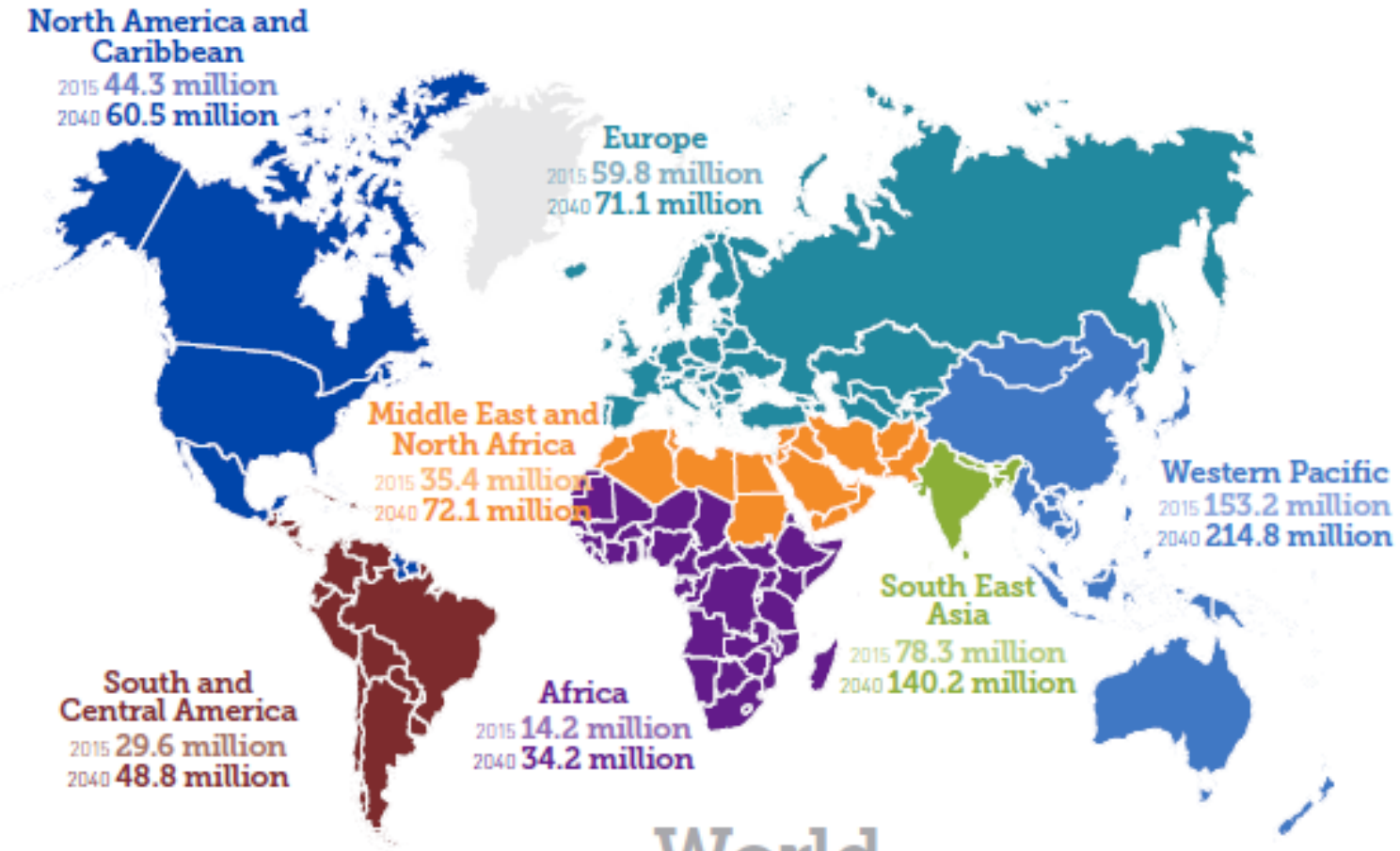
Pharmacological management in T2DM patients

Dr. LOCK Ka Yuen, Athena
Associate consultant
Department of Medicine
Tseung Kwan O Hospital


STAY SUPER
HALT THE RISE
BEAT DIABETES
DIABETES
#diabetes
www.who.int/whd/diabetes

