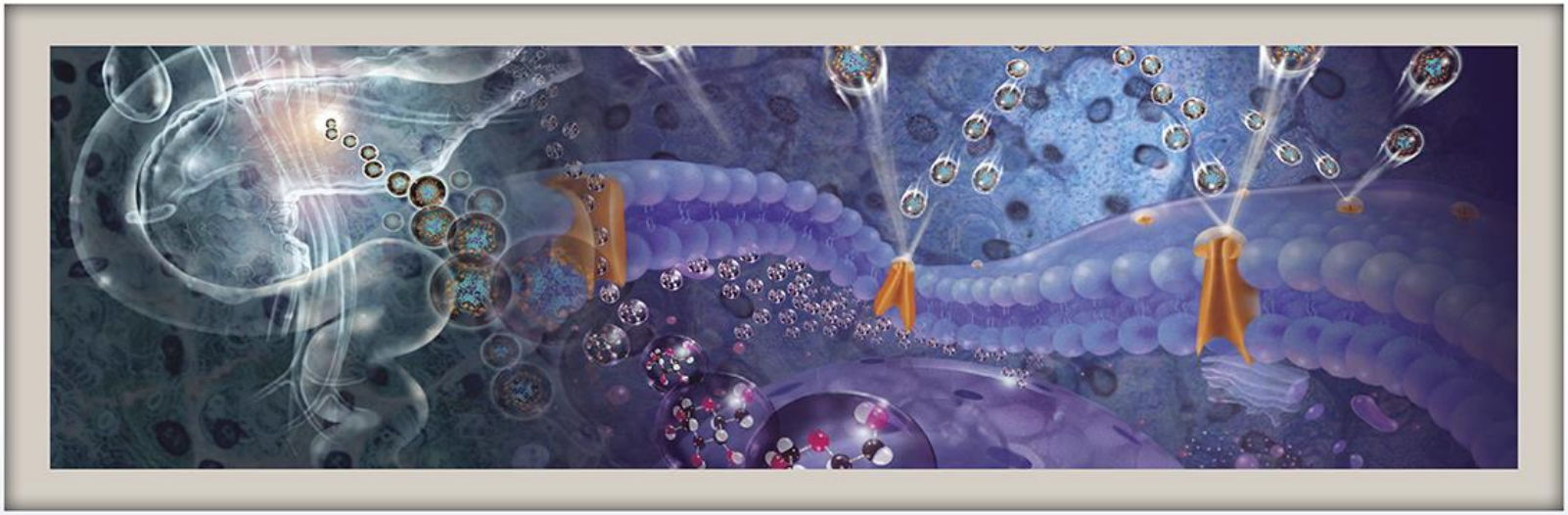
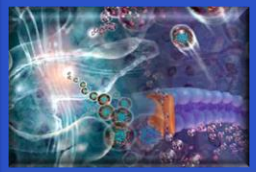
NATIONAL EXPERTS ILLUMINATE, ANALYZE, AND DISCUSS

New Frontiers *and* Advances in Oral Therapy *for* Type 2 Diabetes





آ قای 52ساله بدلیل پرنوشی وپرادراری مراجعه کرده است
پس از بررسی آزمایشات زیر

FBS =354

TG=1500

CHLESTROL= 370

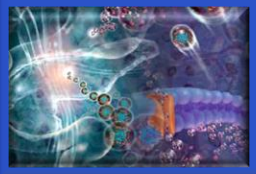
TSH =28

HbA1C=12

CBC=NORMAL

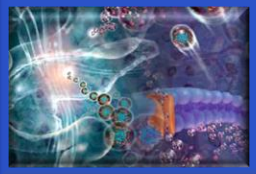
BMI=38

چه بررسی توصیه ایی میکنید



- خانمی 30 ساله بدلیل سفرمکه وبدون علایم بررسی زیر انجام گرفت
- FBS =240
- TG =400
- CHLESTROL=240
- LDL=170
- BMI=39
- BP=1890
- مقاوم به درمان دارویی خوراکی است

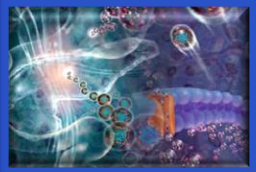
- چرا؟



Case Study

- 67-year-old woman with DM-2, hypertension, obesity, rheumatoid arthritis and COPD presents with A1c of 7.6%. Her BMI is 34.2 and she is looking to lose weight. She tried metformin previously but did not tolerate due to side effects.

- Candidate for DPP-IV monotherapy
- Alternatives: α-glucosidase inhibitor
- Other options



Case Study

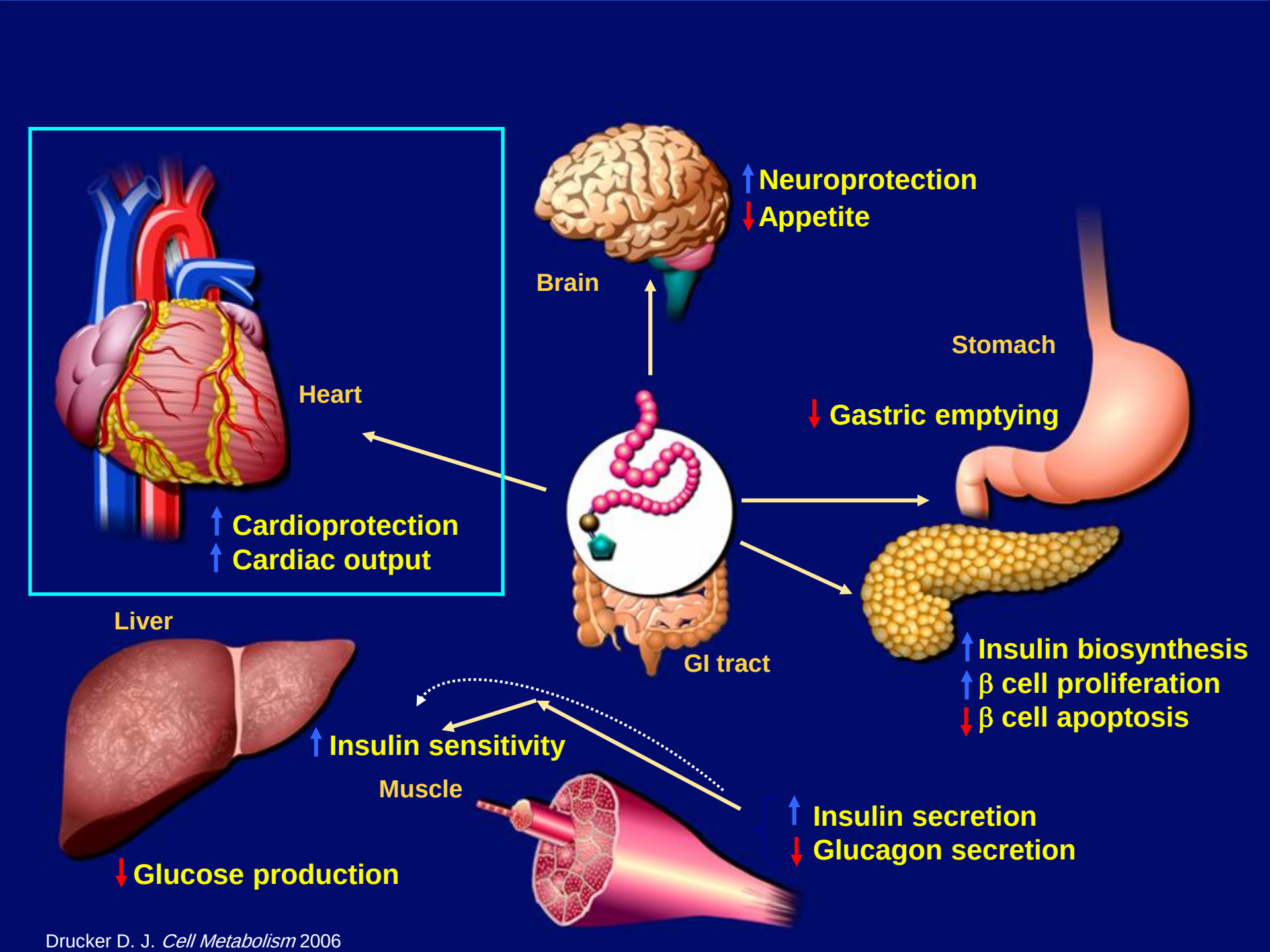
- 82-year-old man with hypertension, hypercholesterolemia, ischemic cardiomyopathy and NYHA class III heart failure presents with a newly diagnosed DM-2 and A1c of 7.4%.

- Candidate for DPP-IV monotherapy
- Alternatives: α-glucosidase inhibitor
- Other options

GLP-1 Analogues: Exenatide

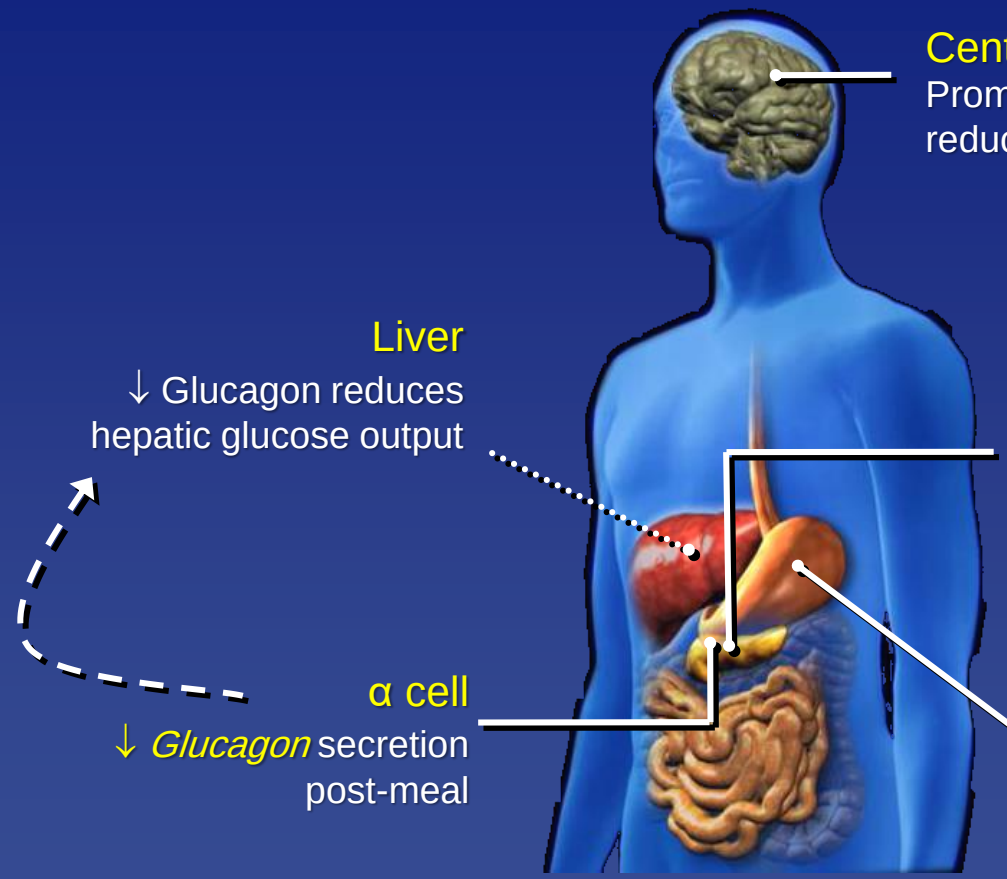
- Naturally occurring peptide from the saliva of the Gila Monster.

- **PK:**
  - Injectable, SC
  - Resistant to DPP4 inactivation
  - Plasma T ½ of 10 hrs; Renal clearance
- **Therapeutic dose:** 5-10 mcg twice daily before meals
- **Adverse effects:** nausea, vomiting, diarrhea, weight loss; necrotizing and hemorrhagic pancreatitis.
- **Contraindications:** severe renal impairment (creatinine clearance <30 mL/min) or ESRD
- Safety in pregnancy not studied



Drucker D. J. *Cell Metabolism* 2006

Summary of GLP-1—Effects in Humans



Central nervous system
Promotes satiety and reduction of appetite

Liver
↓ Glucagon reduces hepatic glucose output

β cell
Enhances secretion of *glucose-dependent insulin*

Potential increase in β-cell mass

α cell
↓ *Glucagon* secretion post-meal

Stomach
Regulates gastric emptying

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

Newer GLP-1 Analogues

- **LIRAGLUTIDE:**

- Approved by the European Medicines Agency (EMEA) on July 2009; FDA in 2015
- Adjuctive therapy

- Longer T ½ (11 hrs): Once daily, SC

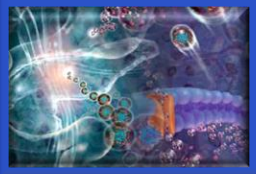
- 0.6 mg SC OD for 1 week initially
  then increase to 1.2 mg OD &
  can increase to 1.8 mg OD

- Injection site and time of administration can be changed without dose adjustment & independent of meals
- Good glycaemic control & wt loss
- S/E- Nausea, Diarrhea, Vomiting, Diarrhea, Constipation
- Hypoglycemia with other therapy
- **Black box warning for thyroid cancer**
  MEN syndrome

- Approved for OBESITY by the FDA December 23, 2014

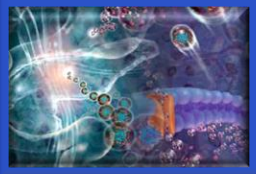
ALBIGLUTIDE

- FDA approved in 2014
- GLP-1 dimer fused with albumin
- T ½ of 6-7 days
- 30-50 mg SC once weekly
- No dose adjustments in renal failure
- Black Box Warning– Risk of thyroid C-cell tumors
- Cautions
  - MEN-2
  - Acute pancreatitis
  - Hypersensitivity
  - Hypoglycemia



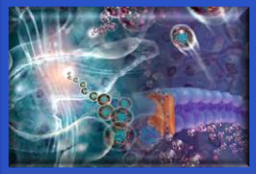
Types Of Diabetes

- Type 1 (Juvenile-Onset)
- Type 2 (Adult-Onset)
- Other types including:
  - Gestational diabetes
  - MODY (maturity onset diabetes of the young)
  - LADA (latent auto-immune diabetes of adults)
  - Others



Cause of Type 1 DM

- Auto-immune destruction of insulin-producing β-cells in the pancreas



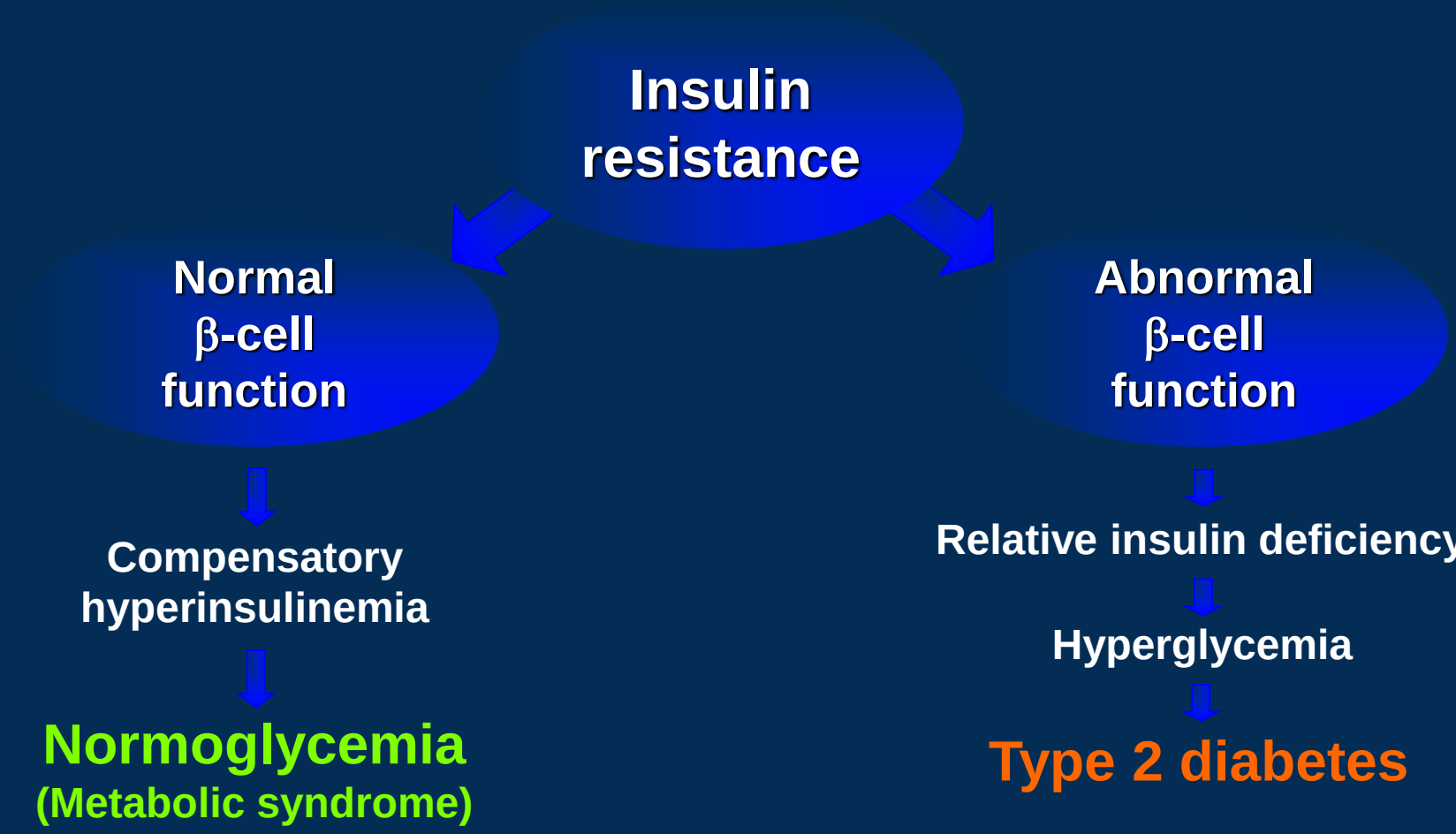
Cause of Type 2 DM

- Insulin resistance (genetics)
  - aggravated by obesity
  - aggravated by lack of exercise
- "Exhaustion" of insulin-producing β-cells

