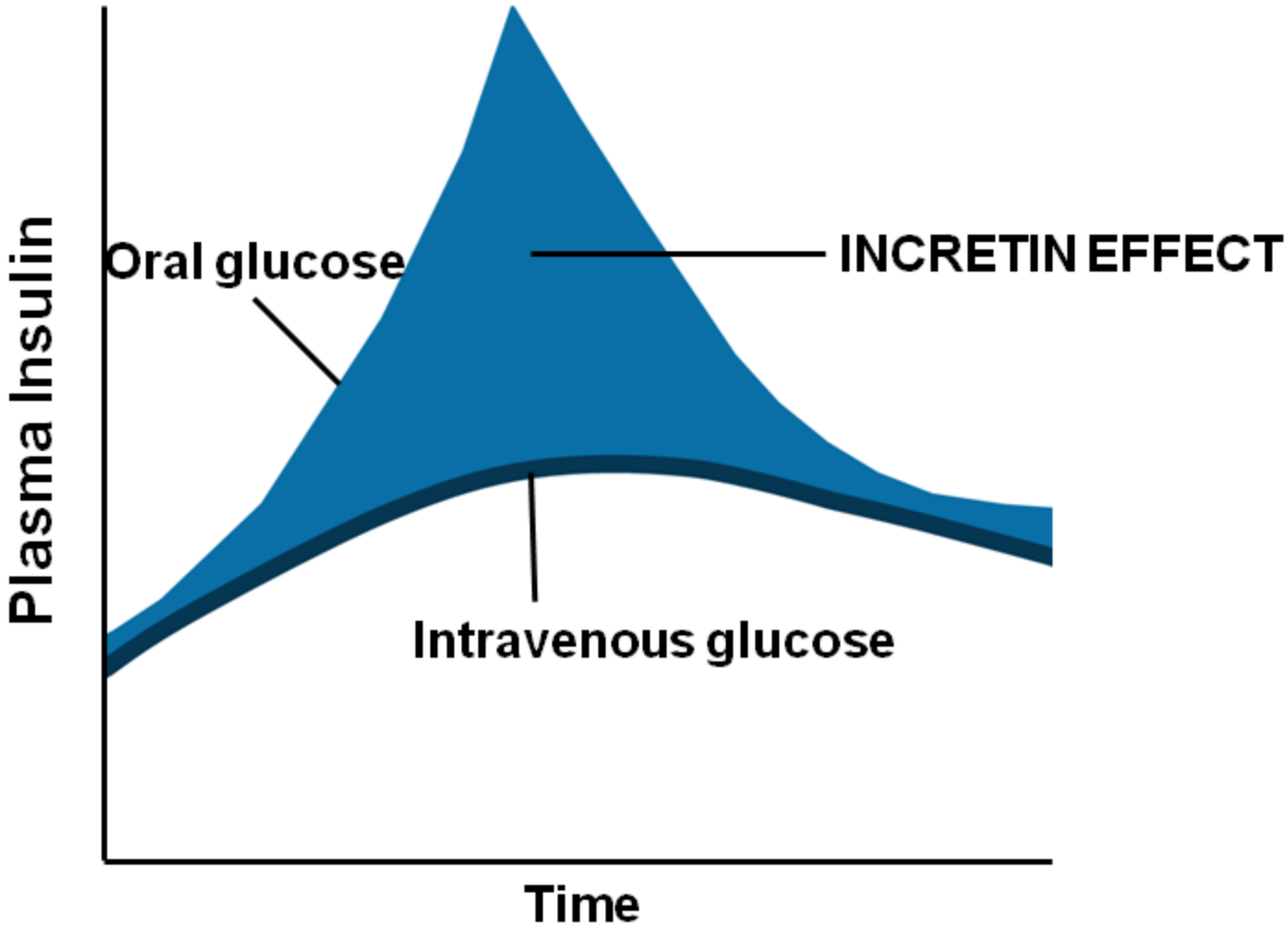
"Gut-derived factors that increase glucose-stimulated insulin secretion"

In · cre · tin

Intestine Secretion Insulin

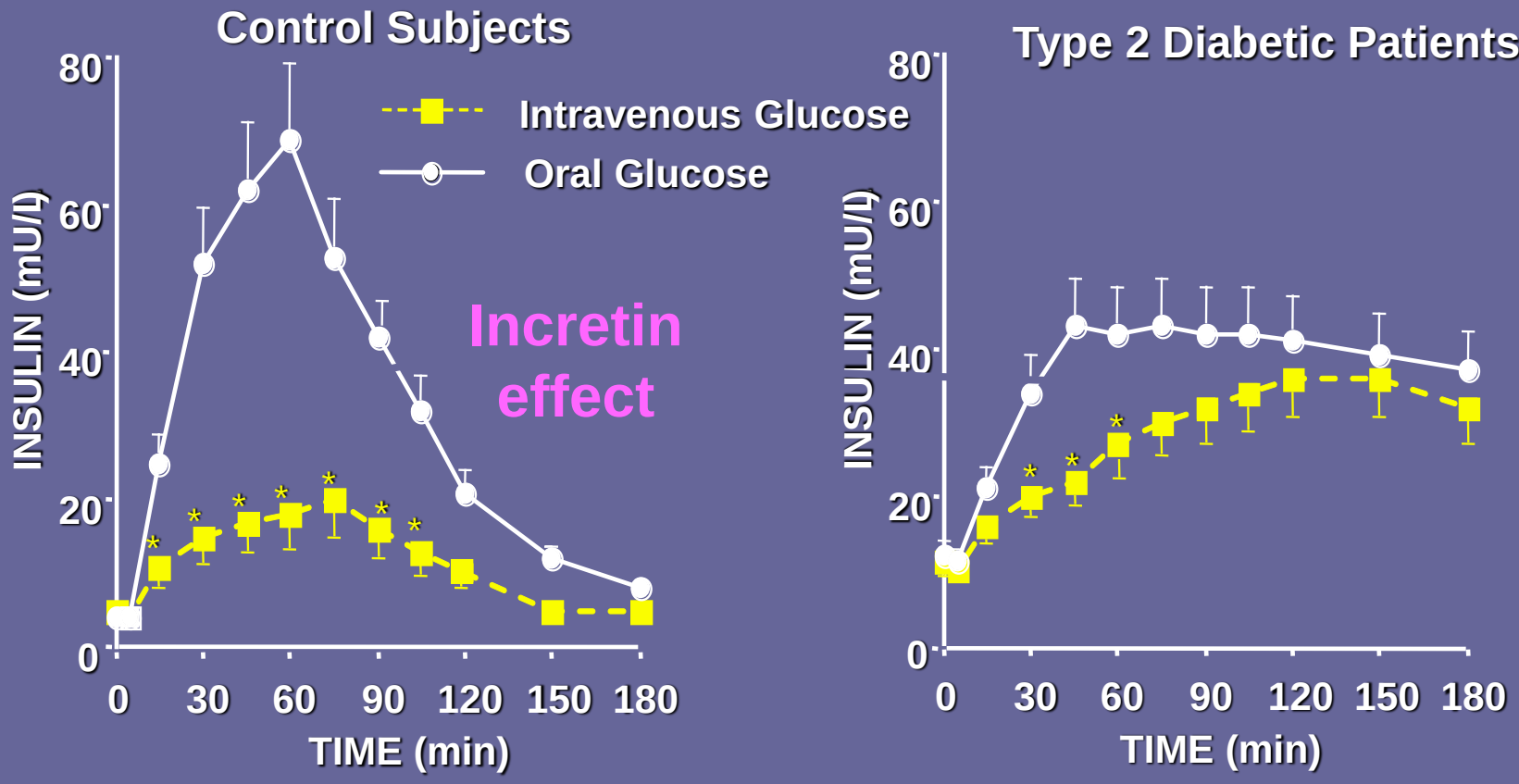

small intestine
absorbed glucose in circulation stimulates insulin secretion by pancreatic beta cells
glucose in lumen of intestine stimulates secretion of incretins
+
beta cell
incretins enhance glucose-dependent insulin secretion
insulin