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



World

2015 **415 million**

2040 **642 million**

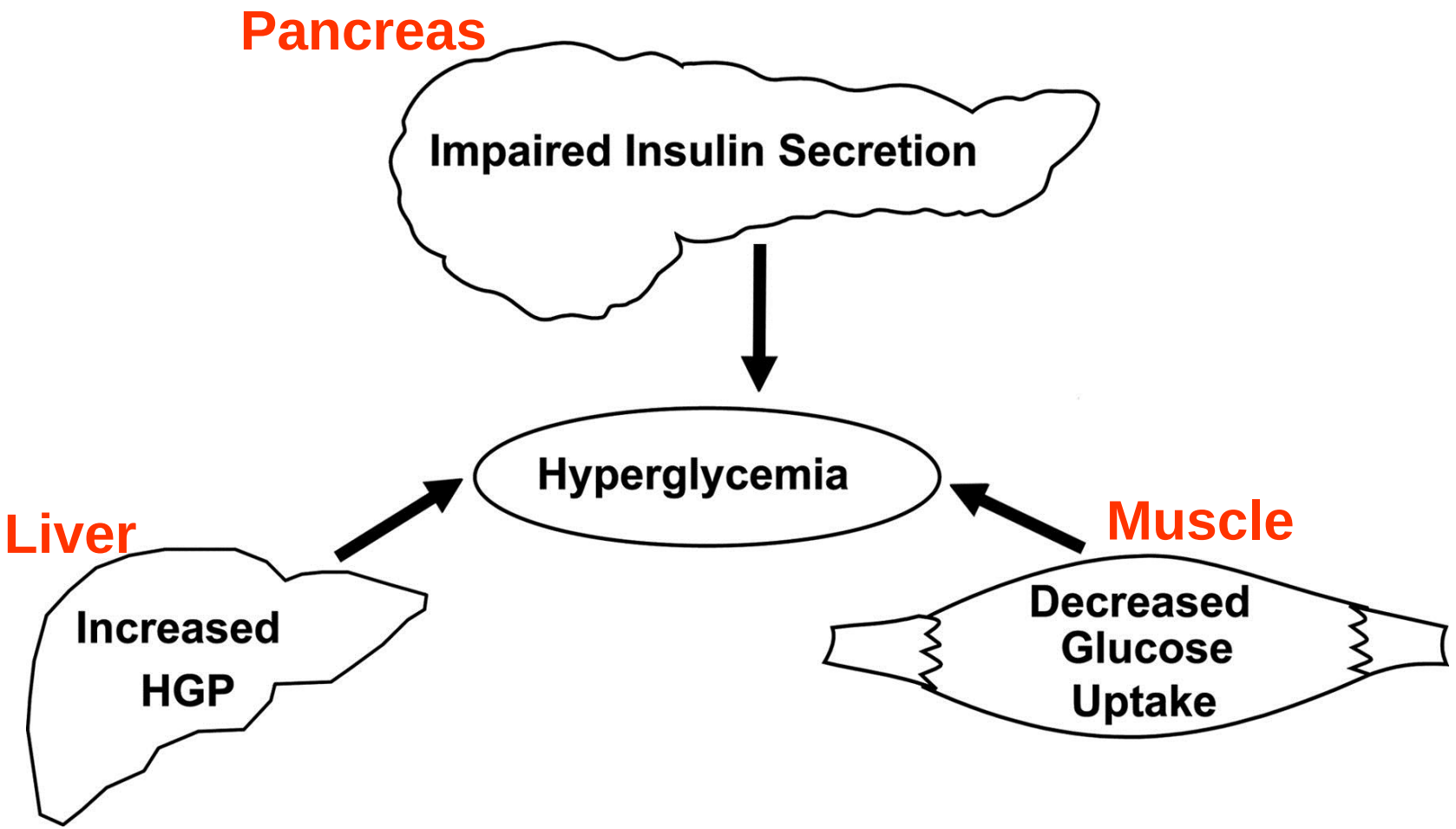
IDF Diabetes Atlas · 7th edition

香港患病趨勢持續上升



- 而現時全港約有七十多萬人患糖尿病，即每十個當中便有一人是病患者，數目亦有持續上升的趨勢。
- 據國際糖尿病聯盟 (IDF) 估計，到了2030年，香港的糖尿病人數將激增至九十二萬人 (即高百份之十三人口患病) 。
- 主要原因是跟港人的不良飲食習慣、肥胖及缺乏運動有莫大關係。
- 根據衛生署資料顯示，港人出現體重過重的情況達四成多，而且有不斷上升的趨勢。

Pathogenesis of type 2 diabetes: the triumvirate.