Type 2 Diabetes: Insulin Resistance Plus Impaired β-Cell Function

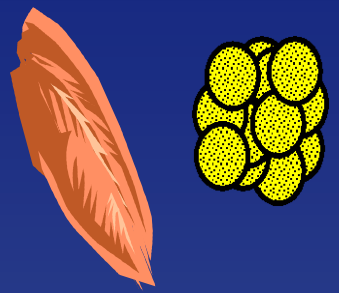
WorldWIDE
Worldwide Initiative for Diabetes Education

Both insulin resistance and β-cell dysfunction are present at the time of diagnosis of type 2 diabetes

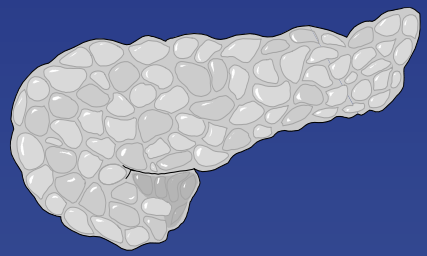


Major Metabolic Defects in Type 2 Diabetes

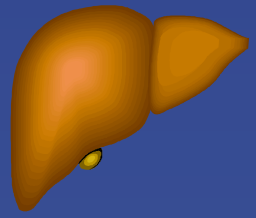
- Peripheral insulin resistance in muscle and fat



- Decreased pancreatic insulin secretion



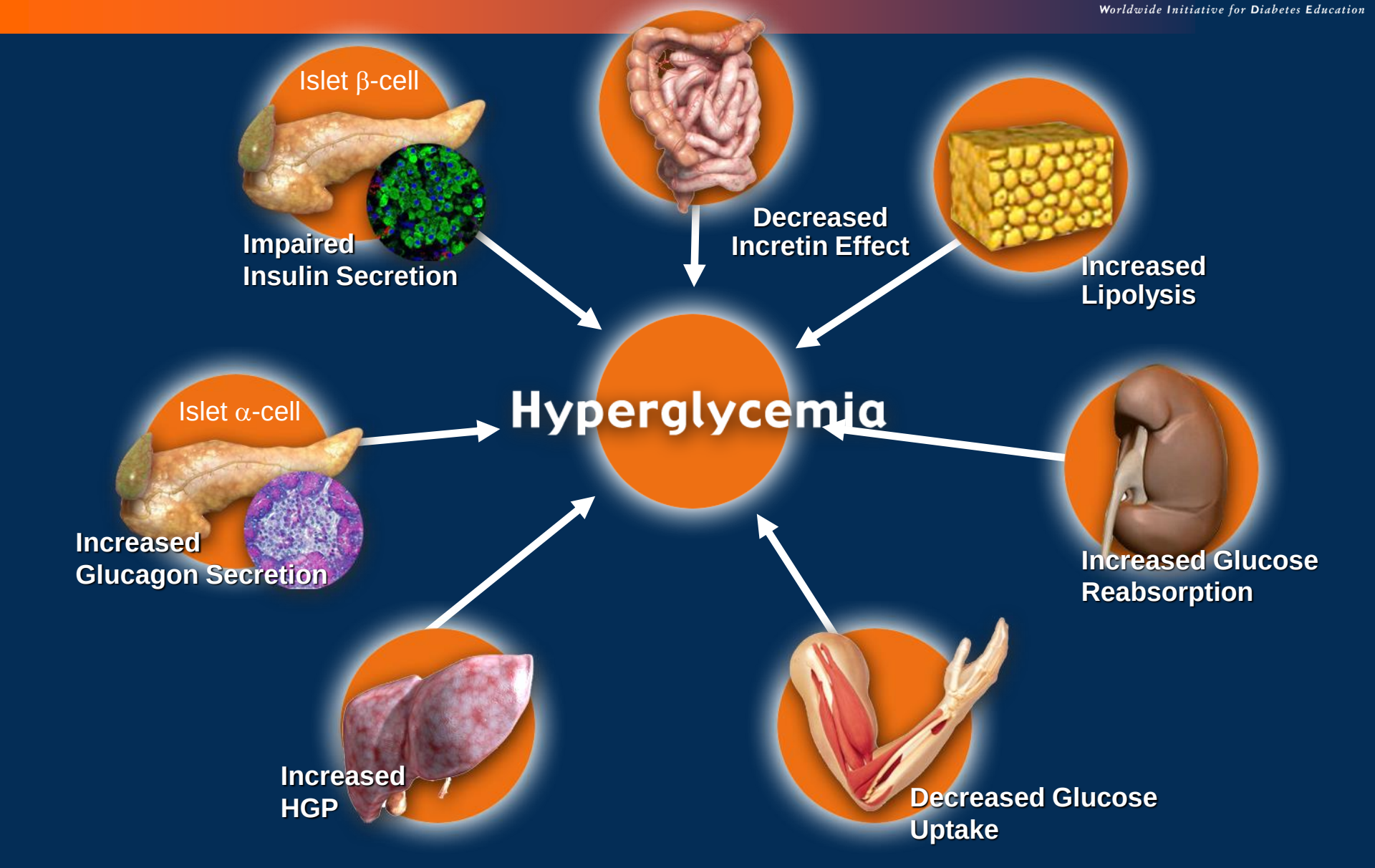
- Increased hepatic glucose output

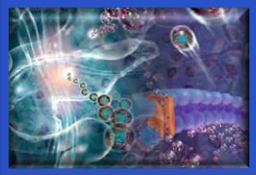


Haffner SM, et al. Diabetes Care, *1999*

The Septicidal Septet

WorldWIDE
Worldwide Initiative for Diabetes Education



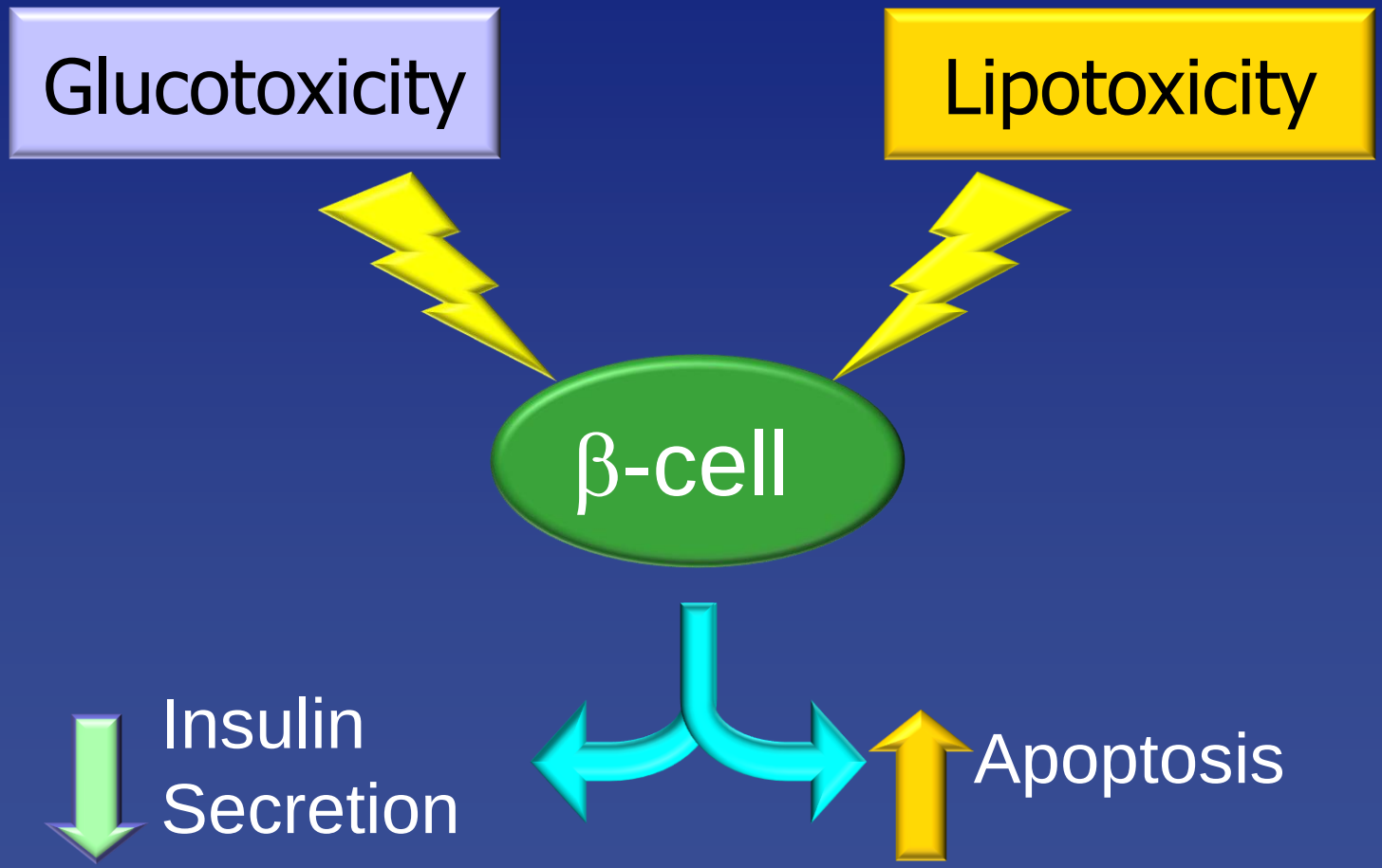


Type 2 Diabetes: Pathogenesis in a Nutshell (cont.)

- Type 2 diabetes has been considered a PROGRESSIVE disease
  - β-cell dysfunction first leads to impaired glucose tolerance, which in some individuals progresses to type 2 diabetes
  - β-cell dysfunction starts long before blood glucose rises and worsens after diabetes develops
- Hyperglycemia may cause additional defects in insulin secretion and insulin action (glucotoxicity)

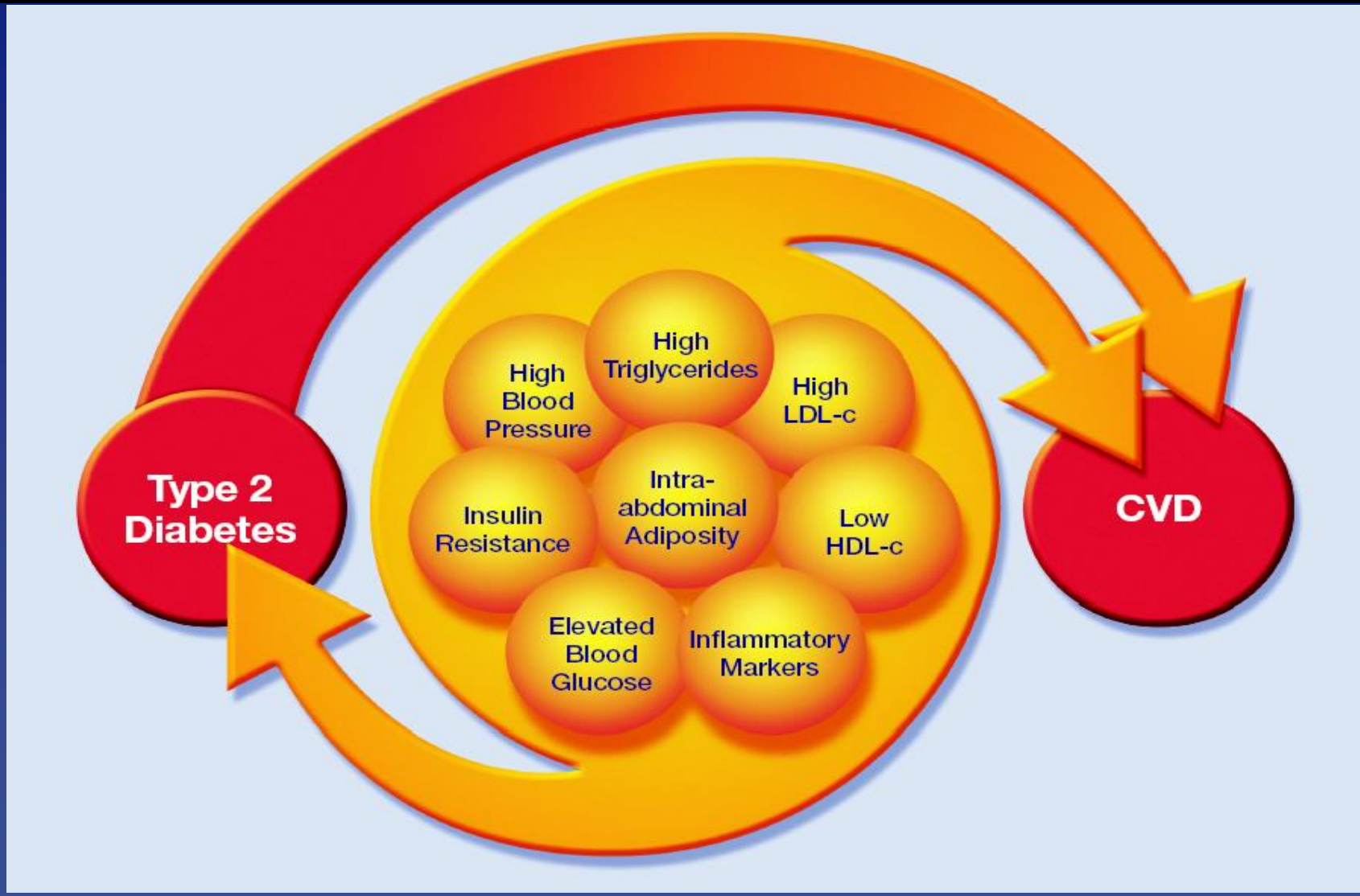
Buchanan TA. *Clin Ther*. 2003;25(suppl B):B32-B46.
DeFronzo RA. *Med Clin North Am*. 2004;88:787-835.
Kahn SE. *J Clin Endocrinol Metab*. 2001;86:4047-4058.

Potential Causes for Declining Insulin Secretion



Prentki M et al. *Diabetes.* 2002;51(suppl 3):s405-s413.

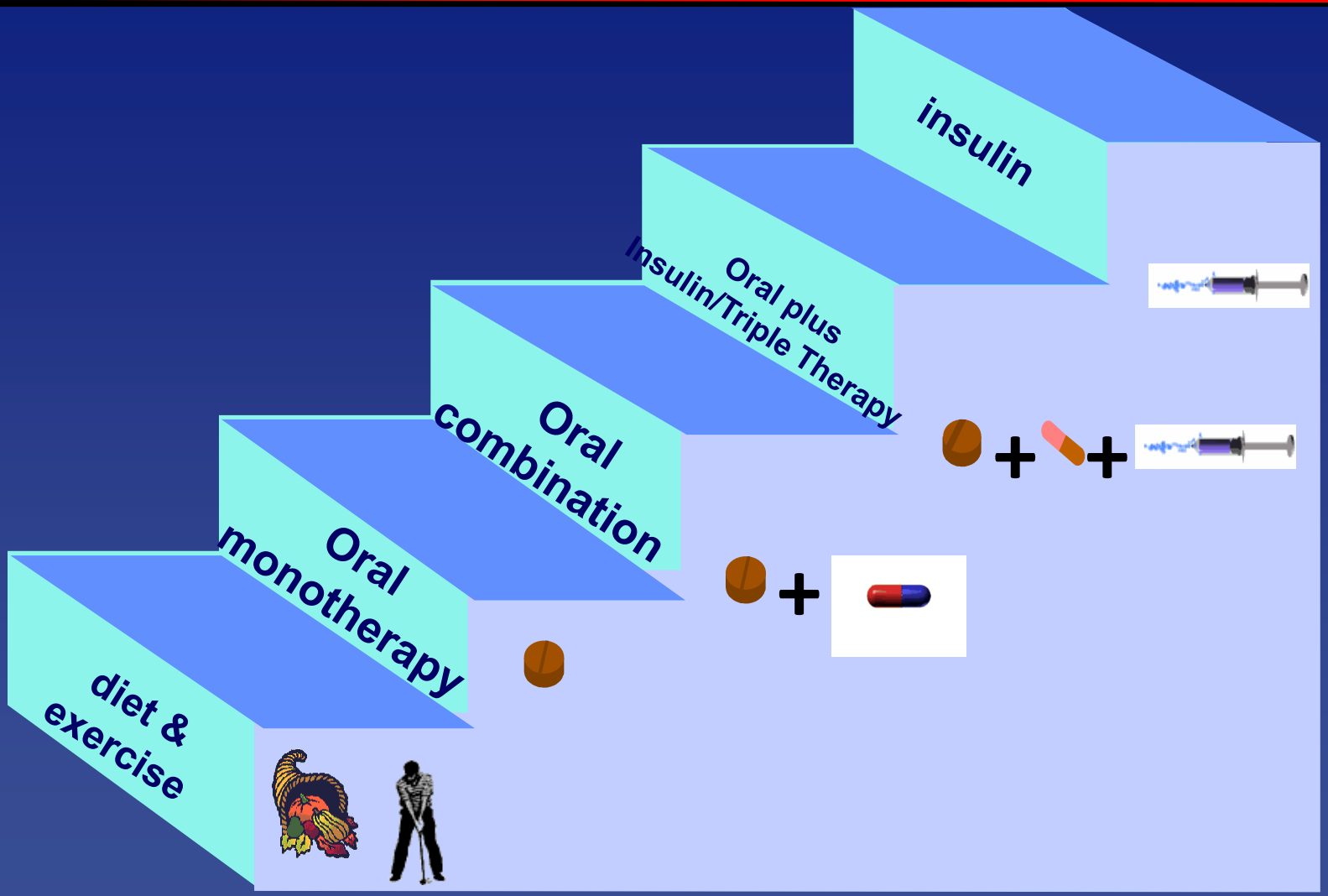
Global Cardiometabolic Risk*



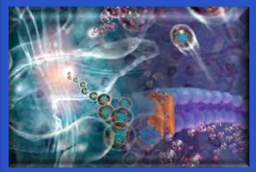
Gelfand EV *et al*, 2006; Vasudevan AR *et al*, 2005