The Incretin Effect



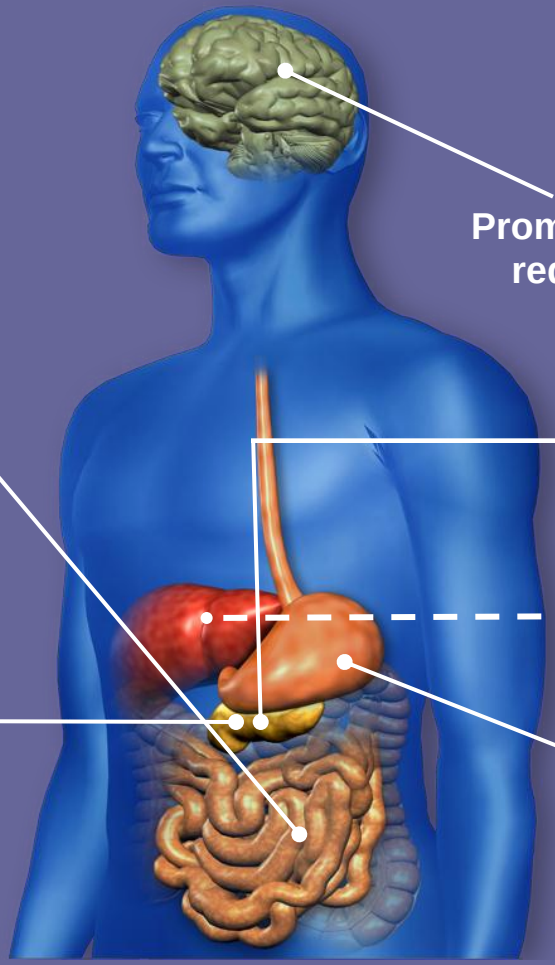
Chahal H, et al. *QJM*. 2007;100:671-677.

Reduced Incretin Effect in Type 2 Diabetic Patients



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

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

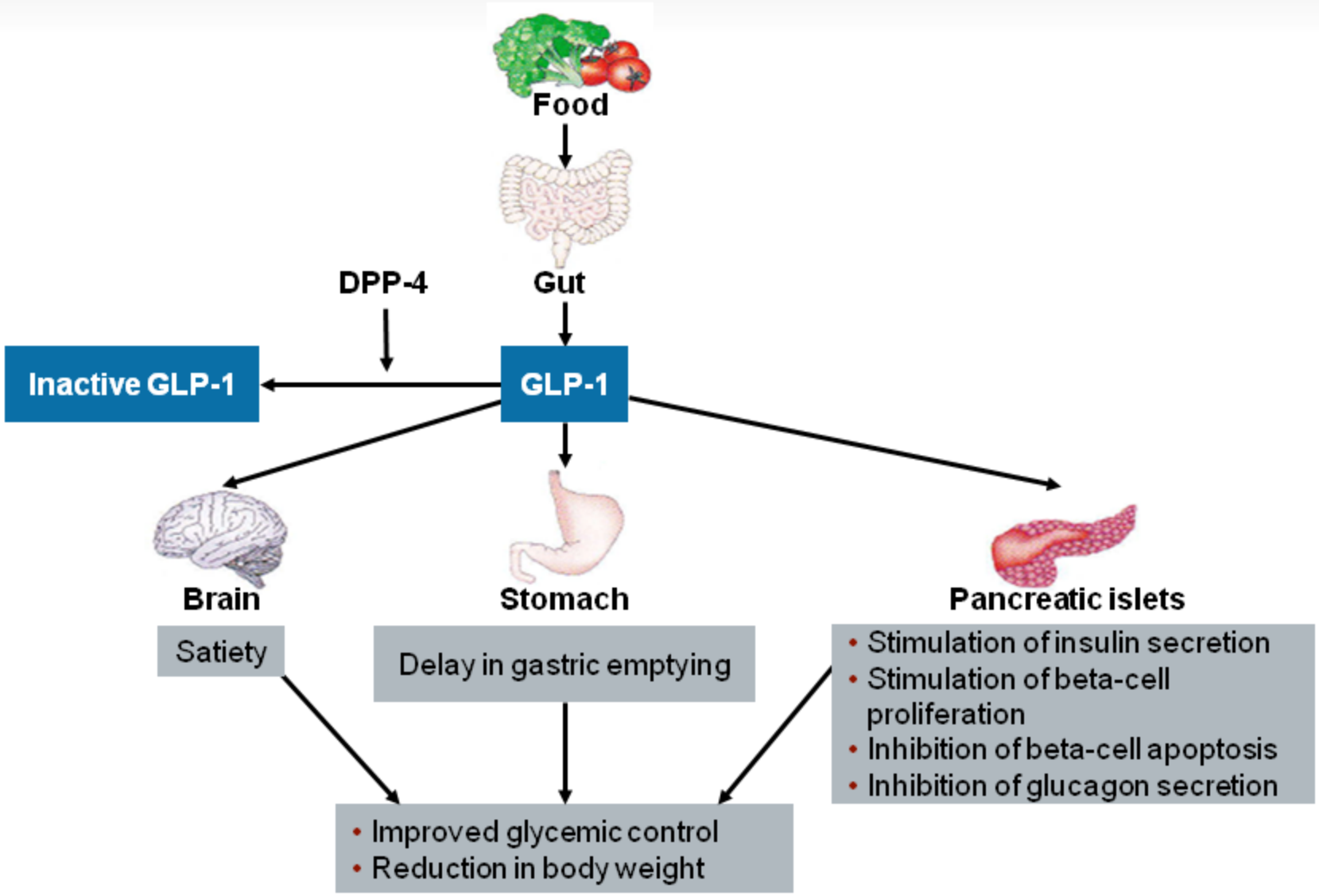
Liver: ↓ Glucagon reduces hepatic glucose output