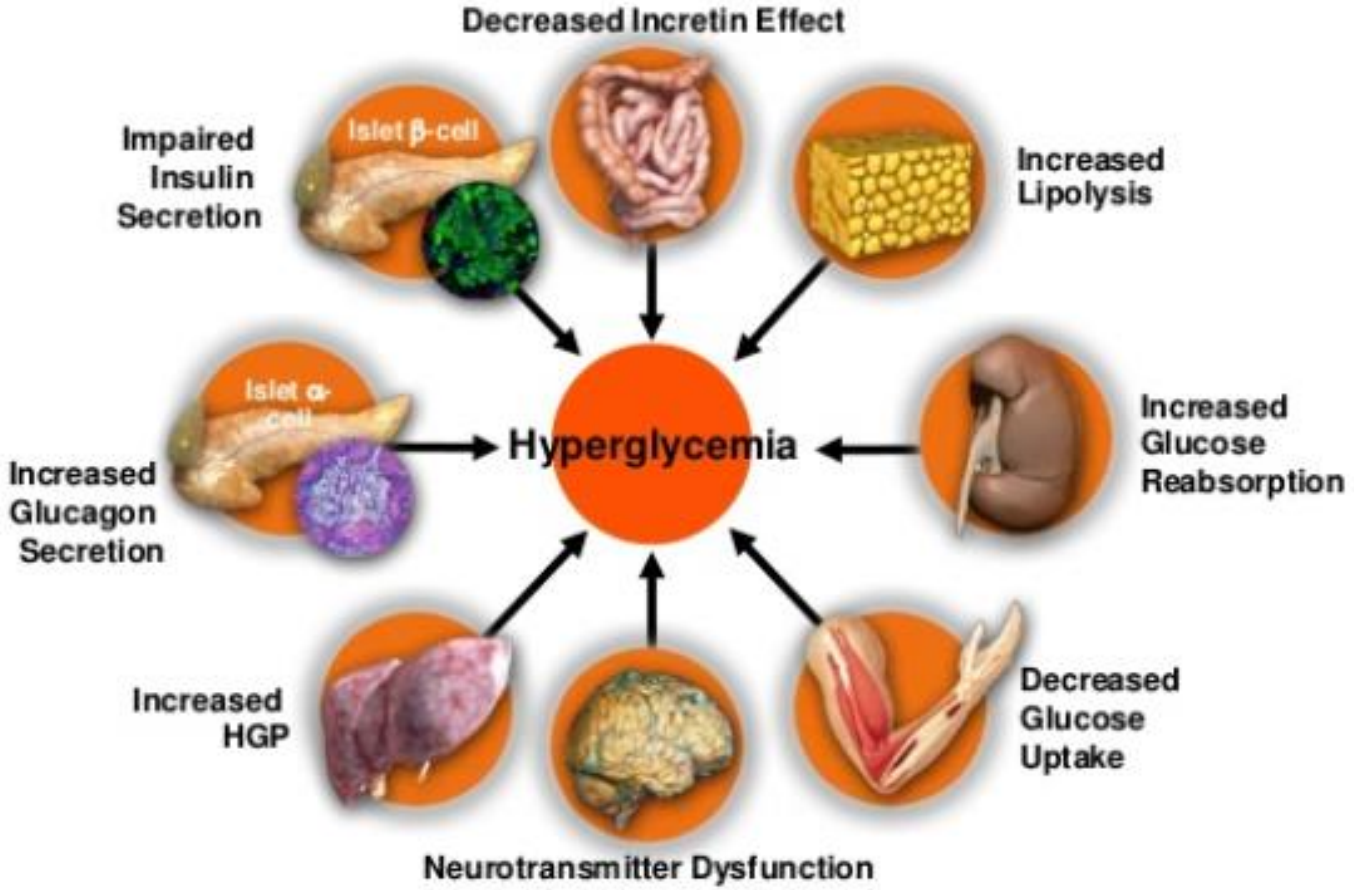


Ralph A. DeFronzo Diabetes 2009;58:773-795

©2009 by American Diabetes Association

American Diabetes Association.