* working definition

Basic Steps in the Management of Type 2 Diabetes

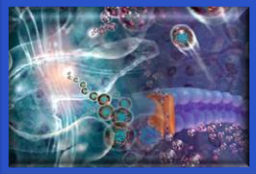


FEROZSONS LABORATORIES LIMITED



Oral Drugs for Rx DM2

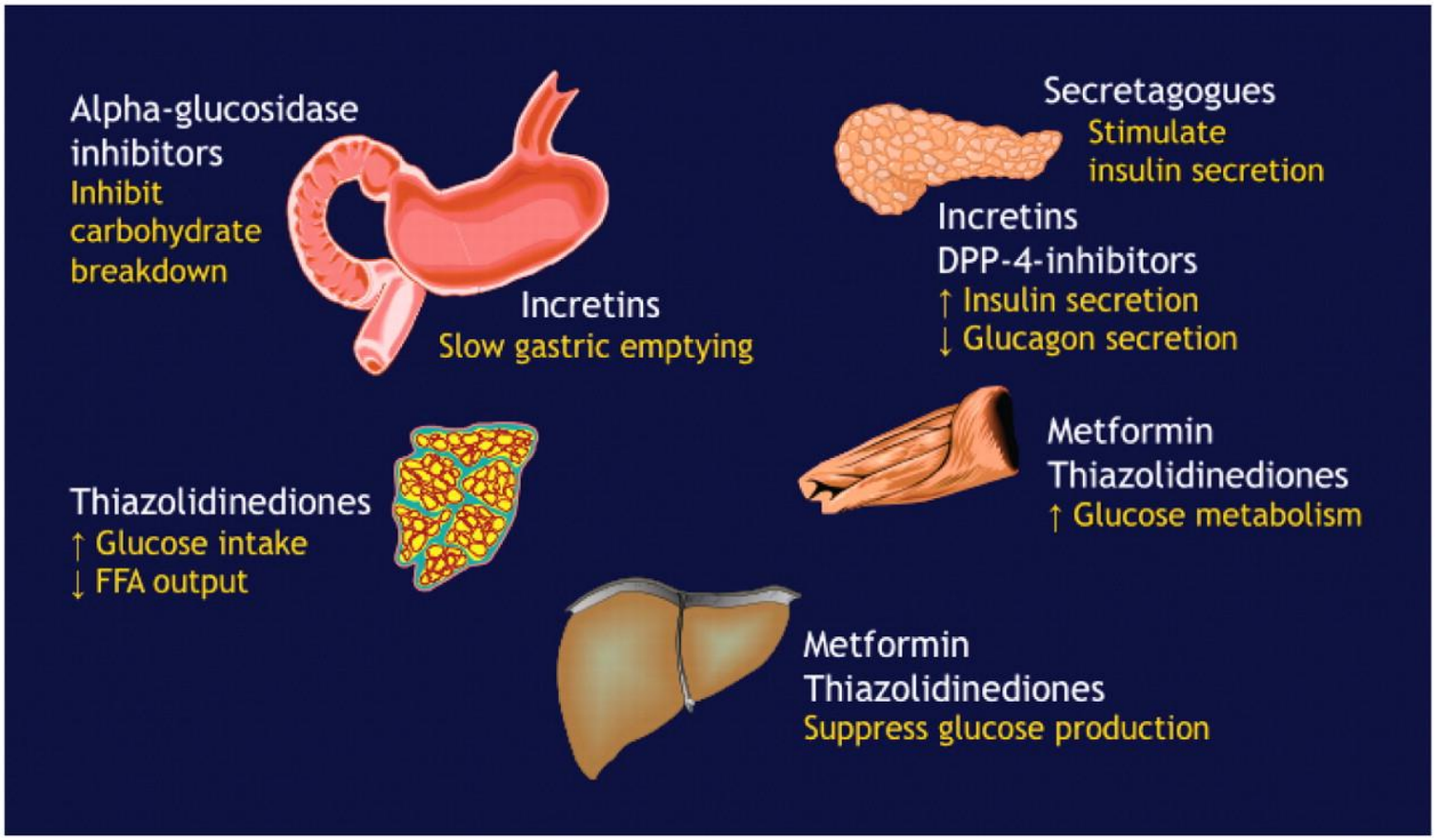
- Metformin (glucophage)
- Sulfonylureas (glyburide, glipizide, glimepiride)
- Thiazolidinediones (actos, avandia)
- DPP-IV inhibitors (januvia, onglyza)
- Glucosidase inhibitors (acarbose, miglitol)
- Others: colesevelam ; bromocriptine



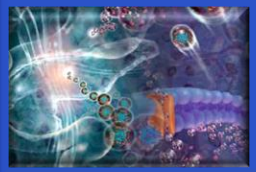
ADOPT—Implications

- Current oral agent therapy is associated with significant adverse events
- Weight gain, edema, lactic acidosis, GI side effects, and hypoglycemia are significant problems
- GLP-1 agonists cause significant weight loss
- DPP-4 inhibitors have no associated weight gain or complications

Mechanisms of Action of Pharmacologic Agents for Diabetes



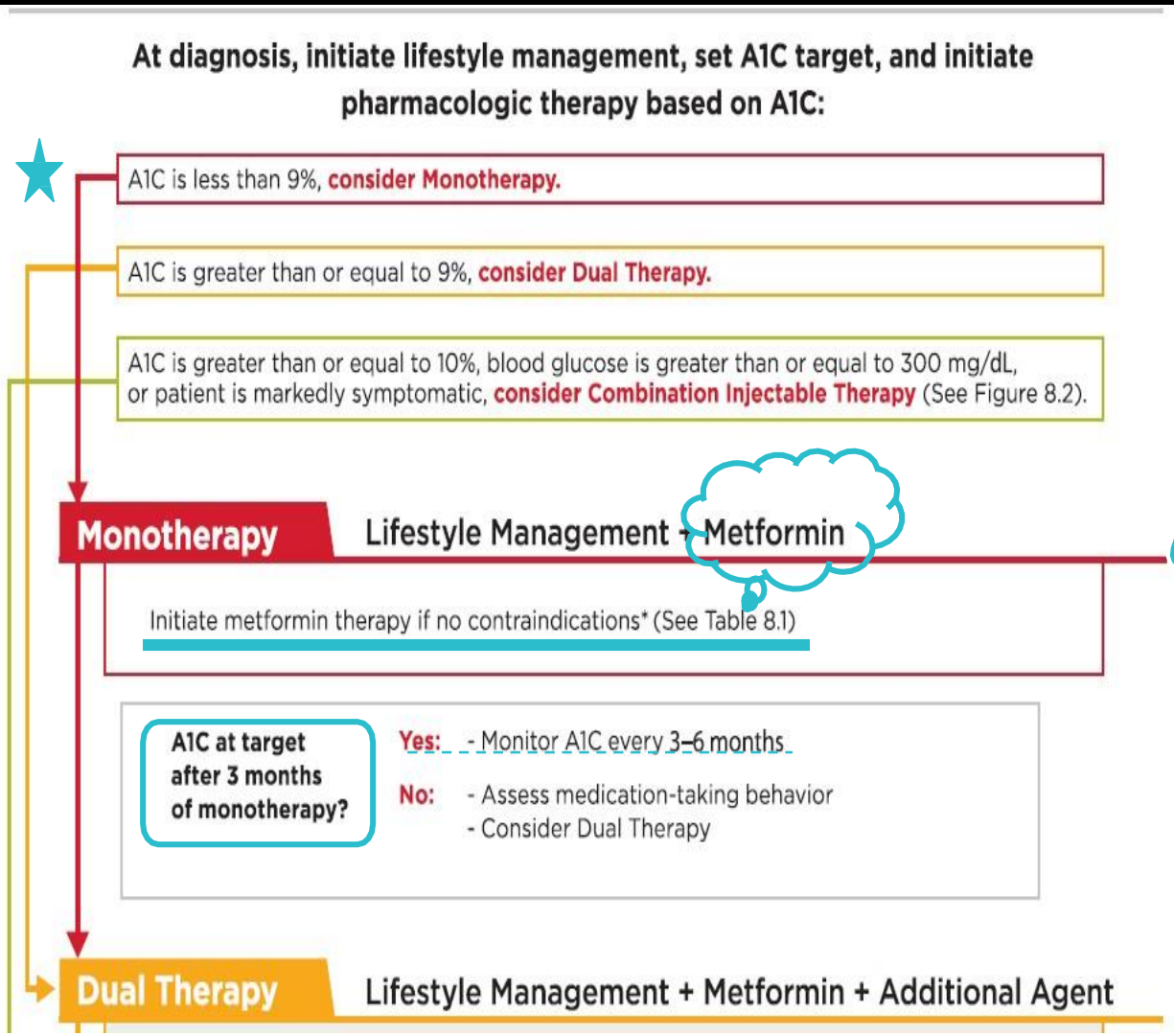
Improving Outcomes in Patients With Type 2 Diabetes Mellitus: Practical Solutions for Clinical Challenges
James R. Gavin, III, MD, PhD; Mark W. Stolar, MD; Jeffrey S. Freeman, DO; Craig W. Spellman, DO, PhD
JAOA • Vol 110 • No 5suppl6 • May 2010 • 2-14



Metformin - Drug Profile

Advantages	No hypoglycemia Weight loss Cardiovascular benefit Reduces LDL-C (approx 10 mg/dL), reduces TG
Disadvantages	Diarrhea is common Contraindicated in renal impairment, liver failure, advanced cardiac failure Risk of lactic acidosis not increased in meta-analyses and systematic reviews
Concomitant use with other drugs	Can be used as monotherapy and with all classes including insulin

Anti-hyperglycemic Therapy in Adults with T2DM (ADA2018)

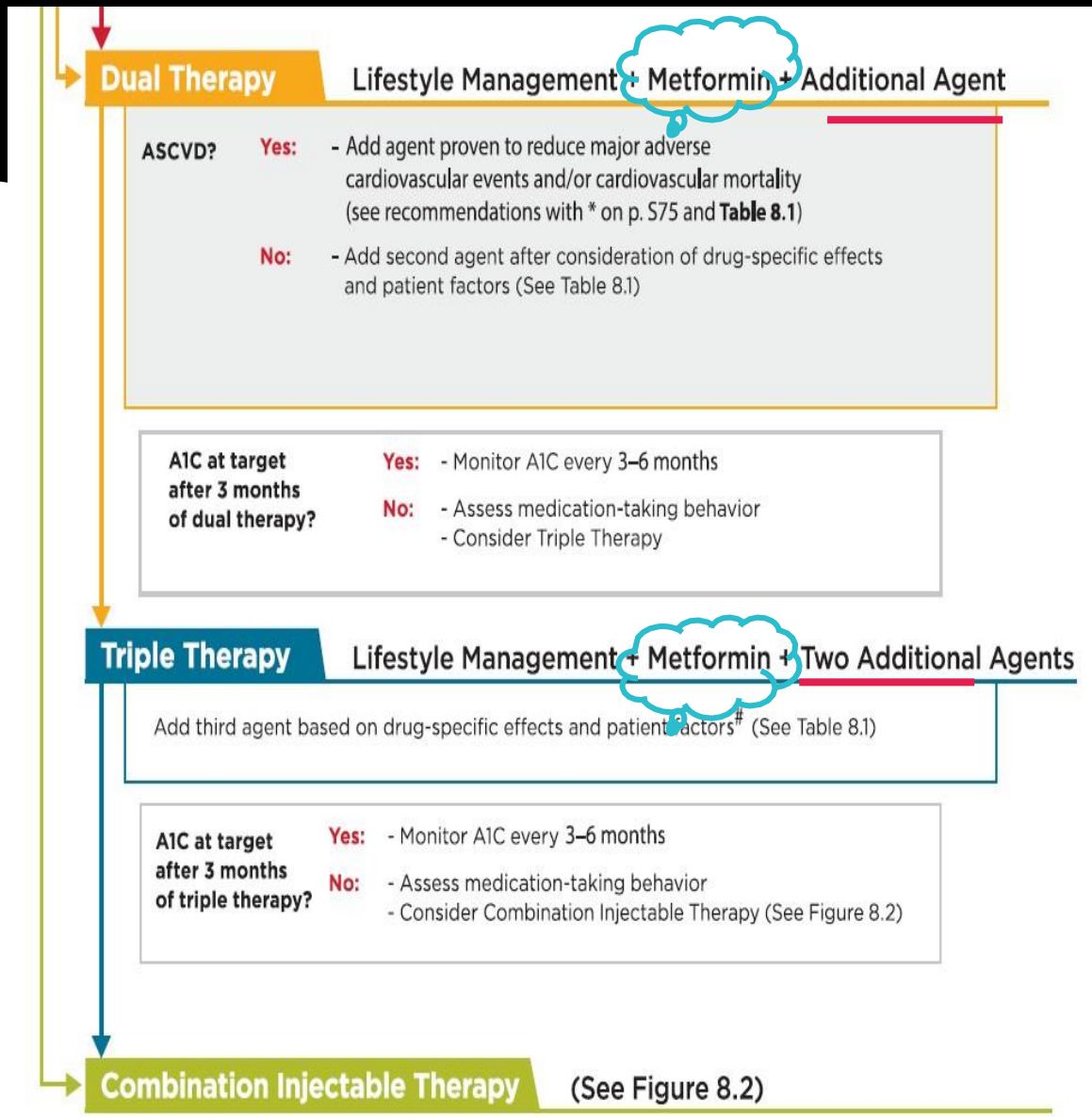


Metformin as First line

:

Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1):

Anti-hyperglycemic Therapy in Adults with T2DM



Add agent to Metformin

Add two agents to Metformin as Triple Therapy

eGFR level (²m1.73mL/min per)	Action
60 ≤	No renal contraindication to metformin Monitor renal fuction annually
45 ≤and 60 >	Continue use Increase monitoring of renal (months 6-3every) function
30 ≤and 45 >	Prescribe metformin with caution Use low dose -flah ro ,50% .g.e) ton oD (esod lamixam no stneitap wen trats nimroftem
30 >	Stop metformin

or

use of metformin based on eGFR

Sitagliptin: Mechanism of Action

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Pancreas

Beta cells

Alpha cells

Glucose-dependent

↑ Insulin (GLP-1and GIP)

↑ Glucose uptake by peripheral tissue

↓ Blood glucose in fasting and postprandial states

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Glucose-dependent

↓ Glucagon (GLP-1)

↓ Hepatic glucose production

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

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

Sitagliptin: Mechanism of Action (cont)

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Pancreas

Beta cells

Alpha cells

Glucose dependent

↑ Insulin (GLP-1and GIP)

↑ Glucose uptake by peripheral tissue

↓ Blood glucose in fasting and postprandial states

Sitagliptin (DPP-4 inhibitor)

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Glucose-dependent

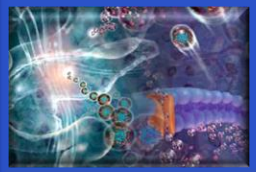
↓ Glucagon (GLP-1)

↓ Hepatic glucose production

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

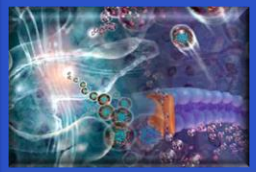
Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the actions of these hormones

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.



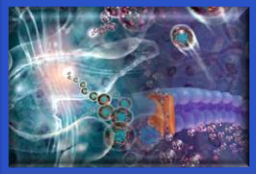
Why DPP-4 Inhibitors?

- Excellent in patients with mild hyperglycemia requiring insulin secretagogue
- No contraindication in heart failure and no risk of edema or lactic acidosis
- Can be used in renal insufficiency without risk of hypoglycemia or lactic acidosis
- No weight gain
- Immediate activity without causing hypoglycemia



DPP4 Inhibitors – Drug Profile

Advantages	Weight neutral Favorable adverse effect profile No hypoglycemia
Disadvantages	Limited track record Nasopharyngitis, upper respiratory infections Rare pancreatitis
Concomitant use with other drugs	Can be used as monotherapy and with SU, TZD, metformin (some have been studied with insulin)



Risks & Benefits

EFFICACY
↓A1c 0.7%
(up to 1.5% if starting A1c higher)

COST
$200 / month*

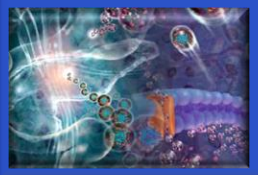
DPP-IV inhibitors

SIDE EFFECTS (common)
- none

SIDE EFFECTS (putative)
- Pancreatitis
- Pharyngitis

CONTRAINDICATIONS
- h/o pancreatitis

* Source – drugstore.com



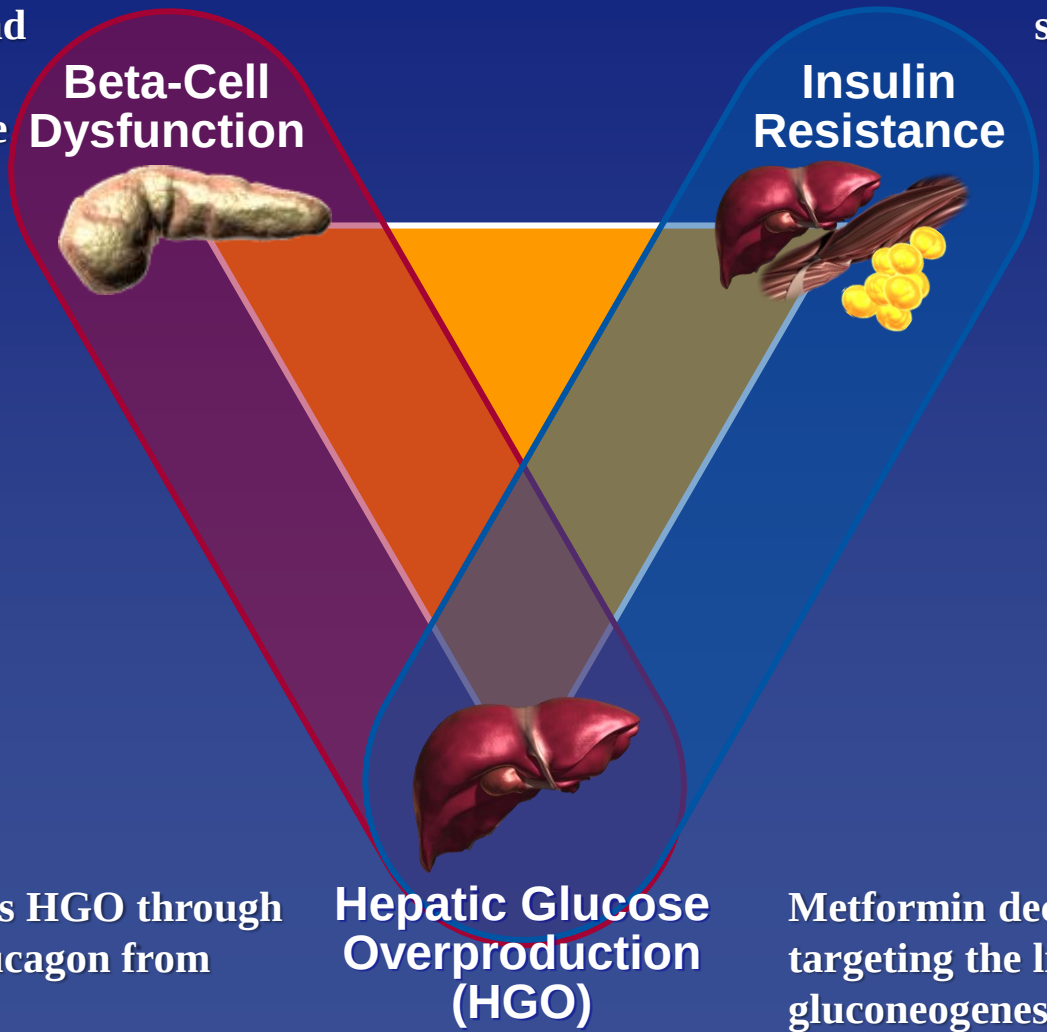
Dosing DPP-4 Inhibitors in Renal Insufficiency

Degree of Renal Insufficiency	Sitagliptin	Saxagliptin
Mild (GFR > 50 mL/min)	100 mg per day	5mg per day
Moderate (GFR ≥ 30-50 mL/min)	50 mg per day	No adjustment
Severe (GFR < 30 mL/min)	25 mg per day	2.5 mg per day

The Combination of Sitagliptin and Metformin Addresses the 3 Core Defects of Type 2 Diabetes in a Complementary Manner

Sitagliptin improves beta-cell function and increases insulin synthesis and release

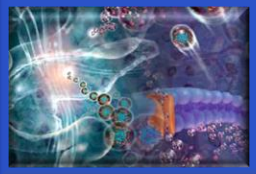
Metformin has insulin-sensitizing properties.