Beta cells: Enhances glucose-dependent insulin secretion

Stomach: Slows gastric emptying

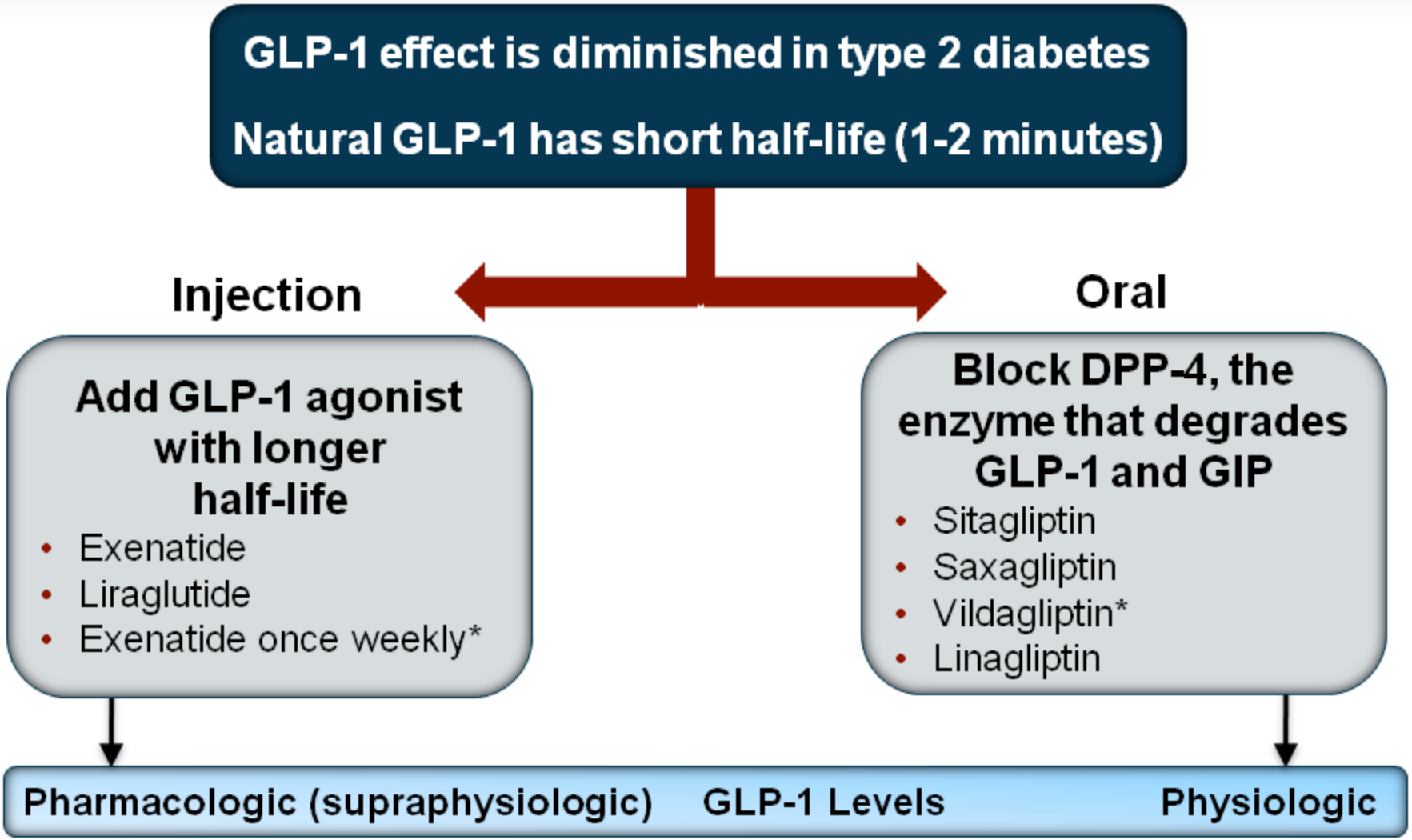
Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

The Incretin Effect



From Ahrén B. *Nat Rev Drug Discov*. 2009;8:369-385. Republished with permission.

Enhancing the Incretin Effect



*

Drucker DJ, et al. *Lancet*. 2006;368:1696-1705.

Incretin-Based Therapies

GLP Receptor Agonists[a]	DPP-4 Inhibitors[b]
Pharmacologic therapy	Physiologic intervention
Extend endogenous GLP-1 action	Block degradation of DPP-4 enzyme
Promote weight loss	Weight neutral
Injectables	Orals

a. Tahrani AA, et al. *Lancet*. 2011;378:182-197.
b. Dicker D. *Diabetes Care*. 2011;34(Suppl 2):S276-S278.

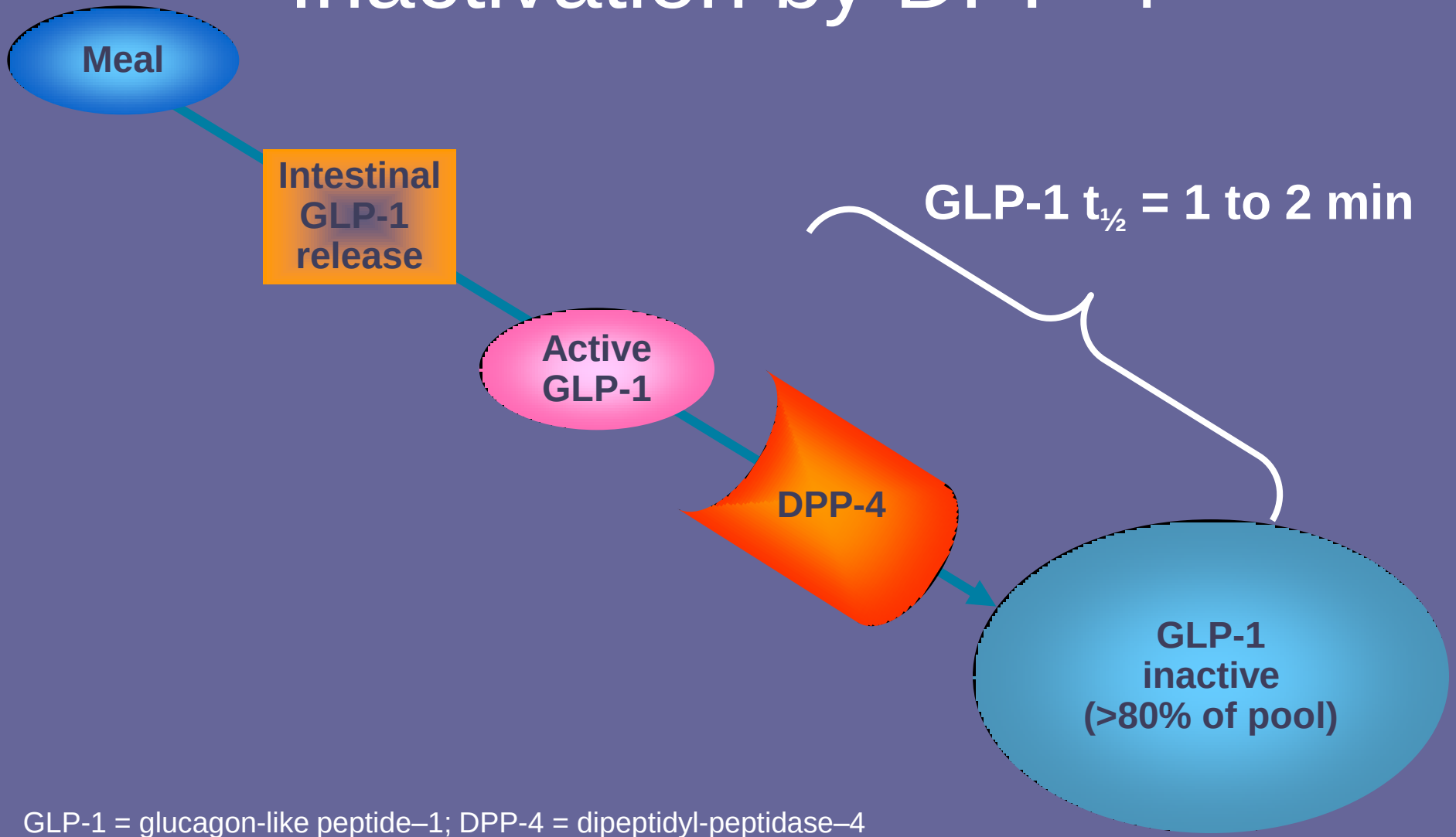
Incretin-Based Therapies

	Drug Name	Clinical Features
GLP-1 Agonists	Exenatide[a]	Injectable, twice a day, weight loss
	Liraglutide[a]	Injectable, once a day, weight loss
DPP-4 Inhibitors	Vildagliptin*[a]	Oral, once a day, weight neutral
	Sitagliptin[b]	Oral, once a day, weight neutral
	Saxagliptin[c]	Oral, once a day, weight neutral
	Linagliptin[d]	Oral, once a day, no renal dose adjustment needed, weight neutral

*The FDA has not approved this medication for use.

a. Drucker DJ, Nauck MA. *Lancet*. 2006;368:1696-1705; b. Pratley RE, et al. *Lancet*. 2010;375:1447-1456; c. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655; d. Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258-267.