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

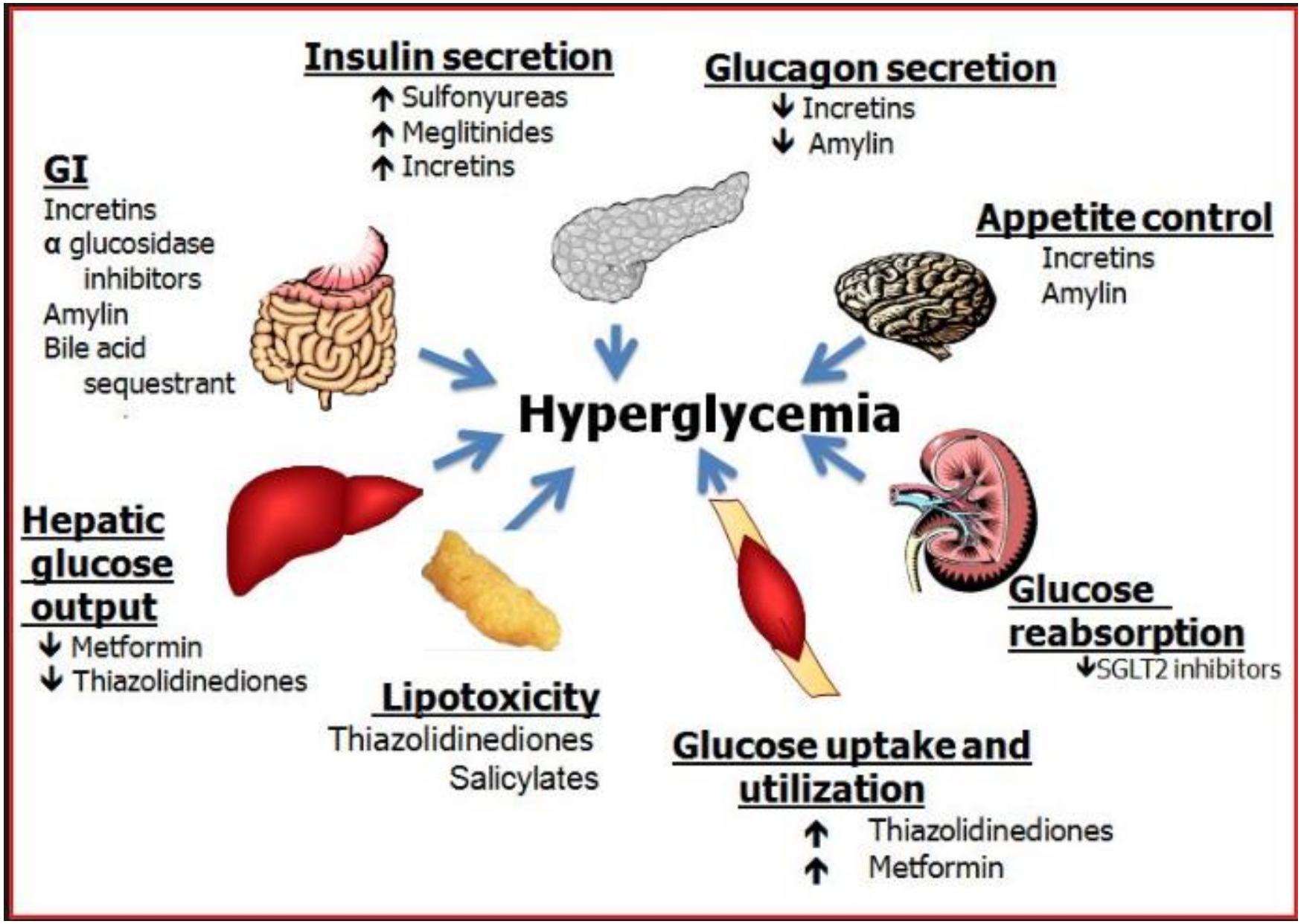
Commonly used agents in T2DM

Oral agents