Sitagliptin reduces HGO through suppression of glucagon from alpha cells.

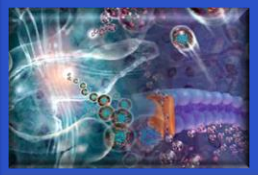
Metformin decreases HGO by targeting the liver to decrease gluconeogenesis and glycogenolysis.

*Please see corresponding speaker note for references.



Sulfonylureas - Drug Profile

Advantages	Potent glucose lowering effect Favorable adverse effect profile
Disadvantages	Hypoglycemia, more with Glyburide Glyburide contraindicated in renal impairment ?Glyburide impairs ischemic preconditioning in heart (UKPDS did not reveal increased cardiac risk)
Concomitant use with other drugs	Can be used as monotherapy and with all classes including insulin



Risk of Hypoglycemia in Type 2 DM

- Hypoglycemia associated with use of sulfonylureas and insulin.
- Severe hypoglycemia is clinically evident, however, mild to moderate hypoglycemia maybe asymptomatic and remain unreported.
- When unreported, asymptomatic hypoglycemia maybe detrimental to patients.
- Asymptomatic hypoglycemia maybe more prevalent in older patients.

Chico A et al Diabetes Care 26: 1153-1157. 2003

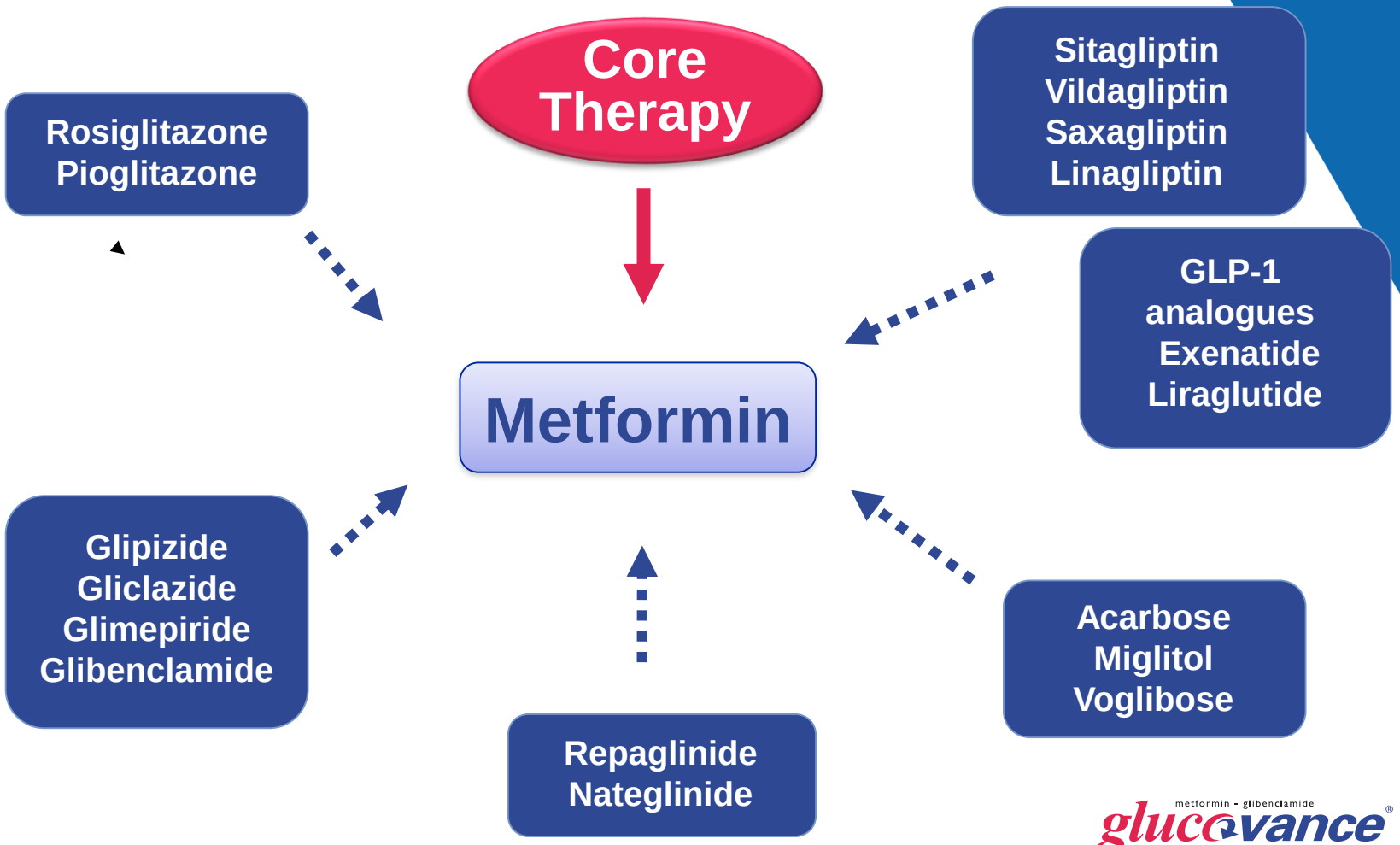
Matyka K et al Diabetes Care 20: 135-141. 1997.

Monami M, et al. Eur J Endocrinol. 2009;160:909-917.

Buse JB, et al. Lancet. 2009;374:39-47.

[a]Hypoglycemia requiring third-party assistance.

Choice of antidiabetic therapies for add-on therapy to metformin



American Diabetes Association

Standards of Medical Care in Diabetes—2017

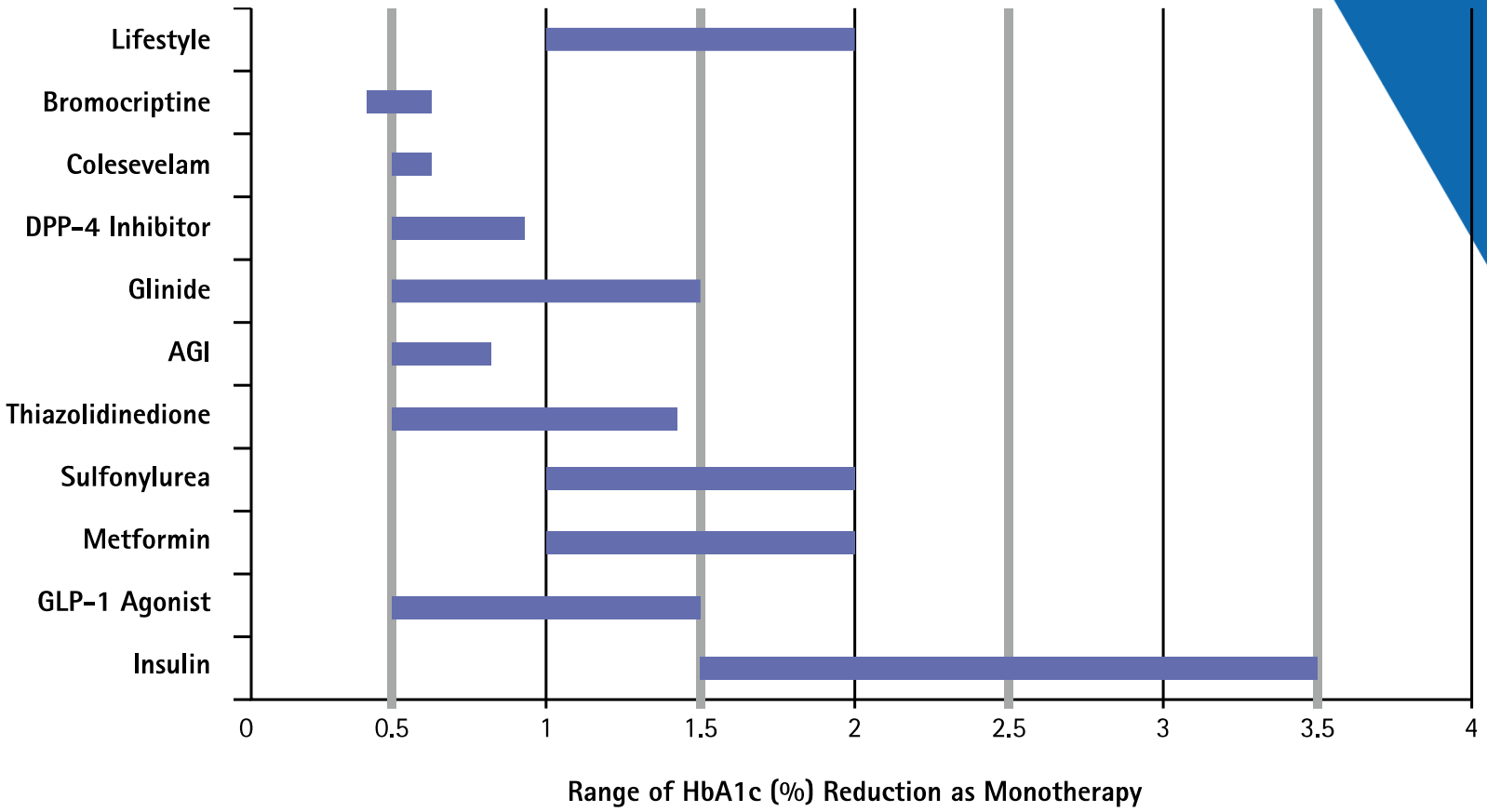
If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

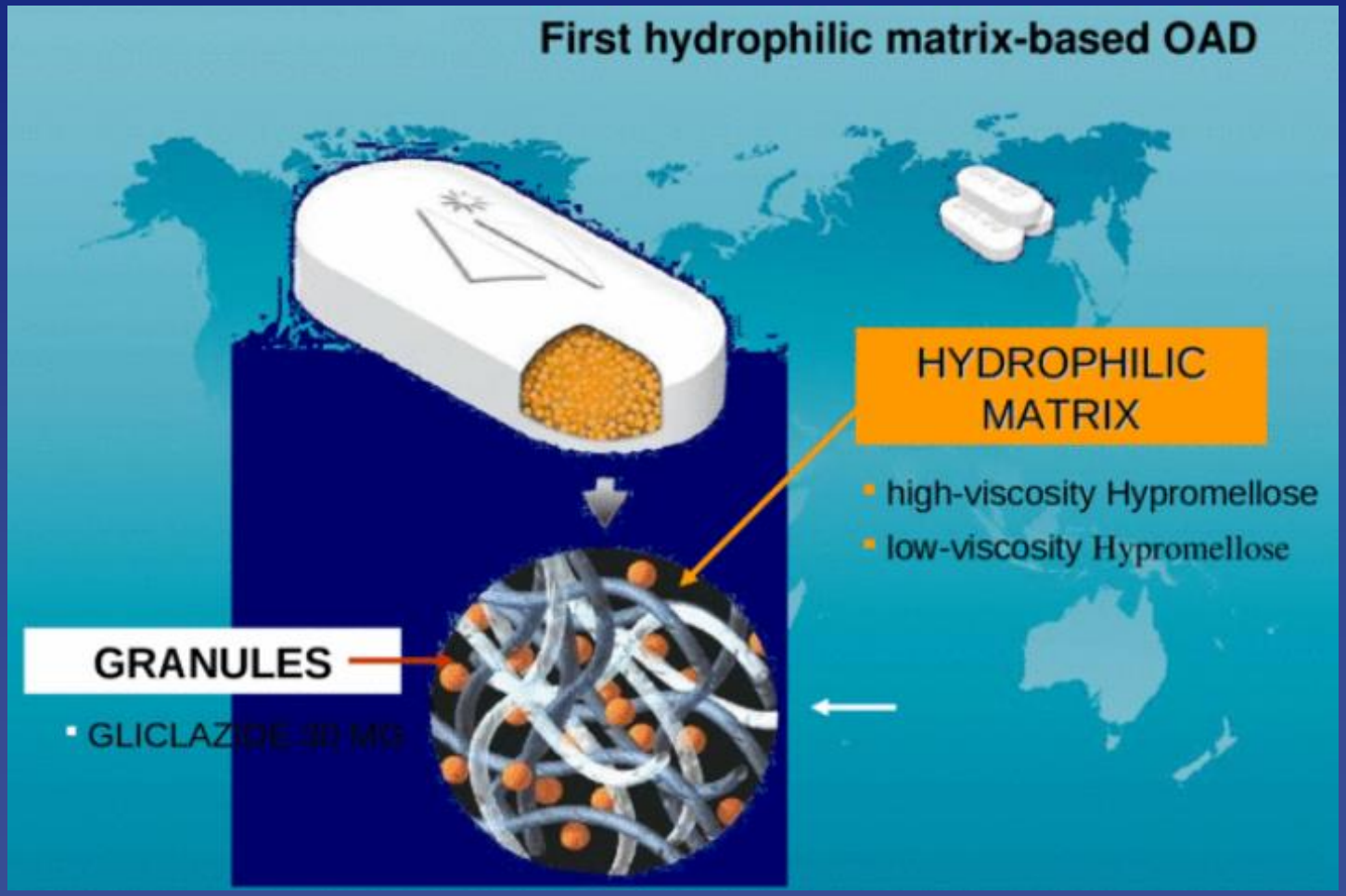
American Diabetes Association. Diabetes Care. 2017 Jan;40(Suppl 1):S64-S74.

Metformin & SUs have the highest effect on HbA1c



Nathan DM, et al. Diabetes Care. 2009;32(1):193-203. Garber A, et al. Lancet. 2009;373(9662):473-481. Rosenstock J, et al. Diabetes Obes Metab. 2008;10(5):376-386. Pijl H, et al. Diabets Care. 2000;23(8):1154-1161. Aminorroaya A, et al. Horm Res. 2004;62(2):55-59. Zieve FJ, et al. Clin Ther. 2007;29(1) 74-83. Bays HE, et al. Arch Intern Med. 2008;168(18):1975-1983.

Gliclazide MR



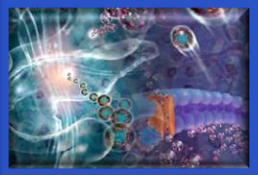
Gliclazide MR:
Dosage and administration

- The daily dose of GLICLAZIDE MR may vary from 30-120 mg (1-4 tablets) once daily.
- The recommended starting dose of GLICLAZIDE MR is 1 tablet per day (30 mg), even in elderly patients (> 65 years old).
- A single daily dose provides effective blood glucose control.
- Dose adjustment should be carried out in steps of 30 mg
- Each step should last for at least two weeks.

Administration

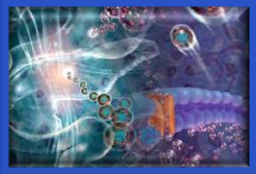
- It is recommended that the medication be taken at breakfast time. The tablets should be swallowed whole and must not be chewed or crushed.
- Previously untreated patients should commence with a dose of 30 mg.
- GLICLAZIDE MR can replace gliclazide 80 mg immediate release tablets.
- GLICLAZIDE MR can replace an antidiabetic treatment without any transitional period.

PRODUCT MONOGRAPH; Gliclazide Modified Release Tablets 30 mg, AA PHARMA INC., June 25, 2010



Alpha Glucosidase Inhibitor (AGI) - Drug Profile

Advantages	No hypoglycemia Weight neutral
Disadvantages	Targets only postprandial glucose GI side effects
Concomitant use with other drugs	Can be used as monotherapy and with all classes including insulin



Repaglinide and Nateglinide: Drug Profiles

Advantages	Less hypoglycemia than sulfonylureas Favorable adverse effect profile
Disadvantages	Less potent than sulfonylureas; target mainly post-prandial glucose Nateglinide less potent than Repaglinide
Concomitant use with other drugs	Can be used with all classes including insulin

Glucose Regulation

Kidney

- Generates glucose through gluconeogenesis pathway
- Reabsorbs glucose through the proximal renal tubules

Liver

- Generates glucose through gluconeogenesis pathway
- Produces glucose by glycogenolysis

Sources: Jabbour SA. *Postgrad Med* 2014;126:111-17; Gerich JE. *Diabet Med* 2010;27:136-42; Meyer C, et.al. *Am J Physiol Endocrinol Metab* 2002;282:E419-E27.