GLP-1 Secretion and Inactivation by DPP-4



GLP-1 = glucagon-like peptide–1; DPP-4 = dipeptidyl-peptidase–4

Adapted from Deacon CF, *et al. Diabetes*. 1995;44:1126-1131.

JANUVIA® (sitagliptin): Dosage & Administration

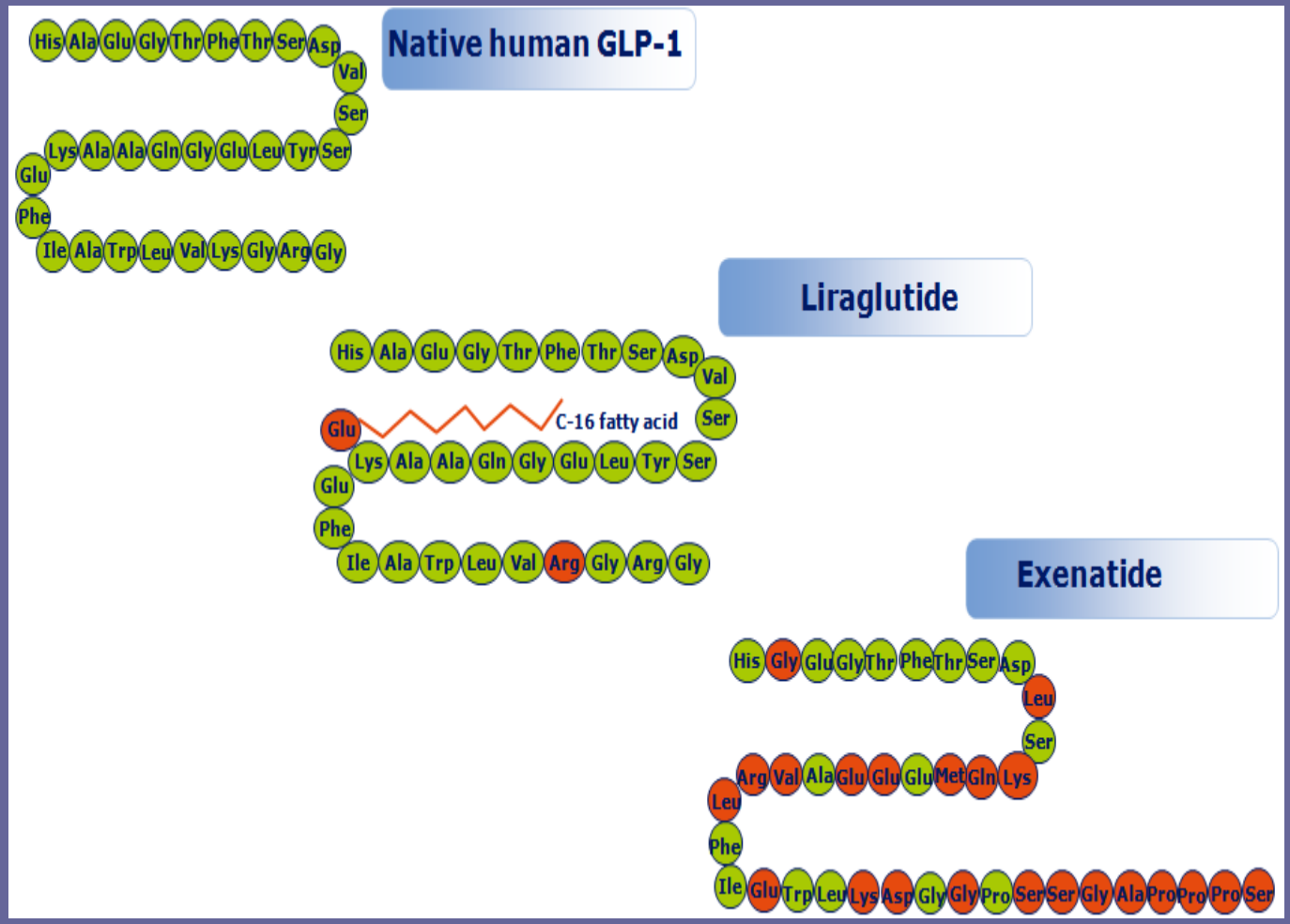
- Usual Dosing for JANUVIA

The recommended dose of JANUVIA is
<u>100 mg once a day</u>
with or without food

Patients With Renal Insufficiency

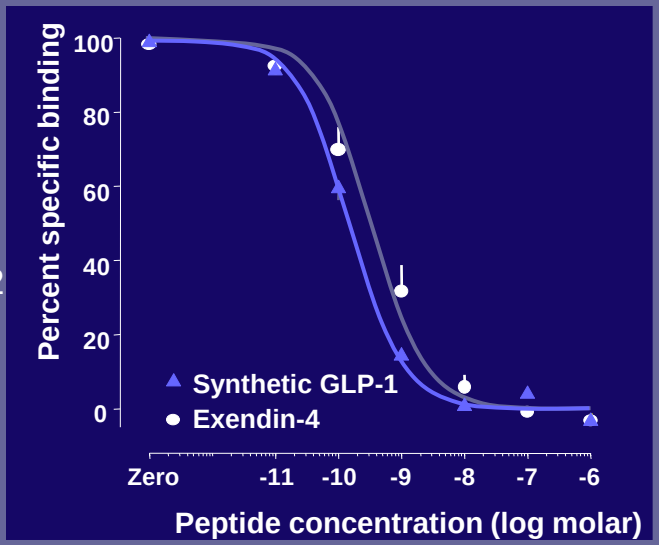
100 mg daily	50 mg daily	25 mg daily
Mild renal insufficiency	Moderate renal insufficiency	Severe or ESRD +/- Dialysis
CrCl ≥ 50 mL/min	CrCl ≥30 to <50 mL/min	CrCl <30 mL/min

Structure of native GLP-1 and two GLP-1 analogues



Development of Exenatide: an incretin mimetic

- Synthetic version of salivary protein found in the Gila monster[1]
- More than 50% overlap with human GLP-1[1]
  - Binds GLP-1 receptors on β-cells (*in vitro*)[2]
  - Resistant to DPP-IV inactivation[3]



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-IV Inactivation[2,3]

- Following injection, exenatide is measurable in plasma for up to 10 hours[4]

[1]Eng J, et al. *J Biol Chem* 1992;267:7402–7405; Adapted from [2]Nielsen LL, et al. *Regul Pept* 2004;117:77–88;
[3]Drucker DJ. *Diabetes Care* 2003;26:2929–2940; [4]Calara F, et al. *Clin Ther* 2005;27:210–215.


© Michael Kern, photographer

Exenatide (Byetta)

- Synthetic exendin-4
- In clinical studies, exenatide exhibited actions that are similar to those of GLP-1:
  - Stimulation of insulin secretion only when blood glucose concentrations are elevated
  - Suppression of postprandial glucagon secretion
  - Slowing of gastric emptying

Exenatide (Byetta)

- Pen prefill- one month's supply
- Given bid, 30-60 minutes prior to meal (250 cal)
- Nausea experienced by almost all initially, typically remits within days
- Start at 5 mcg BID, then increase to 10 mcg BID after 1 month
- Current indication: failing SFU, metformin, or both
- Pancreatitis warning

Lixisenatide* vs Exenatide Twice Daily

Treatment	Change in A1c	Change in Weight	Nausea	Symptomatic Hypoglycemia
Lixisenatide	-0.79%	-2.96 kg	24.5%	2.5%
Exenatide	-0.96%	-3.98 kg	35.1%	7.9%

Add-on therapy in people with type 2 diabetes inadequately controlled on metformin (N = 634)

*Not yet approved by the US FDA or EMA.

Rosenstock J, et al. EASD 2011. Abstract 786.