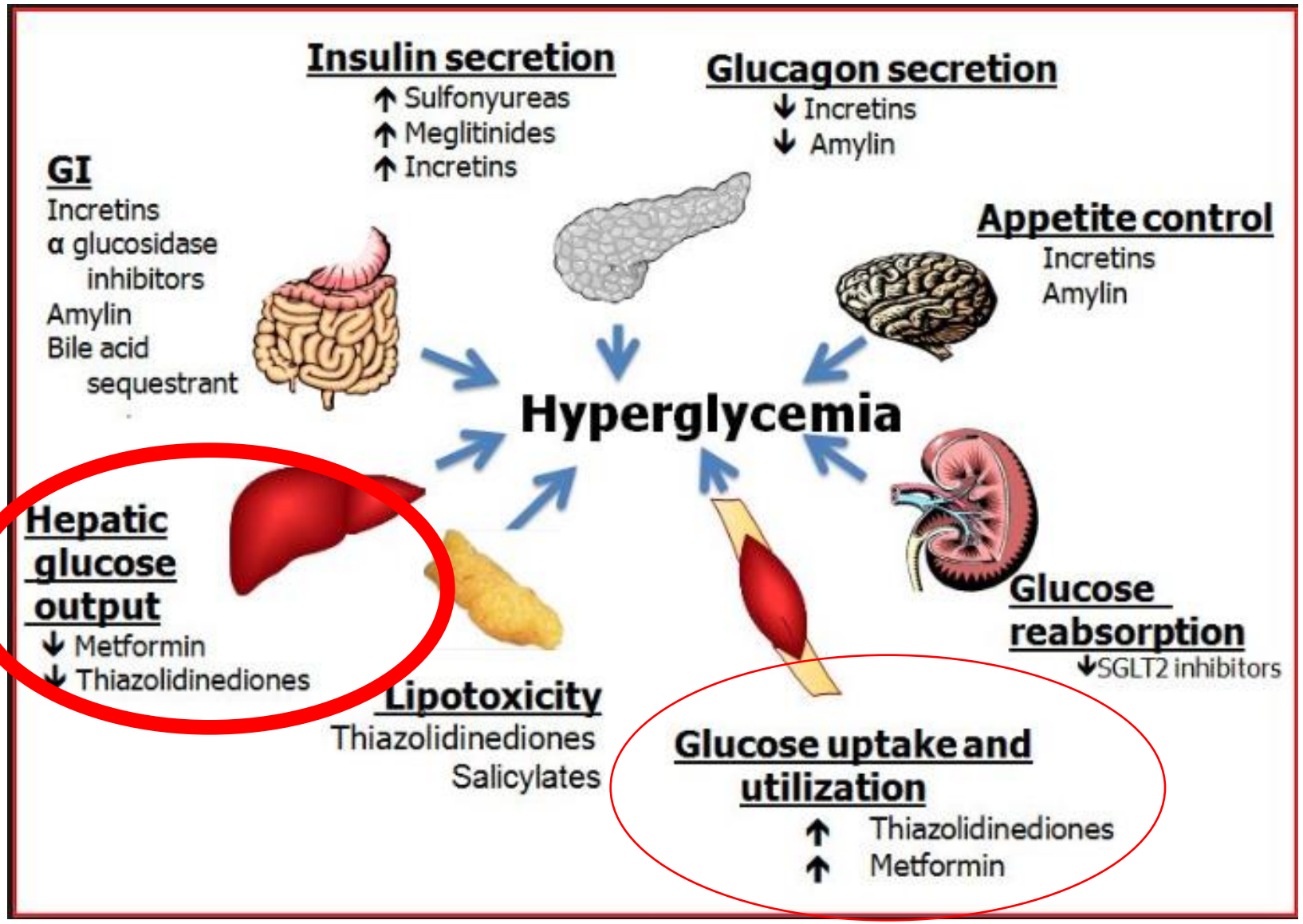
- Metformin
- Sulphonylurea
- α-Glucosidase Inhibitors
- Thiazolidinediones
- DPP4- inhibitor
- SGLT2- inhibitor