Glucose Reabsorption in the Kidney

- Blood glucose freely filtered by glomerulus
- Nearly all of the ~180 g of glucose filtered daily in glomeruli of healthy adult is reabsorbed, mostly in proximal renal tubules[1]
- < 1% excreted in urine[2]
- Glucose transport from tubule to tubular epithelial cells accomplished by sodium-glucose cotransporters (SGLTs)

Sources: [1]Neumiller JJ, et.al. *Drugs* 2010;70:377-85; [2]Bakris GL, et.al. *Kidney Int* 2009;75:1272-77.

SGLT1 and SGLT2

SGLT1

- "Low-capacity, high-affinity receptor"
- Reabsorbs essentially all of the glomerular filtrate glucose not reabsorbed by SGLT2

SGLT2

- "High-capacity, low-affinity receptor"
- Responsible for ~90% of renal glucose reabsorption

Source: Jabbour SA. *Postgrad Med* 2014;126:111-17.

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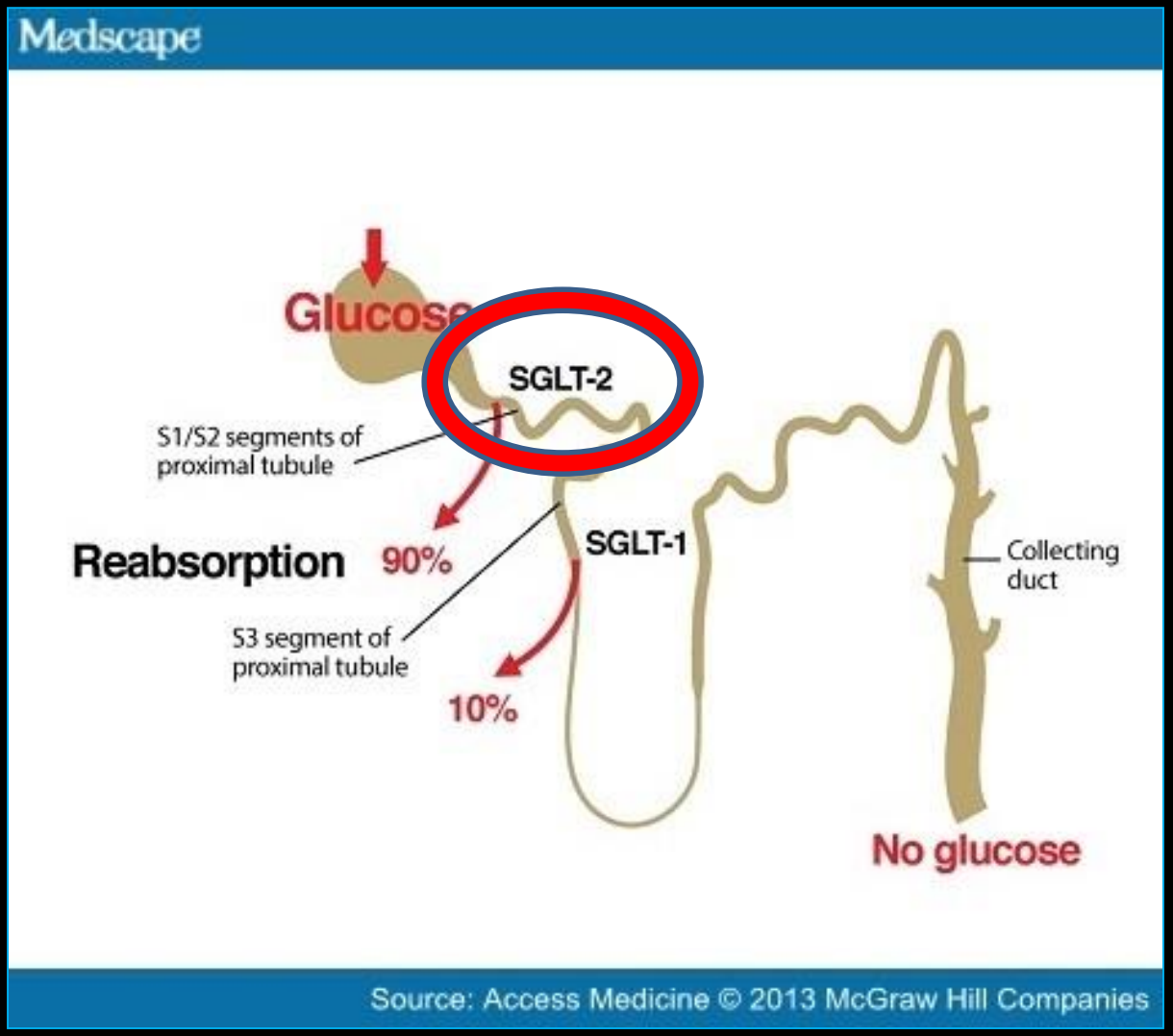
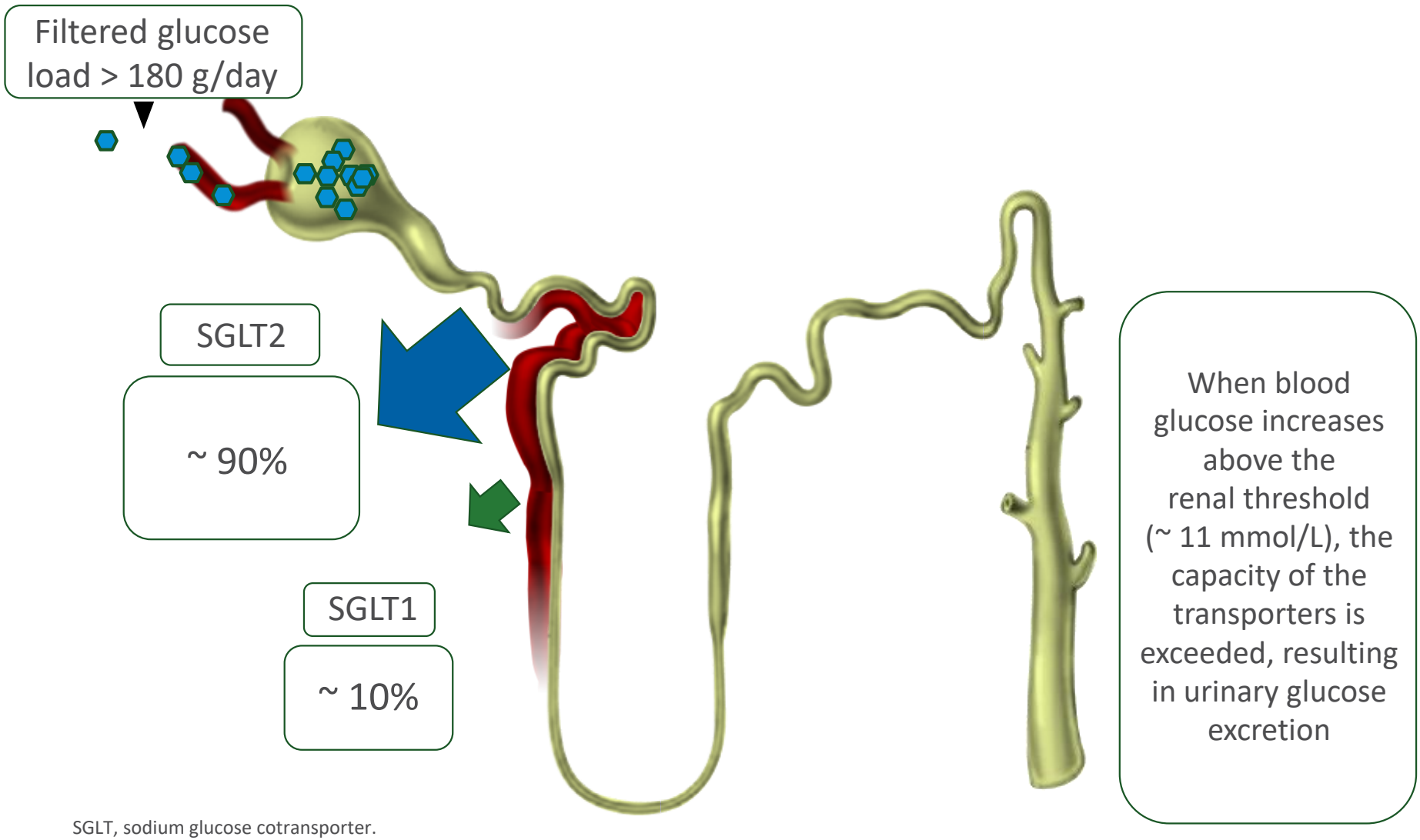

Medscape
Glucose
SGLT-2
S1/S2 segments of proximal tubule
Reabsorption
90%
SGLT-1
S3 segment of proximal tubule
10%
Collecting duct
No glucose
Source: Access Medicine © 2013 McGraw Hill Companies

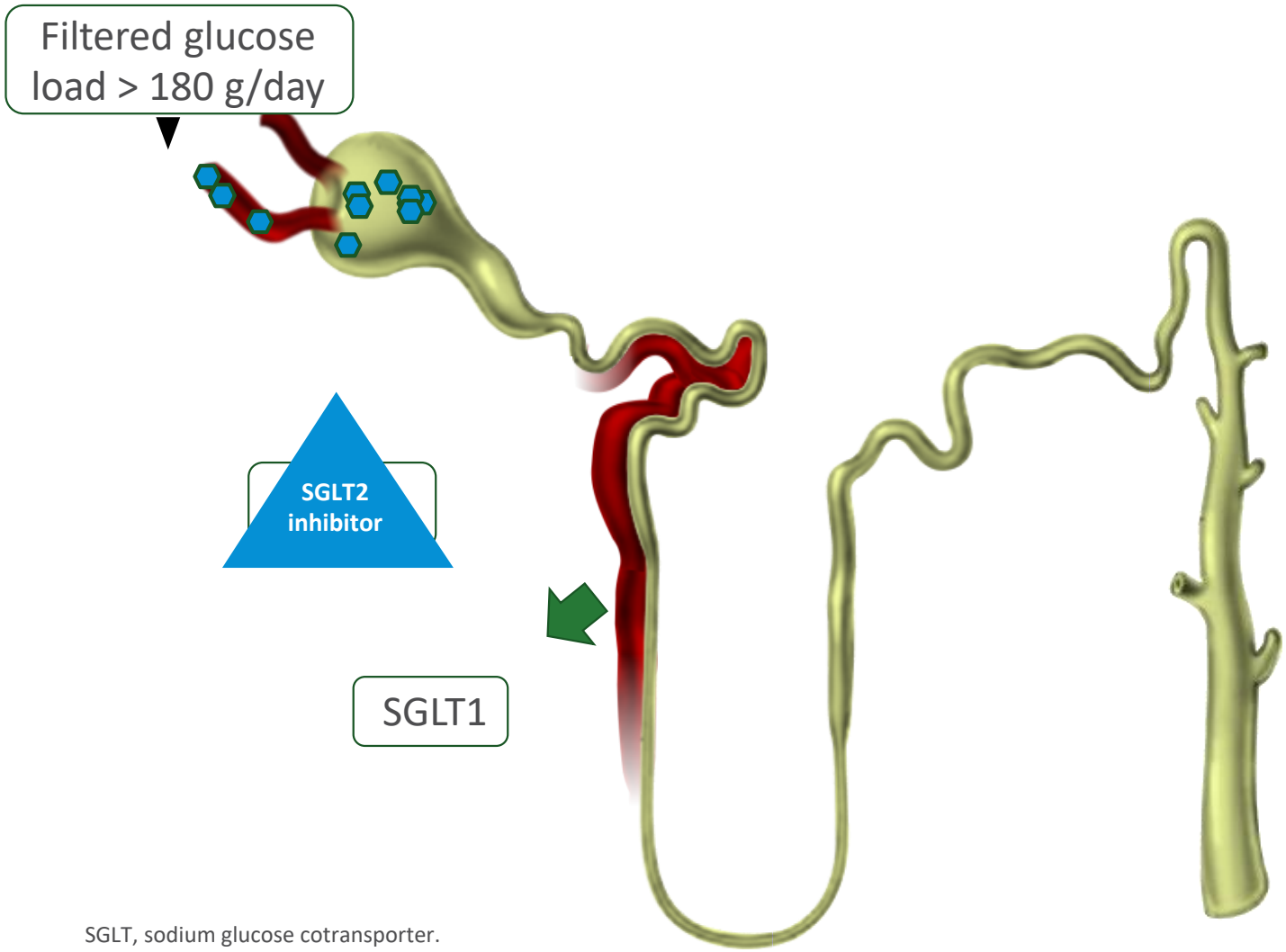
Renal glucose re-absorption in patients with diabetes[1,2]



SGLT, sodium glucose cotransporter.

1. Adapted from: Gerich JE. *Diabet Med*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Urinary glucose excretion via SGLT2 inhibition[1]



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

How SGLT2 Inhibitors Work

- Inhibit reabsorption of 30-50% of glucose filtered daily by the glomeruli[1]
- Lower threshold at which glucose begins to be excreted in urine (typically to ~70 mg/dL)[2]

SGLT2 inhibitors can promote the urinary excretion of 50-90 grams of glucose daily.

Sources: [1]DeFronzo RA, et al. *Diabetes Care* 2013;36:3169-76; [2]Liu JJ, et.al. *Diabetes* 2012;61:2199-204.

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A New Treatment Paradigm

- Elevated glycosuria traditionally viewed as cause for concern
- SGLT2 inhibitors can concomitantly lower A_{1c} and elevate glycosuria

To use SGLT2 inhibitors effectively, clinicians must consider the kidney a potential treatment target (rather than a site of organ damage) in type 2 diabetes.

Source: Bays H. *Curr Med Res Opin* 2009;25:671-81.

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FDA-Approved SGLT2 Inhibitors

- Canagliflozin*
- Dapagliflozin*
- Empagliflozin

*Also available as FDA-approved fixed-dose tablets with metformin hydrochloride.

SGLTs

- Canagliflozin 100-300mg od (£39.20)
- Empagliflozin 10-25mg od (£36.59)
- Dapagliflozin 10 mg (£36.59)

SGLT2 Inhibitors: Indications

- Indicated as adjuncts to diet and exercise to improve glycemic control in adults who have type 2 diabetes (but not for treatment of type 1 diabetes or for diabetic ketoacidosis)

- Contraindicated w/severe renal impairment, end-stage renal disease, dialysis, or hypersensitivity to given agent
- FDA Pregnancy Category C

Sources: Package inserts for canagliflozin, dapagliflozin, and empagliflozin.

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SGLT2 Inhibitors: Side Effects

- Genital mycotic infections*
- Urinary tract infections*
- Increased urination

*More commonly affect women, but are generally mild-to-moderate and usually respond to standard treatment.

Source: Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

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SGLT2 Inhibitors: Antihyperglycemic Efficacy

- Clinically significantly reduce fasting plasma glucose, postprandial plasma glucose, and A_{1c}[1-4]
- Effective as monotherapy or in combination with other oral antihyperglycemics or insulin[5]
- Reduce A_{1c} by -0.66% [95% CI, -0.73% to -0.58%] compared to placebo (45 studies; n=11,232)[5]

Note: Data from single-agent studies only; SGLT2 agents have not been compared in head-to-head trials.

Sources: [1]Bakris GL, et.al. *Kidney Int* 2009;75:1272-77; [2]Bołdys A, Okopień B. *Pharmacol Rep* 2009;61:778-84; [3]Brooks AM. *Ann Pharmacother* 2009;43:1286-93; [4]Polidori D, et al. *Diabetes Care* 2013;36:2154-61; [5]Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

SGLT2 Inhibitors: Hypoglycemia Risk

- Insulin-independent mechanism of action
- Low intrinsic capacity to promote hypoglycemia
- Hypoglycemic risk with SGLT2 inhibitors slightly higher than placebo (odds ratio: 1.28) but comparable to that observed with other antihyperglycemics (odds ratio; 1.01) (45 studies; n=11,232)

Note: Absolute risk reflects combination of agents used.

Source: Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

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SGLT2 Inhibitors: Pleiotropic Effects

- Significant and potentially long-term weight loss (mean reduction of 1.80 kg [95%CI, -3.50 to 0.11 kg]) (45 trials; n=11,232)[1,2]
- Mild osmotic diuresis[3]
- Significant reduction in systolic BP (weighted mean difference, -4.0 mm Hg; 95% CI, -4.4 to -3.5 mm Hg) and diastolic BP (weighted mean difference, -1.6 mm Hg; [95% CI, -1.9 to -1.3 mm Hg]) (27 trials; n=12,960)[4]

Sources: [1]Peene B, Benhalima K. *Ther Adv Endocrinol Metab* 2014;5:124-36; [2]Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74; [3]Bailey CJ. *Trends Pharmacol Sci* 2011;32:63-71; [4]Baker WL, et al. *J Am Soc Hypertens* 2014;8:262-75.

Properties of Oral Antihyperglycemic Agents

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low
SGLT2 inhibitors	• **Inhibits SGLT2 in proximal nephron** • **Increases glucosuria**	• **↓ Weight** • **No hypoglycemia** • **↓ BP** • **Effective at all stages**	• **GU infections** • **Polyuria** • **Volume depletion** • **↑ LDL-C**	**High**

Source: Adapted from slide deck that accompanies Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-49. Available at: http://care.diabetesjournals.org/content/38/1/140/suppl/DC2.

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Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Primary outcome:

Composite of death from cardiovascular causes, nonfatal MI, nonfatal CVA

N Engl J Med 2015;373:2117-2128.

What is the explanation for the reduction in CV death?

Related to modest BP reduction (~4 mmHg)?

Related to modest weight loss (~2 kg)?

Unidentified mechanism?