Exenatide Once Weekly* vs Liraglutide

Treatment	Change in A1c	Change in Weight‡	Nausea
Exenatide once weekly	-1.28%	-2.68 kg	9.3%
Liraglutide	-1.48%	-3.58 kg	20.4%

Difference did not meet the noninferiority criteria

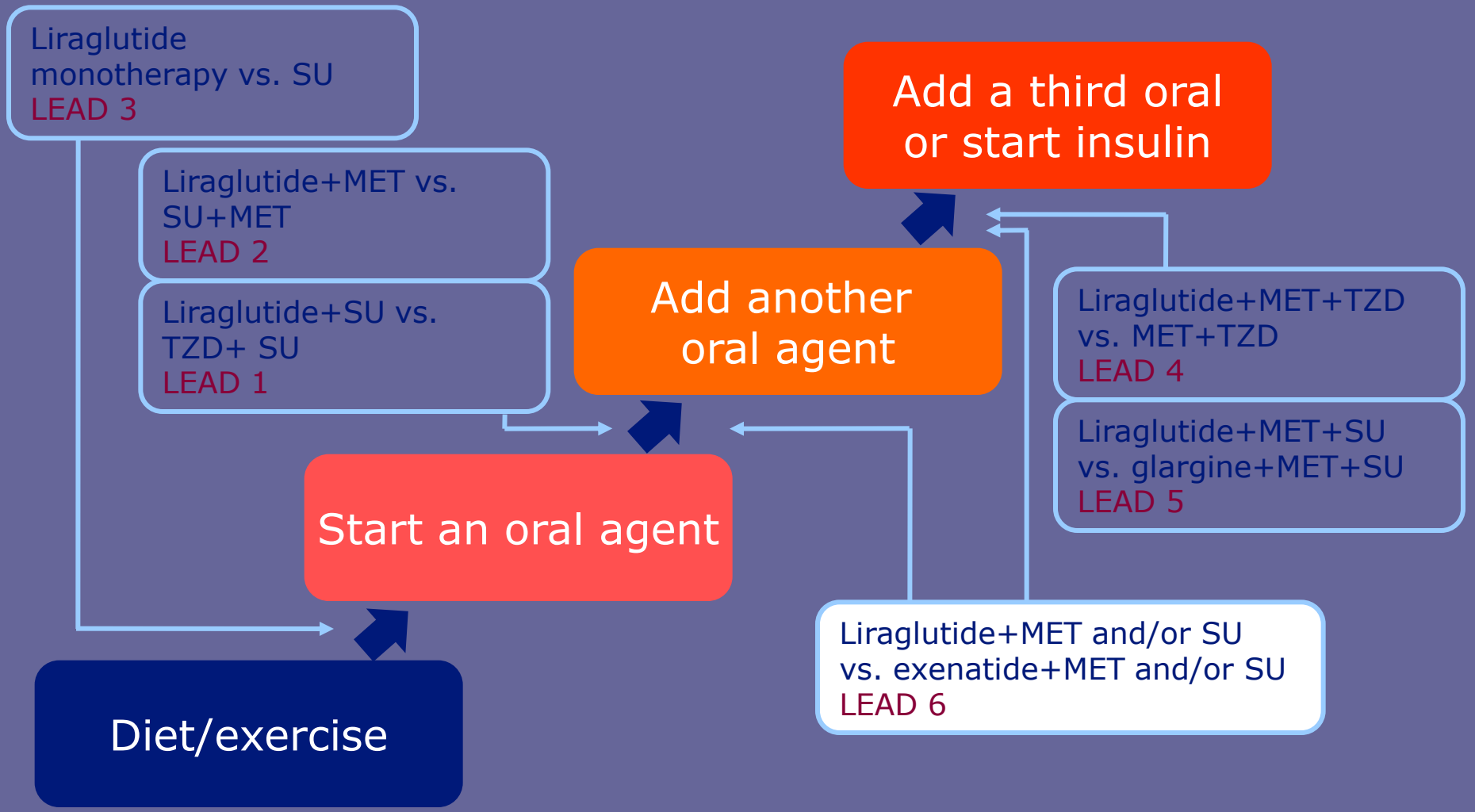
*Not yet approved by the US FDA.
‡Treatment difference: 0.90 kg, 95% confidence interval (0.40, 1.41)
Buse J, et al. EASD 2011. Abstract 75.

Individualizing Therapy

- Longer-acting GLP-1 agonists have a primary effect on fasting plasma glucose.[a,b]
- Short-acting GLP-1 agonists have a predominant effect on postprandial glucose.[b]
- Metformin as first-line therapy if tolerated[c,d]

a. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250.
b. Buse JB, et al. *Lancet*. 2009;374:39-47.
c. Nathan DM, et al. *Diabetes Care*. 2009;32:193-203.
d. Rodbard HW. *Endocr Pract*. 2009;15:540-559.

LEAD covers the continuum of T2D care, compared with standard treatments



LEAD: Liraglutide Effect and Action in Diabetes. All studies 26 weeks' duration (LEAD 3=52 weeks); all RCT; Marre M, *et al. Diabetic Medicine* 2009; 10.1111/j.1464-5491.2009.02666.x (LEAD-1); Nauck MA, *et al. Diabetes Care* 2009; 32; 84–90 (LEAD-2); Garber A, *et al. Lancet* 2008; DOI: 10.1015/S0140-6736(08)61246-5 (LEAD-3); Zinman B, *et al. Diabetologia* 2008; 51 (Suppl. 1): S359 (Abstract 898) (LEAD-4); Russell-Jones *et al. Diabetes* 2008;57(Suppl. 1):A159 (LEAD-5); Blonde L, *et al. Can J Diabetes* 2008; 32 (Suppl.): Abstract 107 (LEAD-6)

Managing Gastrointestinal Effects of GLP-1 Receptor Agonists

- Avoid high-fat meal
- Start at a low dose and titrate as tolerated
- Nausea and vomiting are transient (incidence of nausea: 20%-30% and vomiting: 9%-10% in clinical trials)[a,b]

a. Byetta® (exenatide) full prescribing information. 2010.
b. Victoza® (liraglutide) full prescribing information. 2011.

Safety of Incretin-Based Therapies

- Nonspecificity of inhibition may contribute to the few adverse effects seen with DPP-4 inhibitors.

- Gastrointestinal effects (nausea, vomiting) are most common with GLP-1 receptor agonists, most likely due to slowing of gastric emptying with GLP-1.

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

Risk for Pancreatitis

- Observational reports and clinical trial data suggest an association between use of GLP-1 agonists and acute pancreatitis[a,b]
- Increased risk for pancreatitis in people with type 2 diabetes[c,d]
- Risk for pancreatitis similar with sulfonylurea and metformin use[e]

a. Byetta® (exenatide). Available at: http://pi.lilly.com/us/byetta-pi.pdf
b. Victoza® (liraglutide). Available at: http://www.novo-pi.com/victoza.pdf
c. Noel RA, et al. *Diabetes Care*. 2009;32:834-838.
d. Garg R, et al. *Diabetes Care*. 2010;33:2349-2354.
e. Dore DD, et al. *Curr Med Res Opin*. 2009;25:1019-1027.

Clinical Guidance

- Continued surveillance of persistent abdominal pain, nausea, and vomiting
- Recent association of pancreatitis with DPP-4 inhibitors needs to be studied further.
- People with a history of pancreatitis should not be given incretin-based therapies.