Injectables

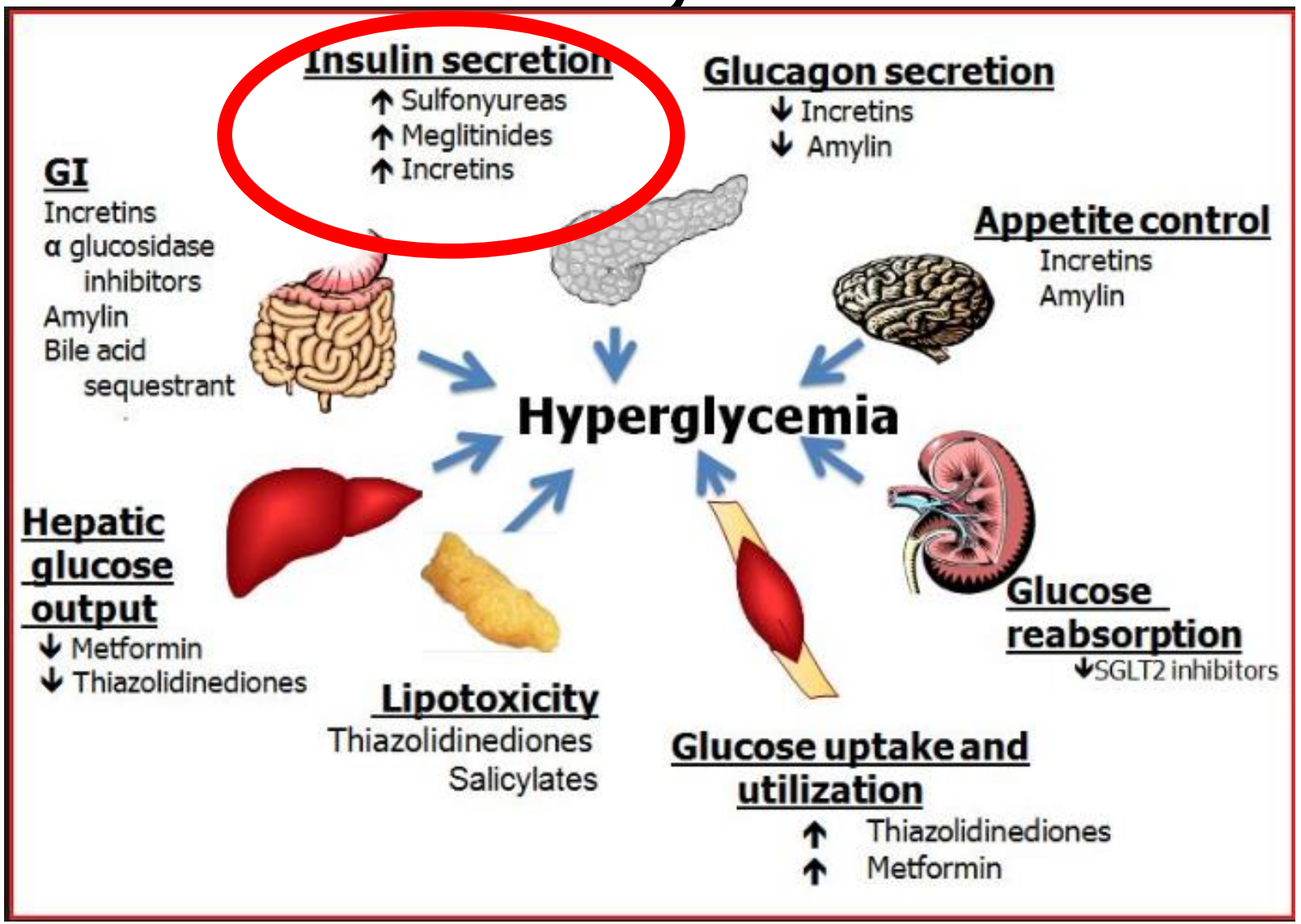
- Insulin
- GLP1 RA


Insulin secretion
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
Appetite control
Incretins
Amylin
Hyperglycemia
Hepatic glucose output
↓ Metformin
↓ Thiazolidinediones
Lipotoxicity
Thiazolidinediones
Salicylates
Glucose reabsorption
↓SGLT2 inhibitors
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin