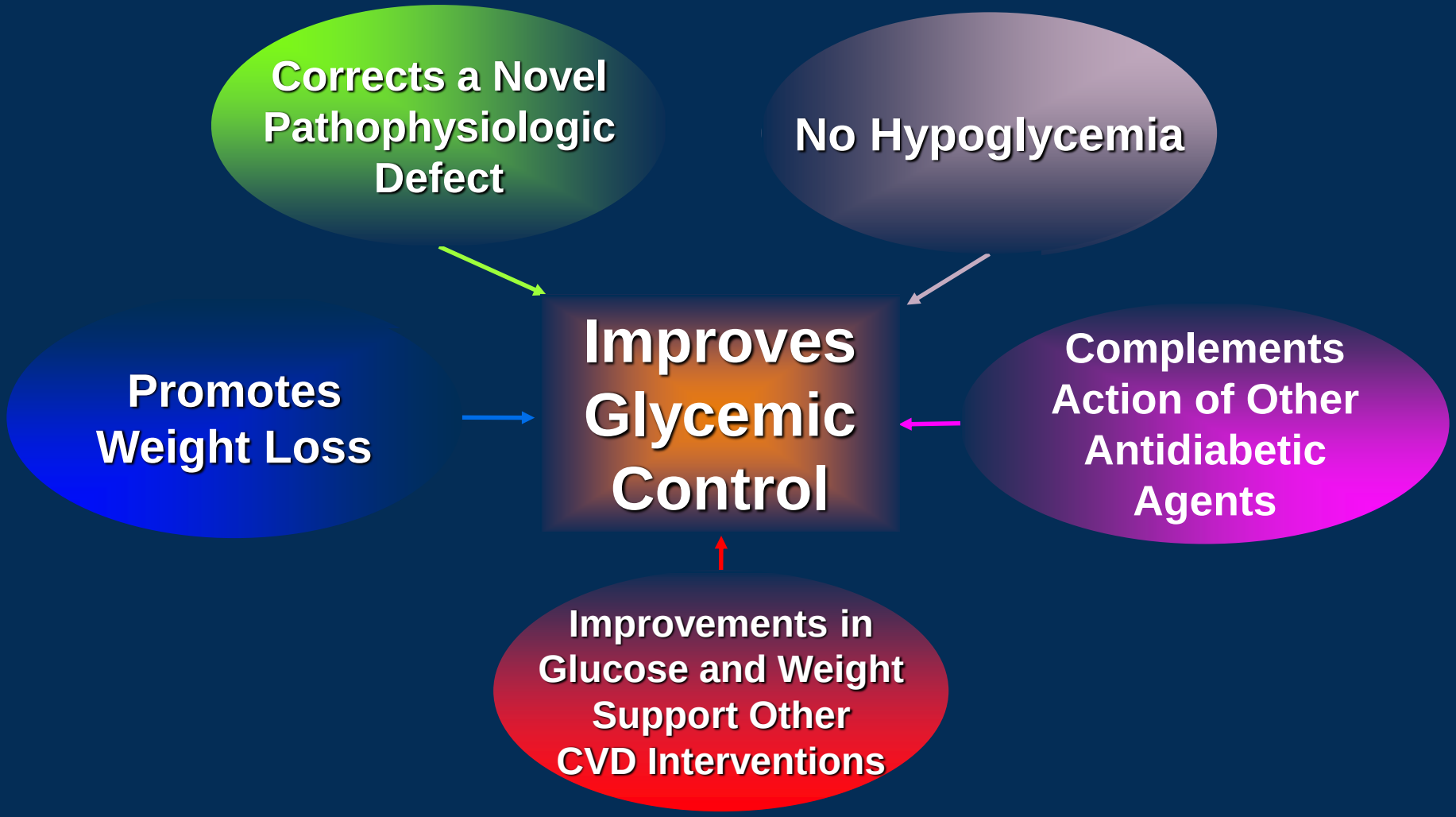
Conclusions

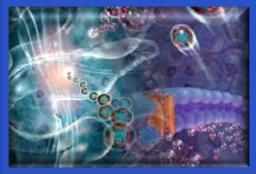
WorldWIDE
Worldwide Initiative for Diabetes Education

- SGLT2 inhibition represents a novel approach to the treatment of type 2 diabetes
- Studies in experimental models of diabetes have demonstrated that induction of glucosuria reverses glucotoxicity
  - Restores normoglycemia
  - Improves β-cell function and insulin sensitivity

SGLT2 Inhibition: Meeting Unmet Needs in Diabetes Care

WorldWIDE
Worldwide Initiative for Diabetes Education

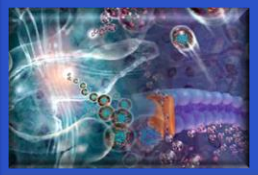




SGLT-2 Inhibitors – Useful Adjuncts?

- Mechanism of action - sodium-glucose transporter inhibition – prevents glucose reabsorption in the proximal tubal resulting in glucose loss (analogous to the apparently benign condition of renal glycosuria).
  Not insulin dependent. Effective in DM2 and DM1.
- Studies to date - monotherapy and as add on to metformin, SU's, TZD's, DPP-IV inhibitors & insulin – most studies preliminary
- Route - oral, daily (contraindicated with severe CKD)
- Efficacy - HbA1c reduction ~ 0.7-0.8% : weight loss – 1-2 kg
- Side effects - small(?) increase in U.T.I.'s & genital moniliasis. No hypoglycemia with monotherapy.

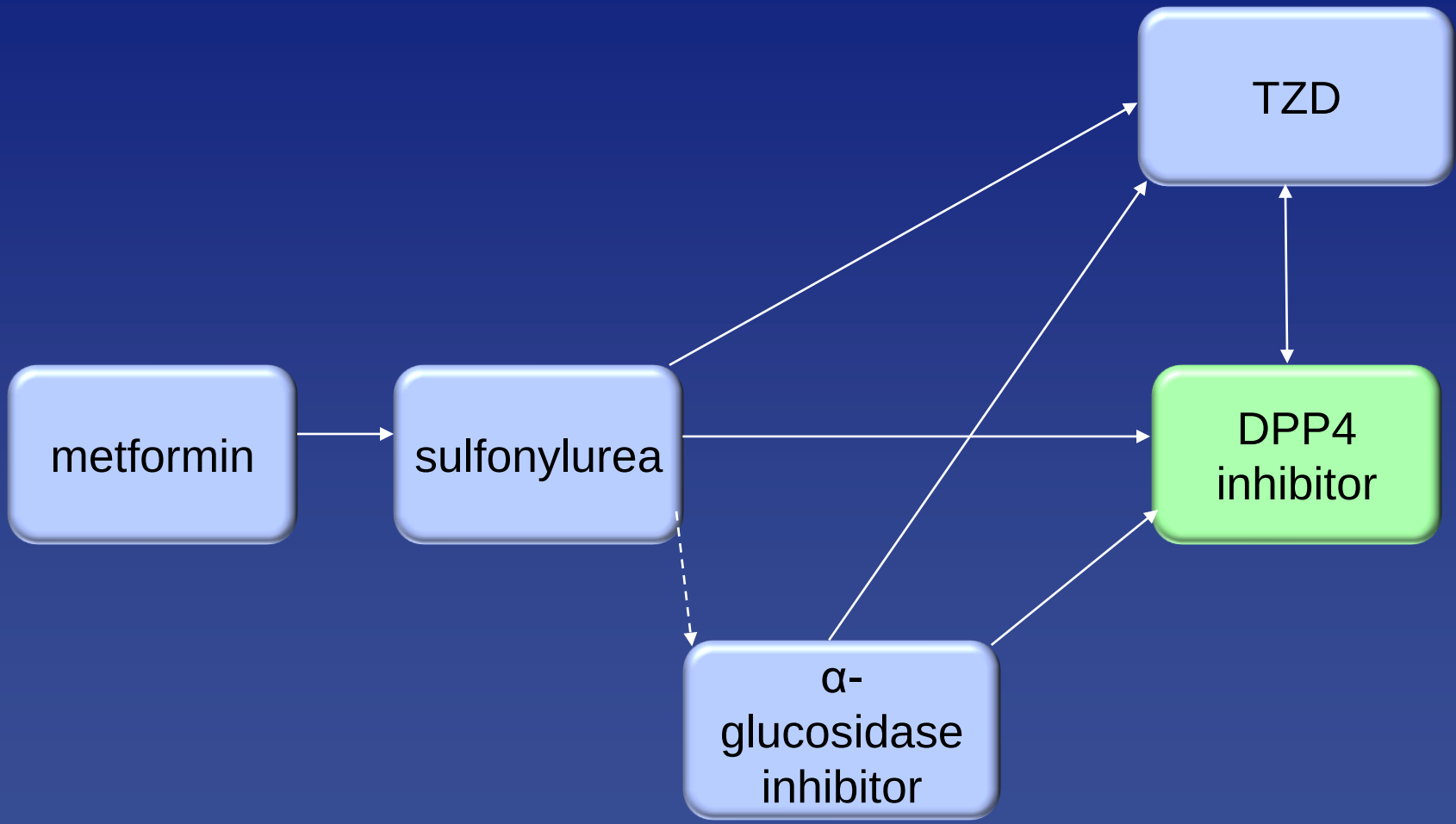
See *Lancet* 2010;375: 2196-98 & 2223-33



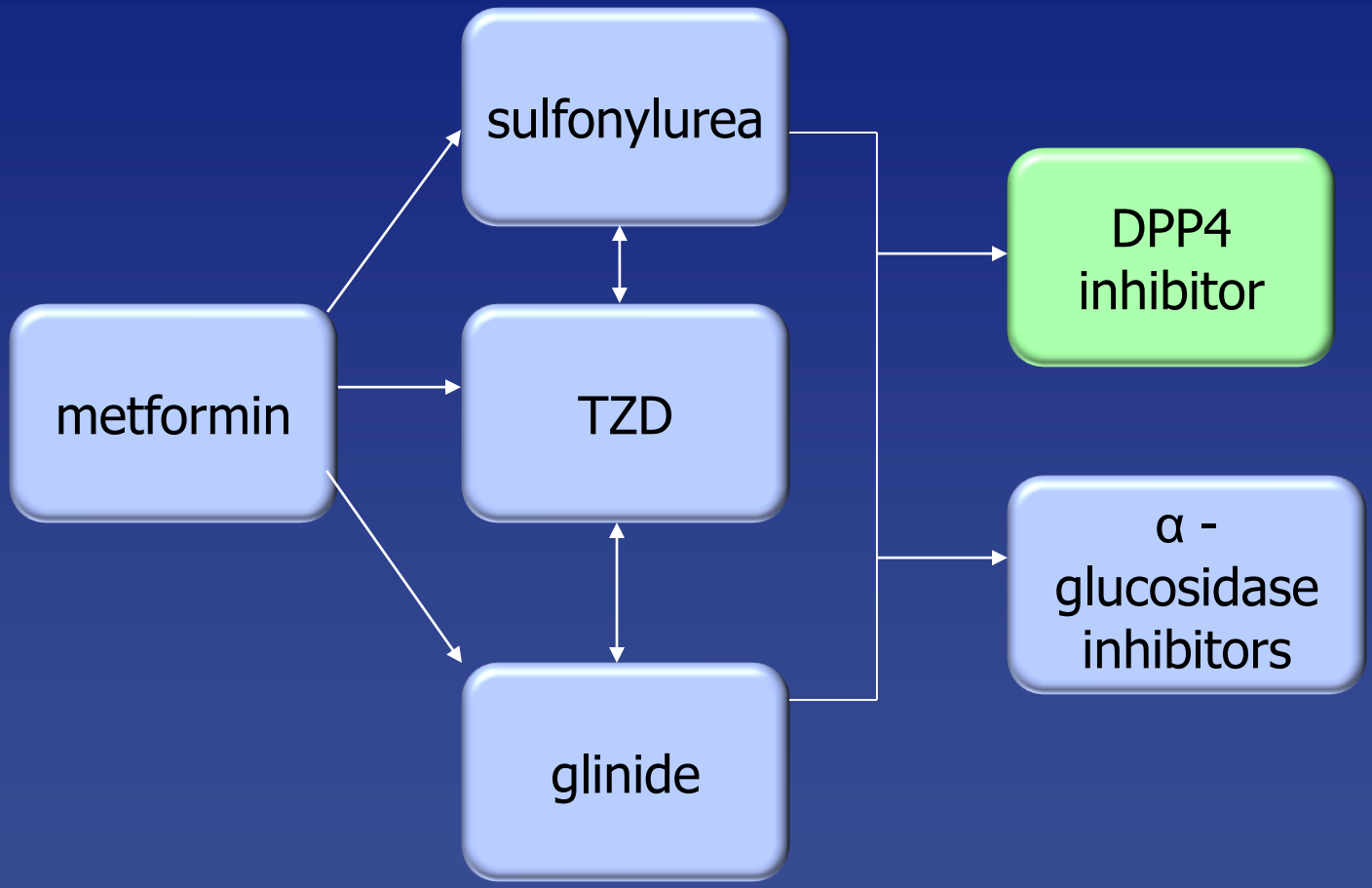
TZDs - Drug Profile

Advantages	No hypoglycemia May be useful in nonalcoholic fatty liver disease
Disadvantages	Increased fracture risk Weight gain Edema and exacerbation of CHF Rosiglitazone increases LDL-C (10mg/dL), TG (15-50mg/dL) and possible increase in MI
Concomitant use with other drugs	Can be used with other classes including insulin. Increased fluid retention and weight gain with insulin