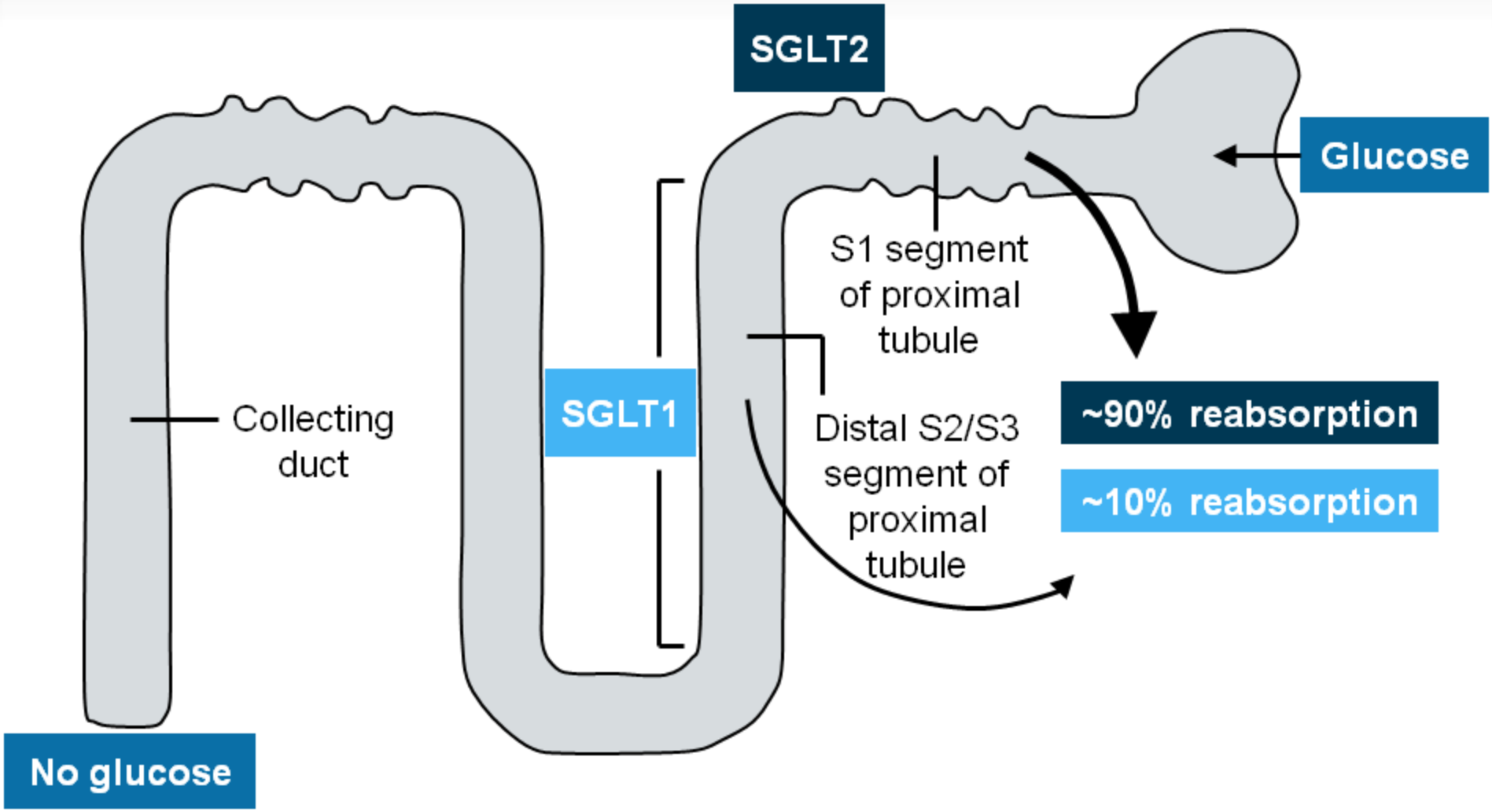
Elashoff M, et al. *Gastroenterol*. 2011;141:150-156.

The Kidney and Glucose Balance

- Insulin-independent mode of action
- The kidney has a role in glucose production, glucose utilization, and glucose filtration and reabsorption

Wright EM, et al. *J Intern Med*. 2007;261:32-43.

Targeting the Kidney



From Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559. Republished with permission.

Mechanism of Action: SGLT2 Inhibitors*

- Inhibit SGLT2 cotransporter
- 50-80 g of glucose/day eliminated in the urine
- Insulin-independent process

*The FDA has not approved these medications for use.

Komoroski B, et al. *Clin Pharmacol Ther*. 2009;85:513-519.
List JF, et al. *Diabetes Care*. 2009;32:650-657.
Wilding JPH, et al. *Diabetes Care*. 2009;32:1656-1662.

Mechanism of Action*

Filtered glucose is reabsorbed by the SGLTs across the membranes of the epithelial cells of the proximal tubule.

- Need good kidney function

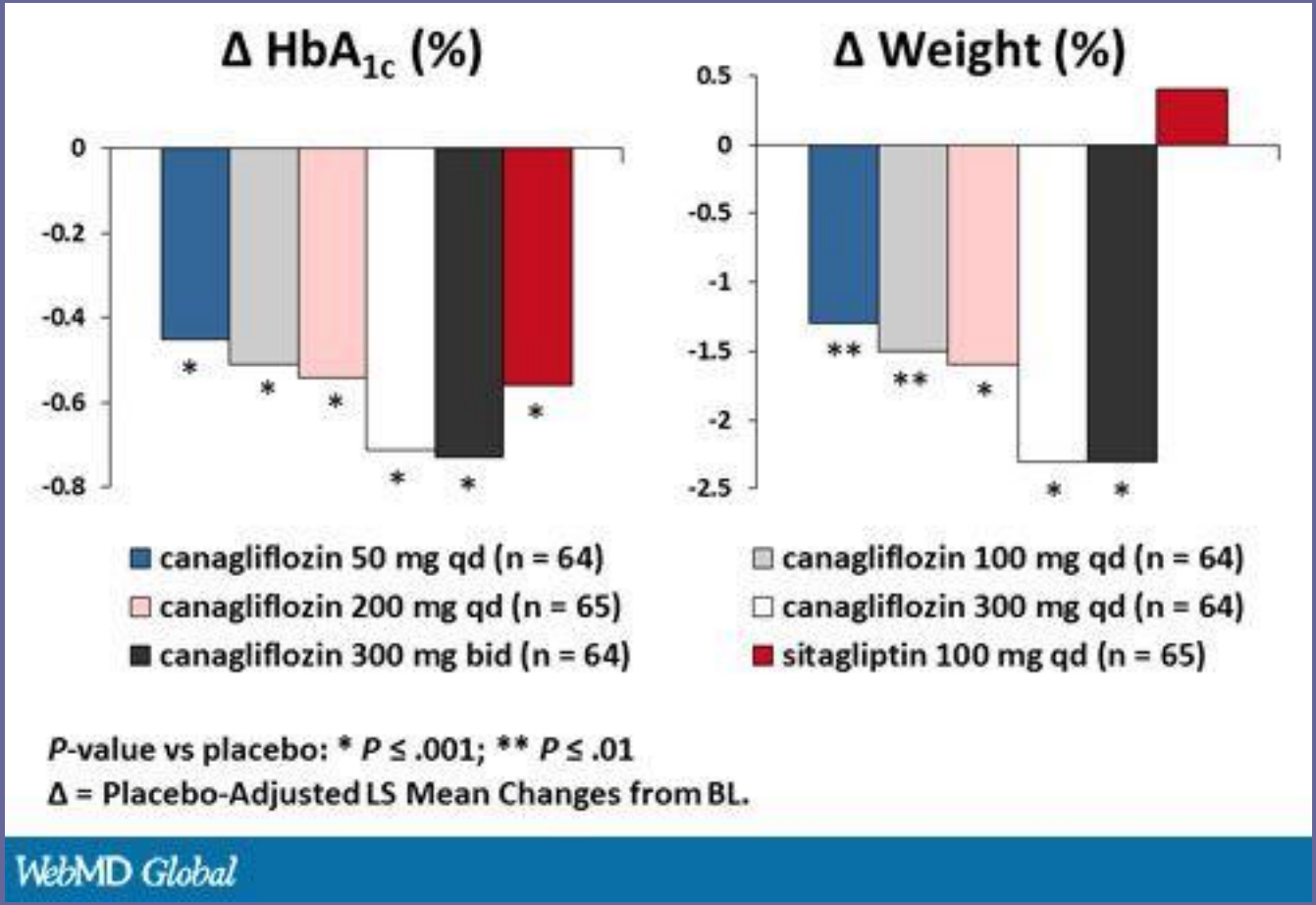
Inhibit SGLT-2 cotransporter

Glucose spills into the urine

*The FDA has not approved these medications for use.