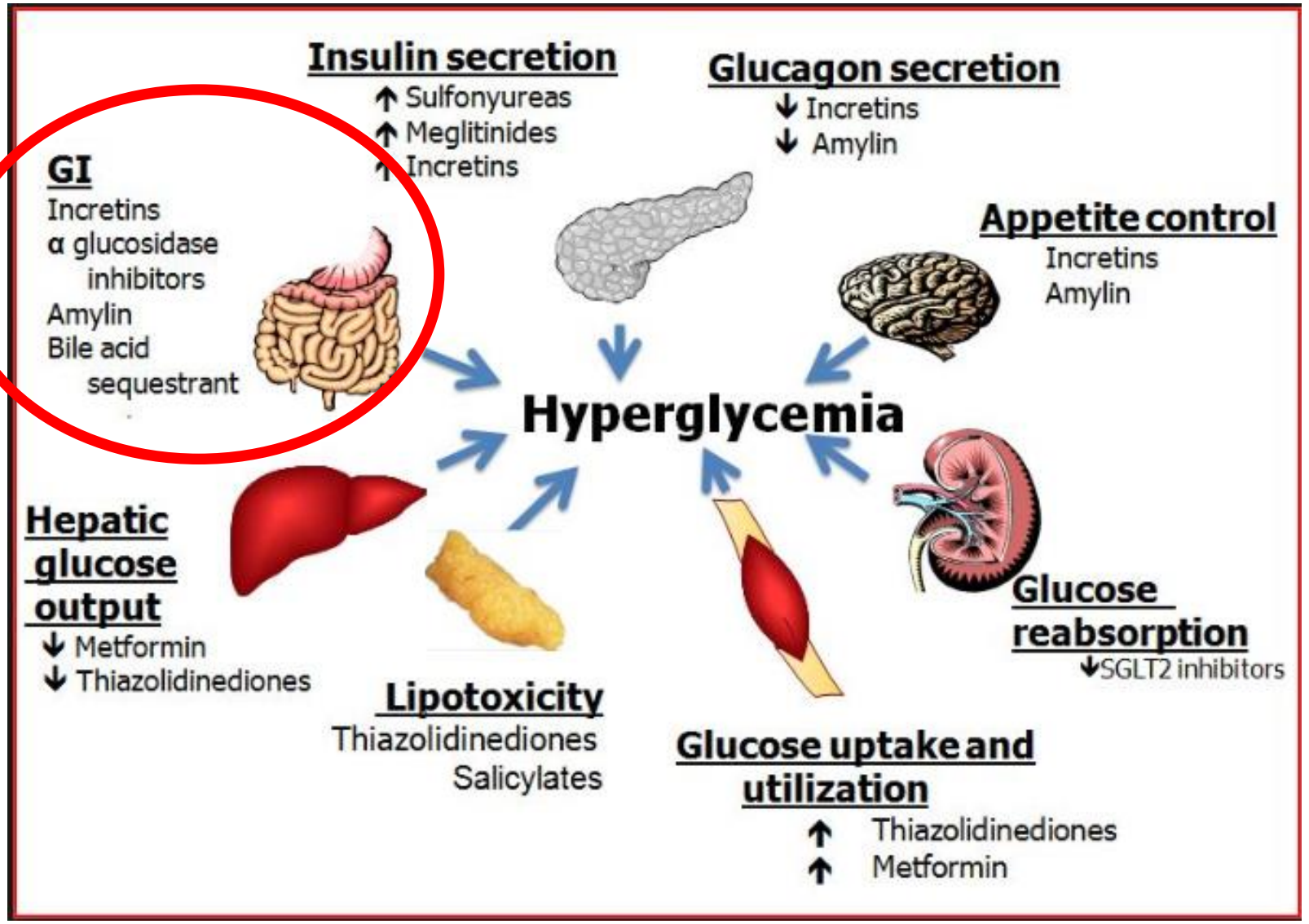
Metformin


Insulin secretion
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
Appetite control
Incretins
Amylin
Hyperglycemia
Hepatic glucose output
↓ Metformin
↓ Thiazolidinediones
Glucose reabsorption
↓SGLT2 inhibitors
Lipotoxicity
Thiazolidinediones
Salicylates
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin