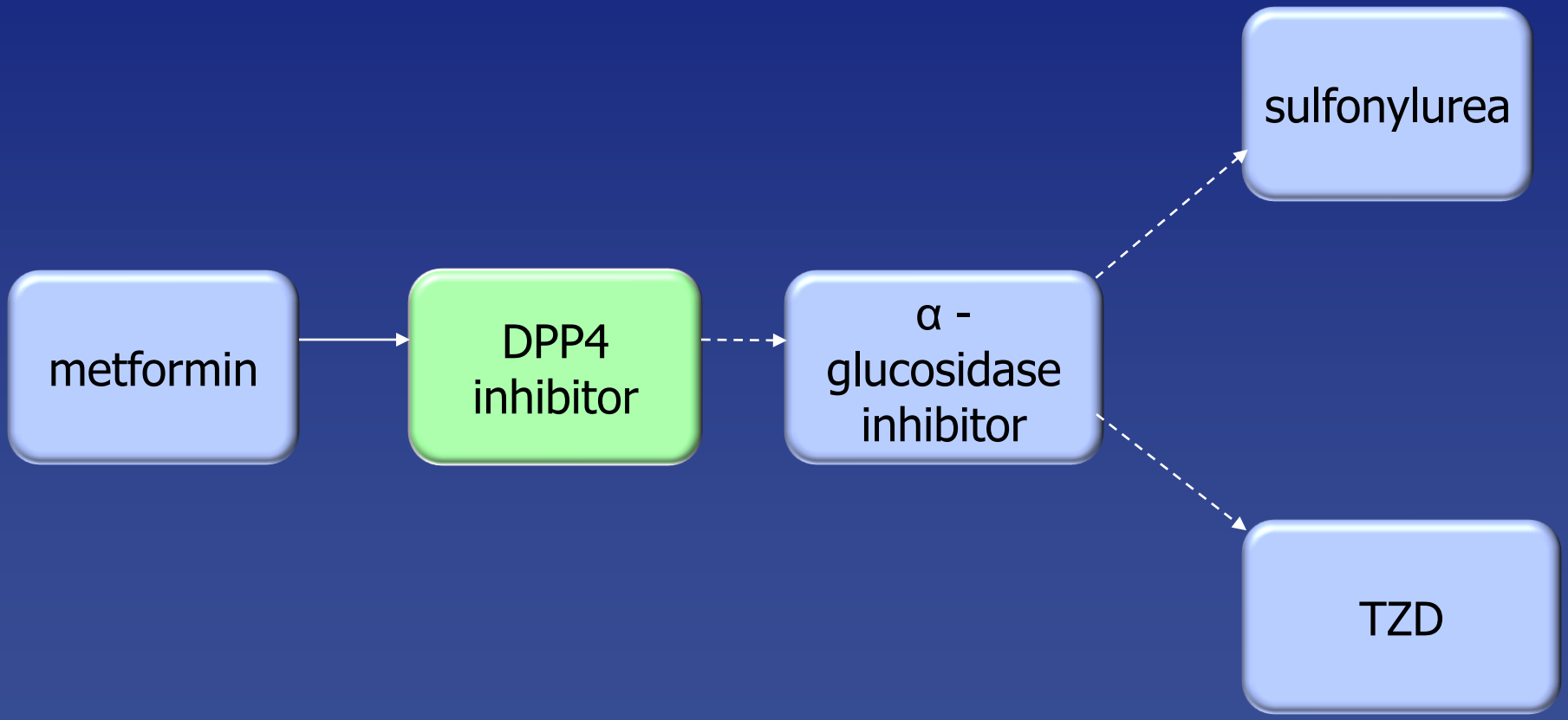
Patient Preference: Cost

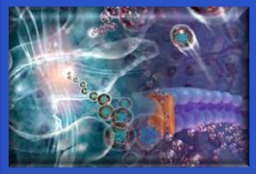


Patient Preference: Efficacy



Patient Preference: Weight



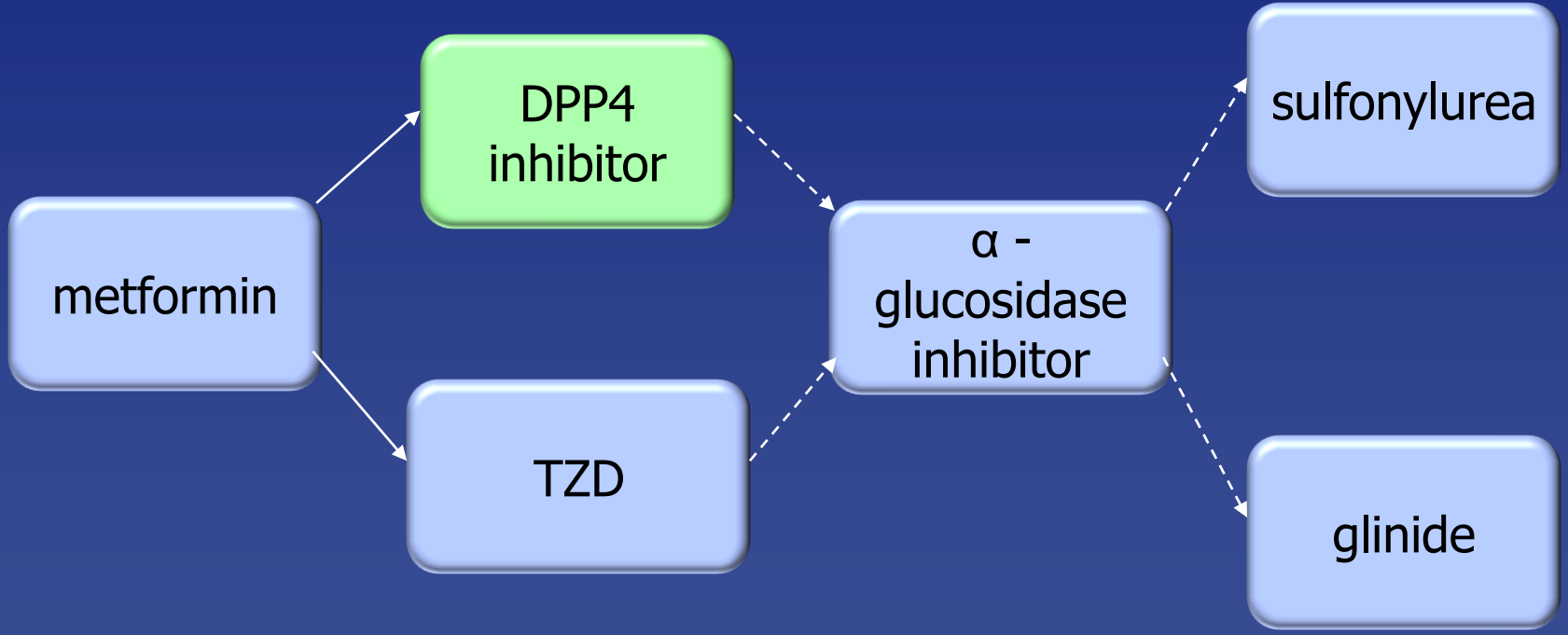


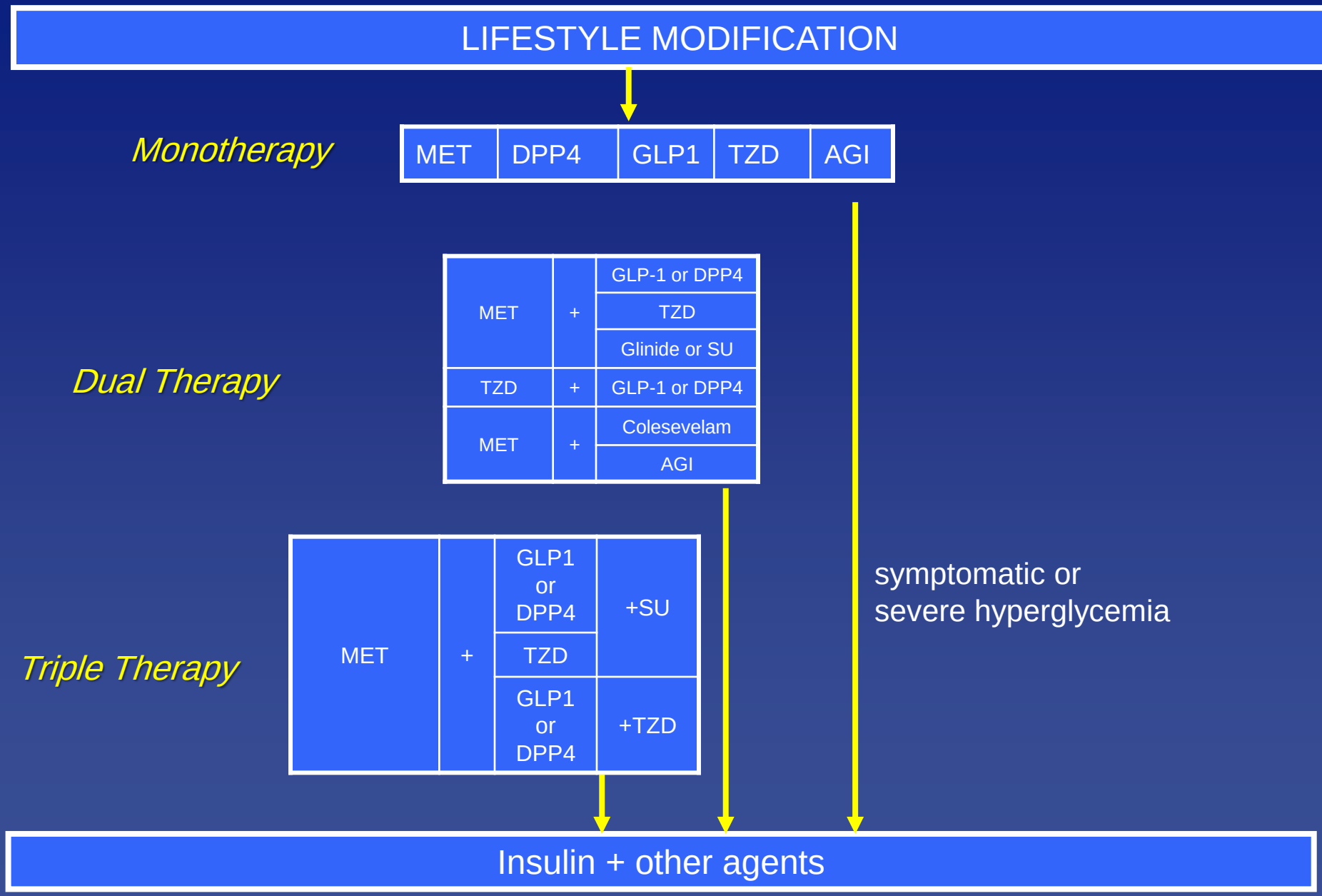
Weight Gain and Glycemic Control

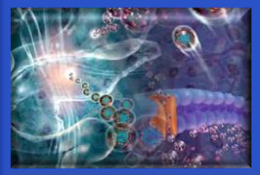
- Weight gain seems to be inseparable from glycemic control with many antidiabetic treatments, including sulfonylureas, insulin, and thiazolidinediones, which have an estimated 2 kg weight gain for every 1% decrease in HbA1C

Buse J et al. *Clin Ther*. 2007;29:139-153.

Patient Preference: Hypoglycemia Avoidance




LIFESTYLE MODIFICATION
Monotherapy
MET
DPP4
GLP1
TZD
AGI
Dual Therapy
MET
+
GLP-1 or DPP4
TZD
Glinide or SU
TZD
+
GLP-1 or DPP4
MET
+
Colesevelam
AGI
Triple Therapy
MET
+
GLP1 or DPP4
+SU
TZD
GLP1 or DPP4
+TZD
symptomatic or severe hyperglycemia
Insulin + other agents

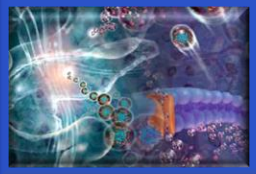


Injectables For RX DM2

- Pramlintide (Symlin)
- Exenatide (Byetta) / liraglutide (Victoza)
- Insulins

Native
- Regular (short-acting)
- Isophane (NPH : intermediate)
- Mixtures

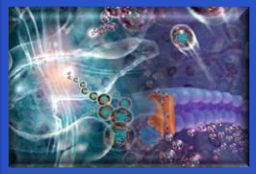
Analogues
- Glargine / Detemir (long-acting)
- Humalog, Novolog, Apidra (rapid)
- Mixtures



Future Rx DM2

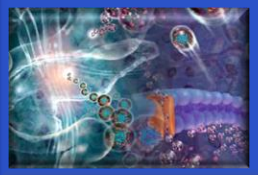
- Longer acting GLP-1 analogues
- More DPP-IV inhibitors
- More TZD's
- Newer drug classes : e.g., SGLT2-inhibitors

NOTE : FDA requires longer duration studies in DM2 to better understand risk / benefit before approval



Prevention of DM

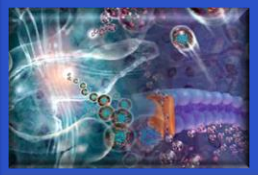
- TYPE 1
  - Immune modulation
- TYPE 2
  - Diet/exercise
  - Drugs: Metformin
    TZD's
    Glucosidase inhibitors
    Others?



Targets for Glycemia Control

Measures	ADA	AACE
HbA_{1c} %	<7.0*	≤6.5
Fasting plasma glucose, mg/dL	70-130	<110
2-hour postprandial plasma glucose, mg/dL	<180	<140

*Recommendations for glycemia control from the American Diabetes Association and the American Association of Clinical Endocrinologists. *The glycated hemoglobin (HbA1c) goal for patients in general is less than 7.0%, while the HbA1c goal for selected patients is as close to normal (<6.0%) as possible without significant hypoglycemia.* ***Sources:*** *American Diabetes Association. Diabetes Care. 2010;33(suppl 1):S11-S61; ACE/AACE Diabetes Road Map Task Force. Endocr Pract. 2007;13:260-268.*



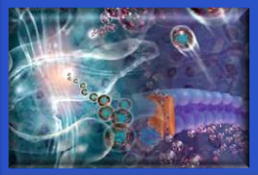
Type 2 Diabetes Medication Choices Experience and Potency

Medication	Route	Year	Efficacy as monotherapy: % ↓ in HgbA1c
Insulin	s.c.	1921	≥2.5
Sulfonylureas	Oral	1946	1.5
Glinides	Oral	1997	1.0-1.5
Metformin	Oral	1995	1.5
α-glucosidase inhibitors	Oral	1995	0.5-0.8
TZDs	Oral	1999	0.8-1.0
GLP analogue	s.c.	2005	0.6
DPP-IV Inhibitors	Oral	2006	0.5-0.8
Amylin analogue	s.c.	2005	0.6
Colesevelam	Oral	2008	0.5
Bromocriptine mesylate	Oral	2009	0.2-0.4

Oral Medications for Type 2 Diabetes

Drug	Initial Dose	Maximum Dose	Usual Dose
Biguanide			
Metformin	500 mg bid	2550 mg/d	500-1000 mg bid
Metformin XR	500 mg/d	2000 mg/d	1500-2000 mg/d
Sulfonylurea			
Glimepiride	1-2 mg/d	8 mg/d	4 mg/d
Glipizide	2.5-5 mg/d	40 mg/d	10-20 mg/d
Glipizide SR	2.5-5 mg/d	20 mg/d	5-20 mg/d
Glyburide	2.5-5 mg/d	20 mg/d	5-10 mg/d
Glyburide Micronized	0.75-3 mg/d	12 mg/d	3-12 mg/d
Thiazolidinedione			
Pioglitazone	15-30 mg/d	45 mg/d	15-45 mg/d
Rosiglitazone	4 mg/d	8 mg/d	4-8 mg/d
α-Glucosidase inhibitor			
Acarbose	25 mg tid	100 mg tid	25-100 mg tid
Miglitol	25 mg tid	100 mg tid	25-100 mg tid
Metiglinide			
Repaglinide	0.5 mg before meals	4 mg before meals	0.5-4 mg before meals
Nateglinide	60-120 mg tid before meals	120 mg tid before meals	60-120 mg tid before meals
DPP4 Inhibitor			
Sitagliptin	100 mg/d	100 mg/d	100 mg/d
Saxagliptin	2.5 mg/d	5 mg/d	5 mg/d
Bile Acid Sequestrants			
Colesevelam	375 mg/day	375 mg/day	375 mg/day

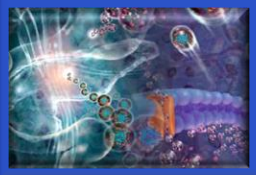
Adapted from: Annals of Internal Medicine, March 2010 “In the Clinic”



Type 2 Diabetes: Assessing the Relative Risks and Benefits of Glucose-lowering Medications

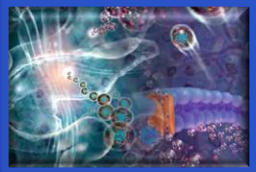
Richard M. Bergenstal, MD, Clifford J. Bailey, PhD David M. Kendall, MD
International Diabetes Center, Minneapolis, Minn; Diabetes Research, Life and Health Sciences, Aston University, Birmingham, UK.

- Glucose-lowering medications have a favorable risk-benefit profile
- The most common adverse event is hypoglycemia, particularly among patients receiving sulfonylureas or insulin.
- Metformin-associated lactic acidosis, exenatide-associated pancreatitis, and sitagliptin-associated hypersensitivity reactions appear to be rare.
- Increased risks of congestive heart failure and bone fractures in thiazolidinedione-treated patients, and reports of increased cardiovascular events in rosiglitazone-treated patients remain an issue.



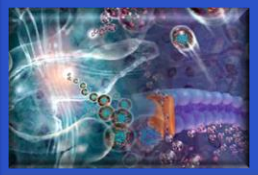
Factors to Consider when Choosing Pharmacological Agent(s) for Diabetes

- Current A1C
- Duration of diabetes
- Body weight (BMI, abdominal obesity)
- Age of patient
- Co-morbidities
- Cost of medication
- Convenience



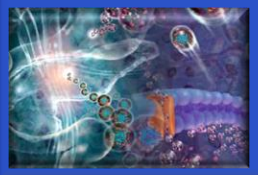
Case Presentation

- 50-year-old patient with type 2 diabetes on glyburide 5 mg/d and metformin 1000 bid presents with a random blood sugar of 240 mg/dL and HbA1c 8.0%
  - Weight 250 lb Ht 5’9” BMI 36.9



What would be the best therapeutic option to treat this patient's diabetes?

1. Add pioglitazone 30 mg/d
2. Add insulin glargine 10 units qhs
3. Start nateglinide 120 mg tid
4. Start sitagliptin 100 mg/d
5. Start exenatide 5 mcg bid



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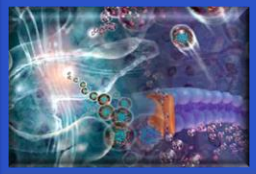
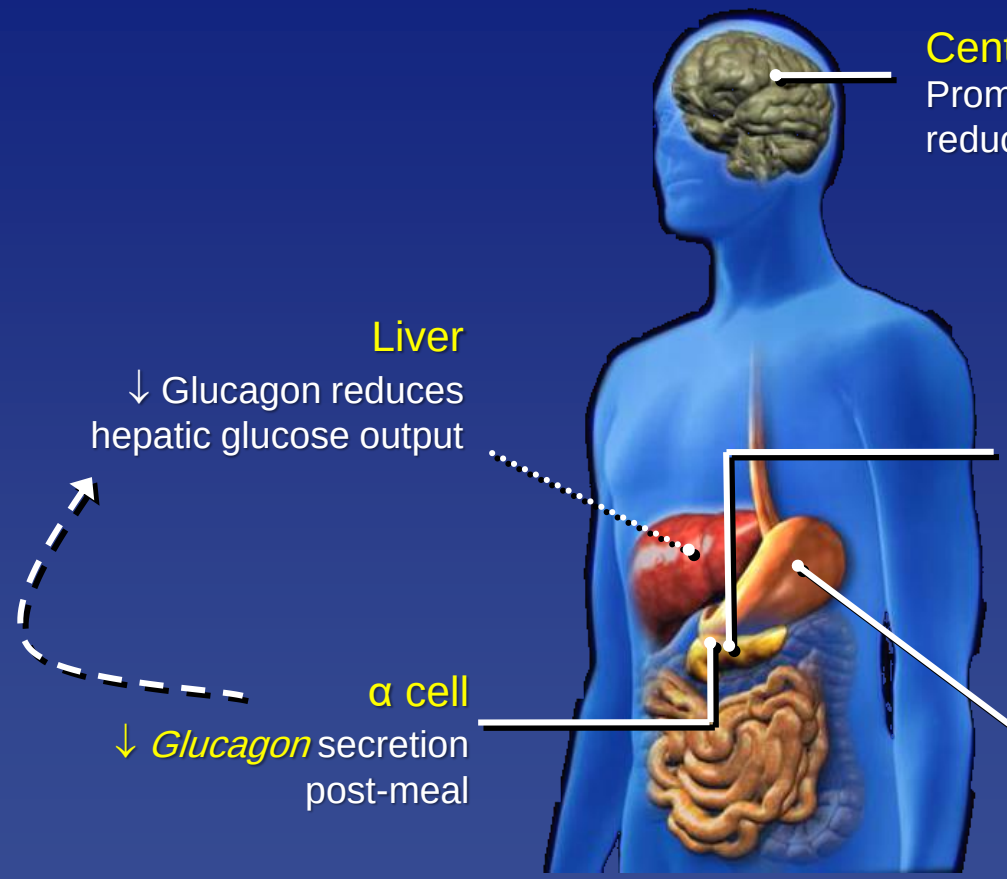


Clinical Role of GLP-1—Mimetics

- Overweight patients with type 2 diabetes requiring initial treatment
- Overweight patients with type 2 diabetes on metformin, sulfonylurea, or combination
- Addition to thiazolidinediones to avoid weight gain