Bakris GL, et al. *Kidney Int*. 2009;75:1272-1277.

T2D Subjects With Inadequate Glycemic Control on Metformin



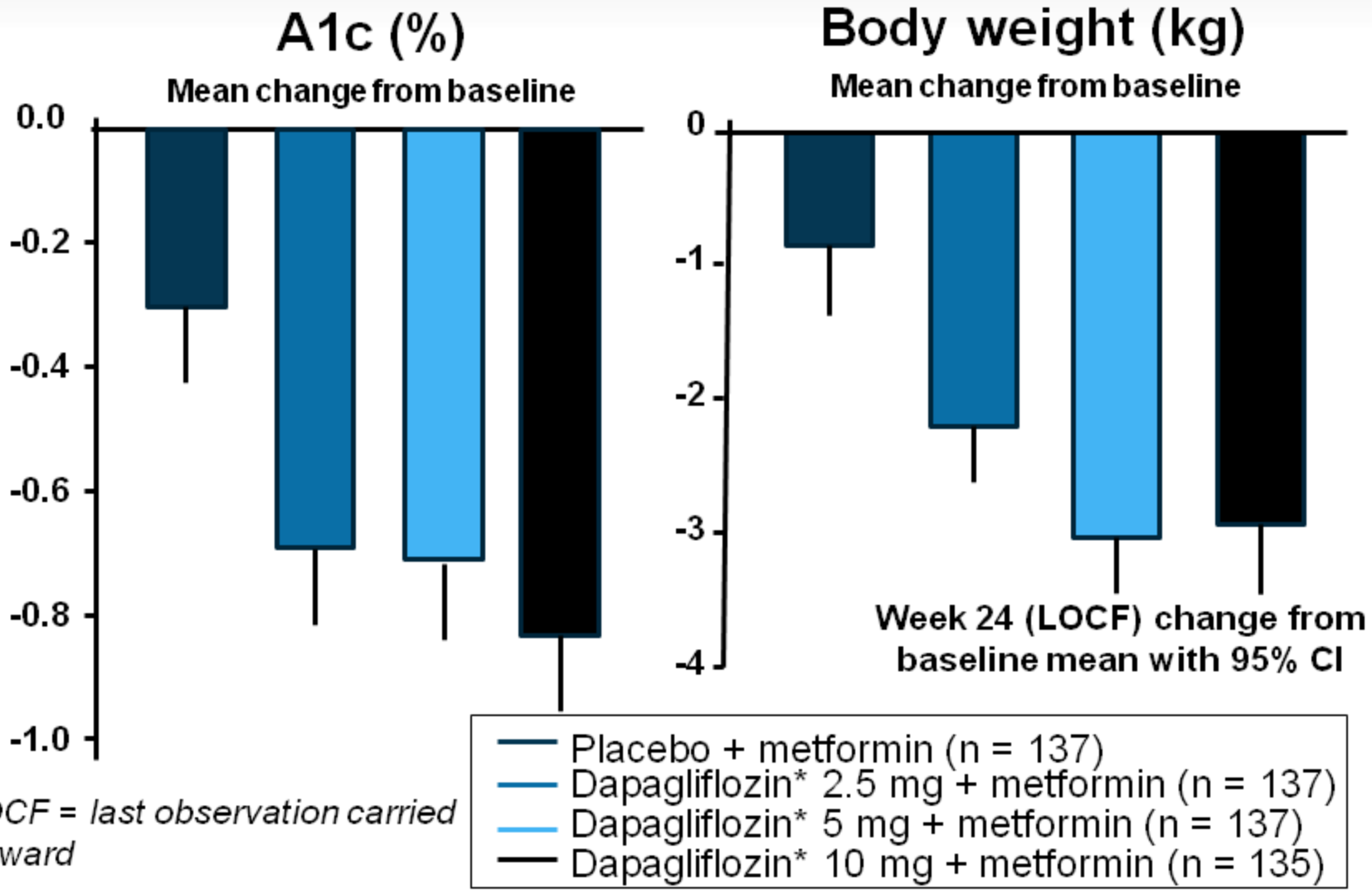
Dapagliflozin* as Add-on to Metformin

- Patients with type 2 diabetes whose disease is inadequately controlled on ≥ 1500 mg metformin
- Average baseline A1c level: 8%
- Multicenter, randomized, double-blind, placebo-controlled trial (n = 546)
- Dapagliflozin 2.5, 5, or 10 mg daily

*The FDA and EMA have not approved this medication for use.

Bailey C, et al. *Lancet*. 2010;375:2223-2233.

Change in A1c and Weight



LOCF = last observation carried forward

*The FDA and EMA have not approved this medication for use.

Bailey C, et al. *Lancet*. 2010;375:2223-2233.

Adverse Events

- No serious hypoglycemic events
- Signs and symptoms of genital and urinary tract infection managed effectively by standard measures
- Genital infections were often managed by the patient

Bailey C, et al. *Lancet*. 2010;375:2223-2233.

Available Basal Insulins

Type of Insulin		Onset (h)	Peak Onset (h)	Duration (h)
Intermediate acting				
	NPH	1 – 3	8	12 - 16
Long acting				
	Glargine	1	No peak	20 - 26
	Detemir			

Insulin glargine and detemir levels may not be therapeutic for 24 hours in all patients.

National Diabetes Information Clearinghouse
http://diabetes.niddk.nih.gov/dm/pubs/medeicines_ez/insert_C.htm

Mayfield JA, White RD. *Am Fam Physician*. 2004;70:489-500.

Comparing Efficacy and Adverse Event Profile of Basal Insulins

- Difficult to show differences in efficacy and effect on A_{1c}
- Insulin detemir has been associated with slightly less weight gain [a]
- Less hypoglycemia and nocturnal hypoglycemia with glargine and detemir [b]

a. Dailey G, et al. *Diabetes Technol Ther*. 2010;12:1019-1027.
b. Rosenstock J, et al. *Diabetes Care*. 2005;28:950-955.

Insulin Degludec*: A Novel Basal Insulin

- Formation or multihexamers results in a half-life of > 24 hours
- Low within-subject variability
- Stable pharmacokinetic profile

*Not yet approved

Heise T, et al. *Diabetes.* 2011;60(Suppl 1):960-P.

PPAR Agonists

PPAR-alpha: Fibrates

PPAR-alpha agonists stimulate lipid oxidation, decrease circulating triglycerides, increase HDL-C, and have anti-atherosclerotic activity.

PPAR-gamma: TZDs

PPAR-gamma agonists stimulate adipocyte differentiation, improve insulin sensitivity, reduce hyperglycemia, and have shown experimental pleiotropic prevention of atherosclerosis.

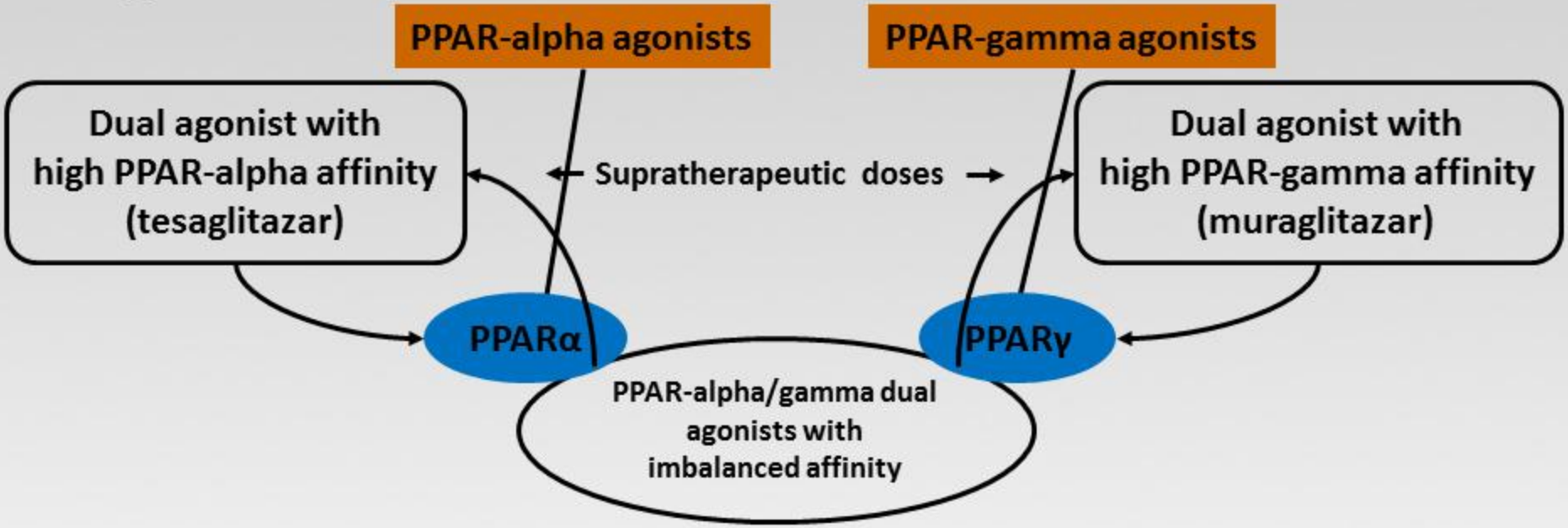
TZDs = thiazolidinediones

Thiazolidinediones: Cons – Safety Issues

- Fluid retention, edema, risk for decompensation/congestive heart failure
- Weight gain
- Bone demineralization and bone fractures
- Potential increased risk for bladder cancer under investigation

Nesto RW, et al. *Circulation*. 2003;108:2941-2948.

The Concept of Dual PPAR-alpha/gamma Agonists

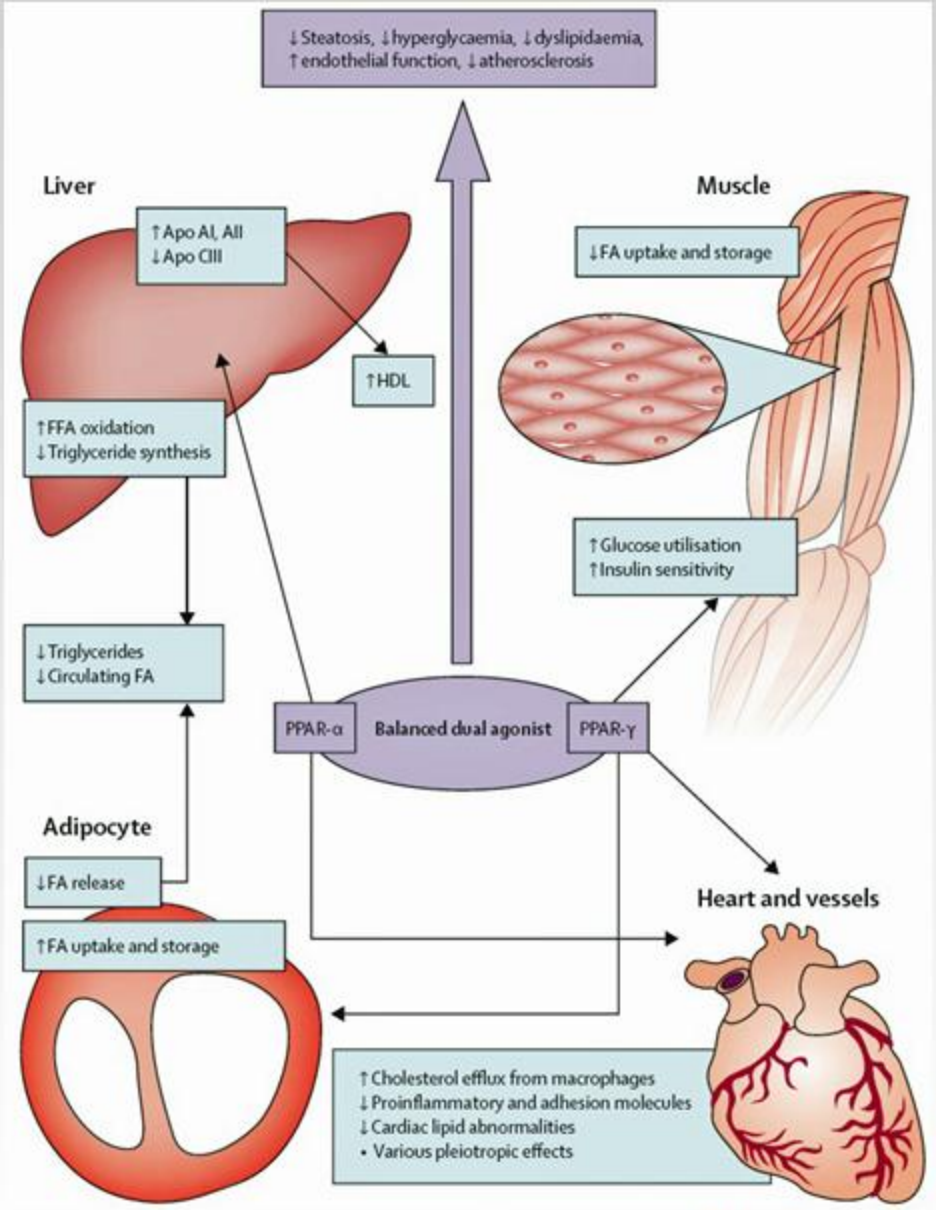


Muraglitazar and tesaglitazar were assessed in clinical trials before discontinuation because of safety concerns, including:

- Increase in serum creatinine level and decrease in glomerular filtration rate (tesaglitazar)
- Increased risk for cardiovascular events (muraglitazar)

Dual PPAR-alpha/gamma Agonists in Development

- Aleglitazar seems to be promising.
- Aleglitazar is a balanced dual PPAR-alpha/gamma agonist designed to optimize glycemic and lipid benefits and minimize weight gain and edema.



Charbonnel B. *Lancet*. 2009;374:96-98.

ALECARDIO: A Study With Aleglitazar in Patients With a Recent Acute Coronary Syndrome and Type 2 Diabetes Mellitus

- A double-blind, parallel, 2-arm study to evaluate the potential to reduce cardiovascular risk and evaluate the tolerability and long-term safety profile of aleglitazar compared with placebo in addition to standard care
- Patients with recent acute coronary syndrome and type 2 diabetes
- The study will last until at least 950 events occur, but time on study treatment will be at least 2.5 years
- The target sample size is 6000-7000 patients

Closing Comments

- Treatment of type 2 diabetes remains increasingly complex but the emphasis moving forward should be on individualization of therapy and on the use and development of safer and better-tolerated drugs

- Growing role of incretin-based therapies:
  - Pathophysiology of type 2 diabetes
  - Cardiovascular risk reduction?
  - Beta-cell preservation
  - Weight reduction or neutrality

Thanks…