Summary of GLP-1—Effects in Humans



Central nervous system
Promotes satiety and reduction of appetite

Liver
↓ Glucagon reduces hepatic glucose output

β cell
Enhances secretion of *glucose-dependent insulin*

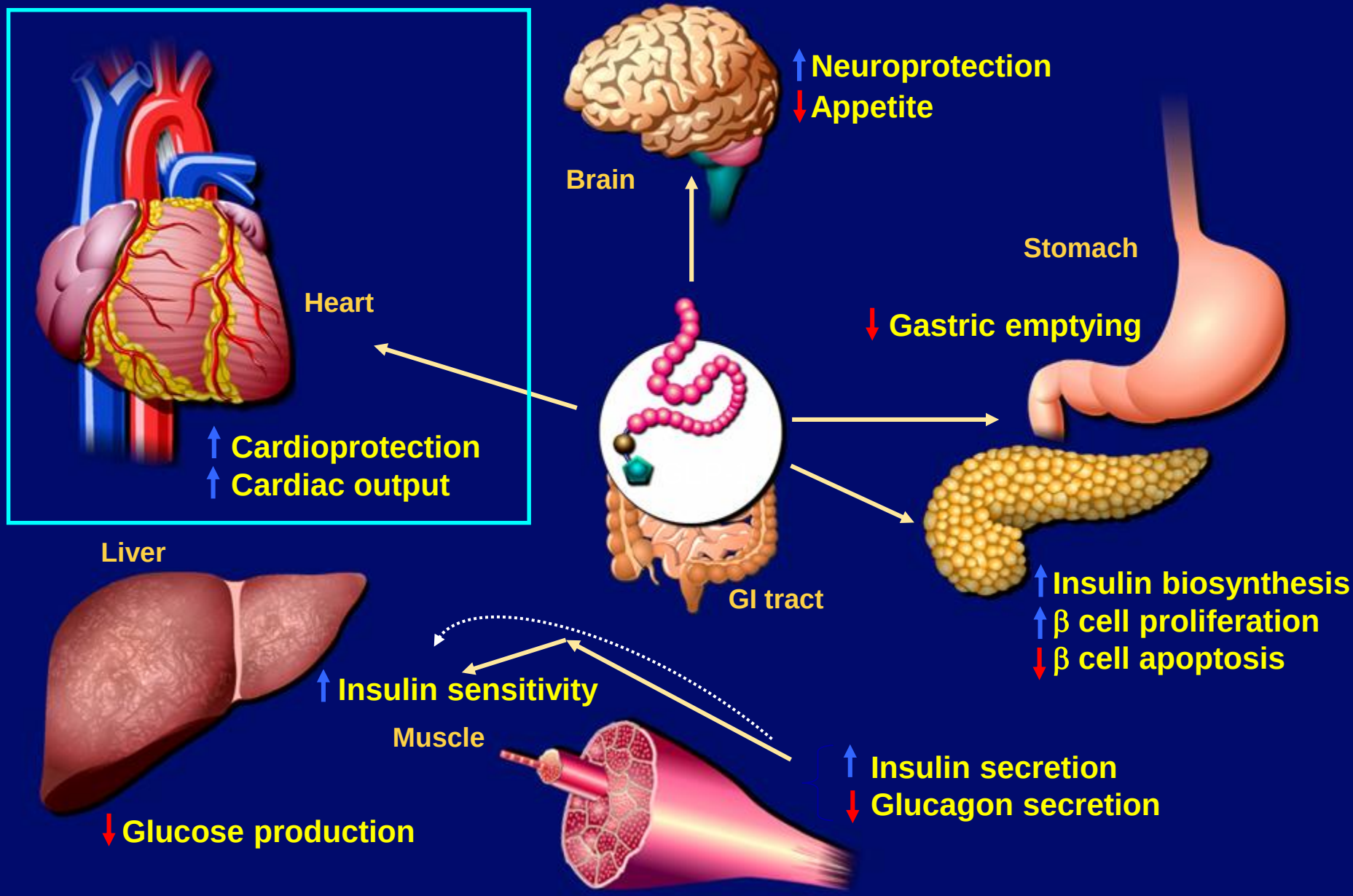
Potential increase in β-cell mass

α cell
↓ *Glucagon* secretion post-meal

Stomach
Regulates gastric emptying

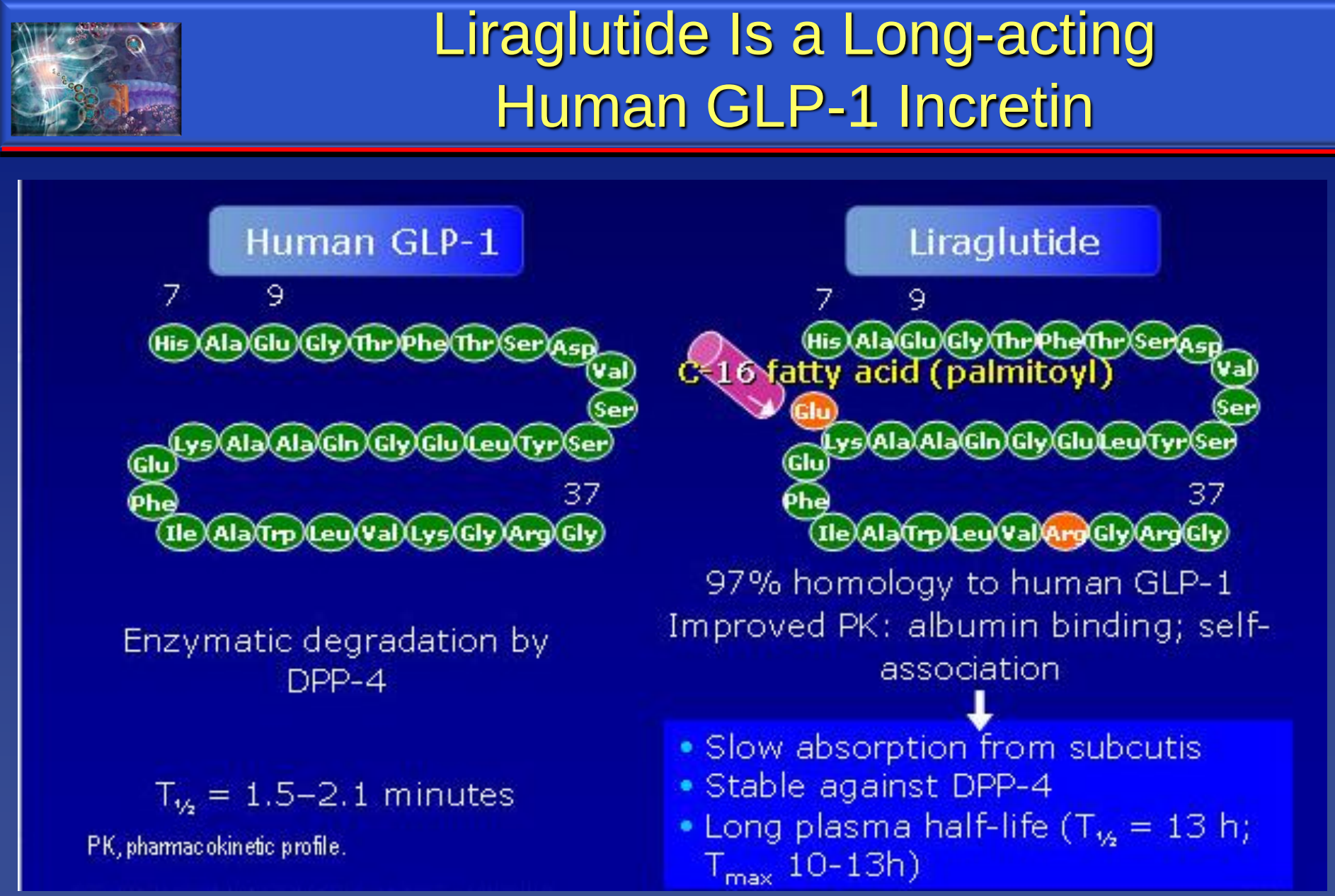
Flint A et al. *J Clin Invest*. 1998;101:515-520. Larsson H et al. *Acta Physiol Scand*. 1997;160:413-422. Nauck MA et al. *Diabetologia*. 1996;39:1546-1553. Drucker DJ. *Diabetes*. 1998;47:159-169.

Summary of Incretin Actions on Different Target Tissues

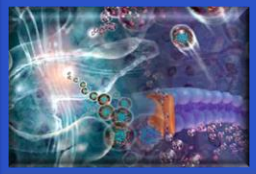


Drucker D. J. *Cell Metabolism* 2006

Liraglutide Is a Long-acting Human GLP-1 Incretin

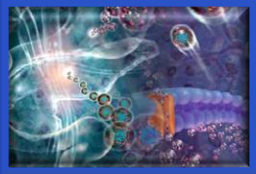


Knudsen LB et al. *J Med Chem*. 2000;43:1664-1669; Degn KB et al. *Diabetes*. 2004;53:1187-1194.



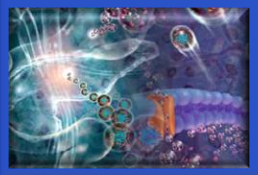
Potential Roles of GLP-1 Mimetics

- Once-weekly injection of exenatide-LAR in overweight patients with T2DM who require initial therapy or combination with other oral agents
- Potential treatment for overweight nondiabetic patients
- Potential treatment of overweight, insulin-treated patients with T2DM



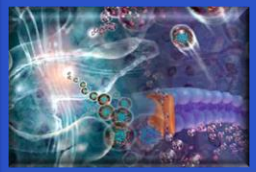
Role of DPP-4 Inhibitors

- Approved as single agents or in combination with a glitazone, sulfonylurea, or metformin
- Sitagliptin approved to be used in combination with insulin



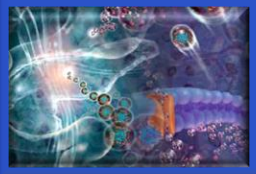
Addition of Sitagliptin to Insulin—Effect on HbA1c at 24 Weeks

- Sitagliptin change from baseline in A1C at Week 24 -0.59 ($P<0.001$)
- Placebo change from baseline -0.03



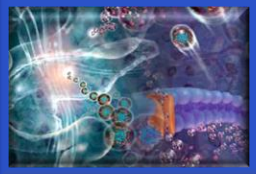
Should DPP-4 Inhibitors Be First-line Agents?

- If β-cell-sparing effect shown in rats proves to be true in humans, DPP-4 inhibitors could become the preferred first-line agents
- Appropriate for patients with mild elevation of glucose with contraindications to other agents that cause hypoglycemia
- Should be considered early in overweight patients
- Should be considered in patients with heart failure
- Strongly considered in patients with renal failure



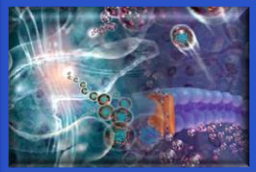
Conclusions—GLP-1 Mimetics

- GLP-1 mimetics are important new therapeutic options that have important roles in current therapy and major potential future roles
- GLP-1 mimetics have excellent glucose-lowering efficacy and are associated with significant weight loss
- Combination with glitazones prevents glitazone-induced weight gain
- Long-acting GLP-1 mimetics will increase their acceptance
- β-cell preservation, if proven in humans, may make these mimetics early treatment options in the future
- Use in patients with glucose intolerance or simple obesity for weight reduction needs further evaluation



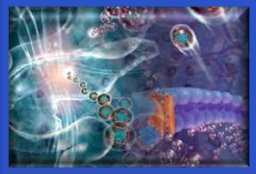
Conclusions—DPP-4 Inhibitors

- DPP-4 inhibitors have a major role in diabetes management
- Ability to use in renal insufficiency, heart failure, and hepatic disease markedly increases therapeutic options for our patients
- Quick onset of action and lack of hypoglycemia may make these first-line agents in hospitalized patients
- Excellent agents for the growing population of patients requiring modest glucose lowering
- Efficacy is enhanced with increased baseline HbA1C
- New data support efficacy with sulfonylureas, which will greatly enhance the usefulness of DPP-4 inhibitors
- May be used as single agents or in combination with metformin, glitazones, sulfonylurea, or insulin



Future Management Directions in DM2

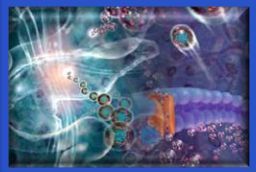
- Longer – acting incretin mimetics
- Other DPP-IV inhibitors
- Other agents - e.g., SGLT-2 inhibitors
- Newer insulin formulations (oral / inhaled)
- Weight ("girth") control - medical / surgical
- DM2 prevention - action in the pre-diabetes (impaired tolerance) phase



SGLT-2 Inhibitors – Useful Adjuncts?

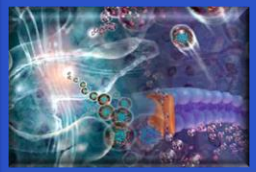
- Mechanism of action - sodium-glucose transporter inhibition – prevents glucose reabsorption in the proximal tubal resulting in glucose loss (analogous to the apparently benign condition of renal glycosuria).
  Not insulin dependent. Effective in DM2 and DM1.
- Studies to date - monotherapy and as add on to metformin, SU's, TZD's, DPP-IV inhibitors & insulin – most studies preliminary
- Route - oral, daily (contraindicated with severe CKD)
- Efficacy - HbA1c reduction ~ 0.7-0.8% : weight loss – 1-2 kg
- Side effects - small(?) increase in U.T.I.'s & genital moniliasis. No hypoglycemia with monotherapy.

See *Lancet* 2010;375: 2196-98 & 2223-33



Topics

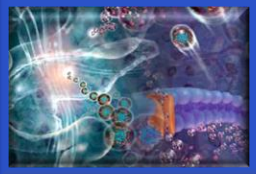
- DPP-4 inhibitors as monotherapy or combination therapy with metformin, sulfonylureas, and TZDs - constructing outcome-optimizing oral regimens
- Aligning oral therapy with appropriate patient subgroups: how to choose and what to choose - a systematic, guideline-consistent approach based on clinical evidence



Case Study #1

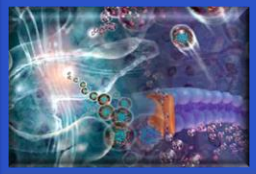
- 47-year-old male with type 2 diabetes mellitus diagnosed 5 years ago, returns for a follow-up visit.

- He reports feeling well. For exercise, he walks his dog daily for about a mile. He feels he could "do better with his diet"; he has seen a nutritionist and diabetes educator, but says he lacks motivation.



Case Study #1

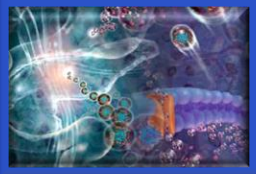
- On exam he has a BMI of 36, Pulse 74, BP 130/80. Rest of the exam is normal
- His current meds are metformin 1000 mg bid, glyburide 10 mg bid, lisinopril 10 mg daily, simvastatin 40 mg daily, and ASA 81 mg daily.
- Downloaded meter reveals BG testing about once daily; BG range 55-320, average 162 mg/dl.
- A1C 7.8 %, serum creatinine 1.1 mg/dl , LDL-C 66 mg/dl



Case Study #1

What is your recommendation for him?

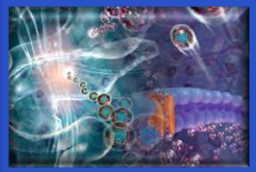
1. Add basal insulin
2. Stop glyburide and start basal bolus insulin treatment
3. Add pioglitazone (Actos) 45 mg daily
4. Add sitagliptin (Januvia) 100 mg daily
5. Do not change drug therapy and refer back to the diabetes educator
6. Add exenatide (Byetta) bid



Case Study

- 67-year-old woman with DM-2, hypertension, obesity, rheumatoid arthritis and COPD presents with A1c of 7.6%. Her BMI is 34.2 and she is looking to lose weight. She tried metformin previously but did not tolerate due to side effects.

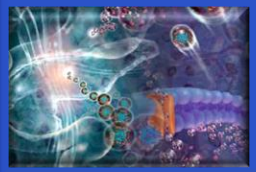
- Candidate for DPP-IV monotherapy
- Alternatives: α-glucosidase inhibitor
- Other options



Case Study

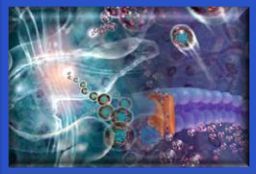
- 82-year-old man with hypertension, hypercholesterolemia, ischemic cardiomyopathy and NYHA class III heart failure presents with a newly diagnosed DM-2 and A1c of 7.4%.

- Candidate for DPP-IV monotherapy
- Alternatives: α-glucosidase inhibitor
- Other options



Case Study #4

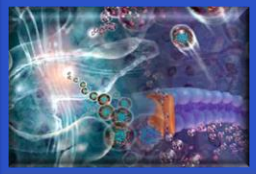
- 59-year-old man with DM-2 treated with metformin, hypertension, dyslipidemia, prostate cancer and osteoporosis presents with A1c of 7.9%. He was previously taking glyburide but had several episodes of severe hypoglycemia (had to be assisted in treatment) and discontinued it 3 months ago. He has a hectic work schedule (marketing executive) and is not always able to have meals at regular times.
- Candidate for DPP-IV as 2nd line agent (after metformin)
- Alternatives: α-glucosidase inhibitor
- Other options



Case Study #5

- 52-year-old man with no past medical history presents with newly diagnosed DM-2. His A1c is 9.1%. He is adamant in refusing to consider injectable medications.

- Candidate for DPP-IV as 3^{d} line agent (after metformin + sulfonylurea and / or TZD)
- Alternatives: α-glucosidase inhibitor
- Other options



Case Study #6

73-year-old African-American female - T2DM for the past 5 years

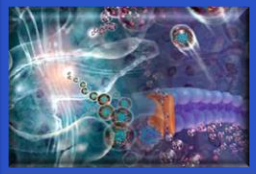
PM History: GI intolerance with metformin
Longstanding hypertension
MI at age 65, ejection fraction 40%

Meds: Glimepiride 4 mg, Aspirin 325 mg, Metoprolol 50 mg
Rosuvastatin 10mg, Furosemide 20mg, Lisinopril 10mg daily

Vitals: BMI 29, BP 130/80

Bloods: TCHOL 193, LDL 70, HDL 58, TG 81
FPG 127 mg/dl, A1C 7.5%
Creatinine 1.4 mg/dl, GFR 49 ml/min

What's the next step in managing her diabetes?

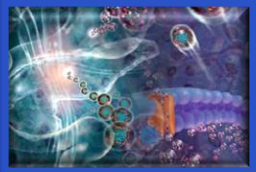


Case Study #6

What's the next step in managing her diabetes?

The following should not be used in this patient, except one class:

A. Metformin
B. Sulfonylureas
C. Thiazolidinediones
D. Incretin mimetics/ DPP-IV inhibitors
E. Insulin



Case Study #6

What are some of the major risk factors in treating Type 2 diabetic patients?

1. Cardiovascular disease
2. Renal Failure
3. Aging
4. Hypoglycemia