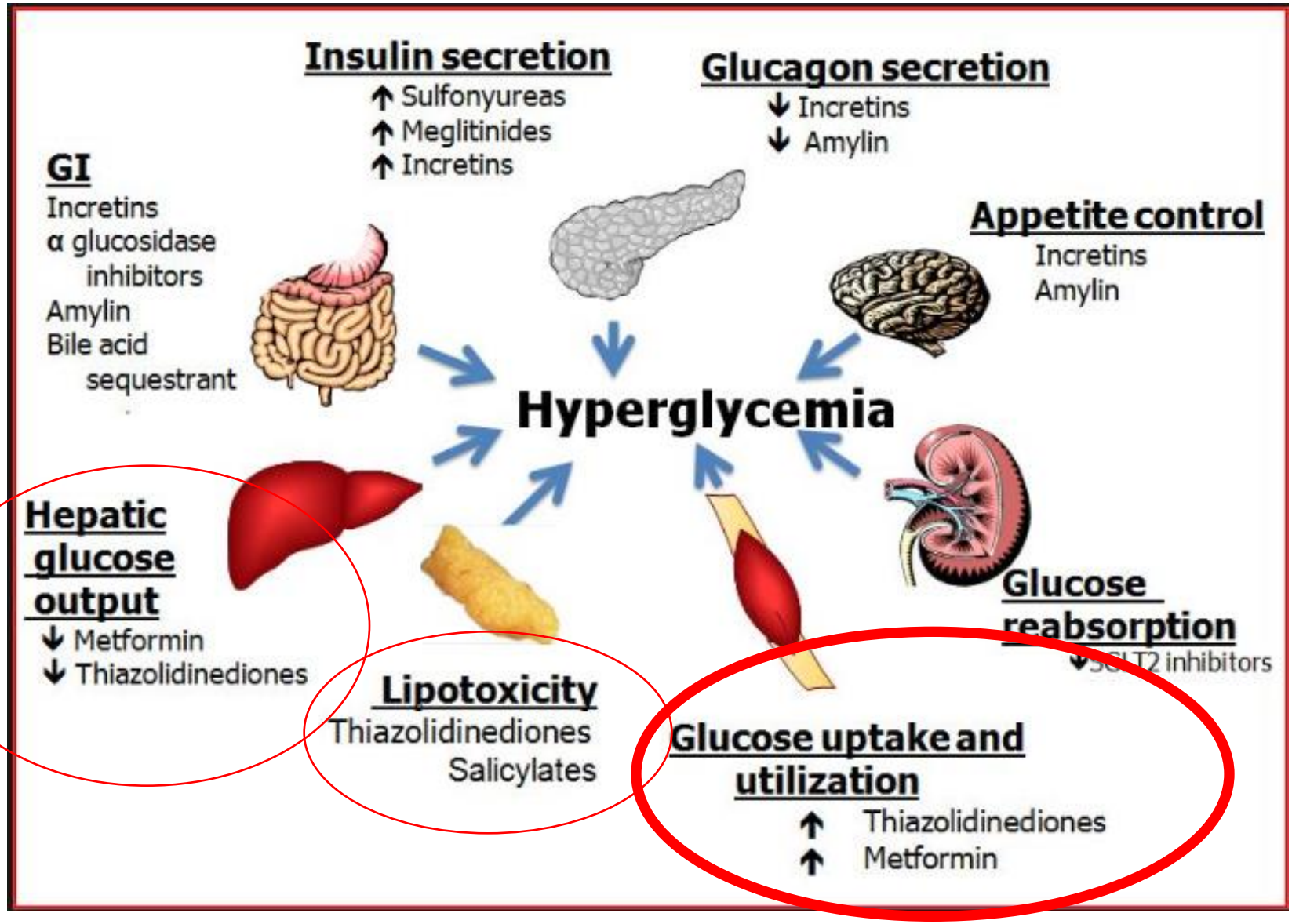
Sulfonylurea



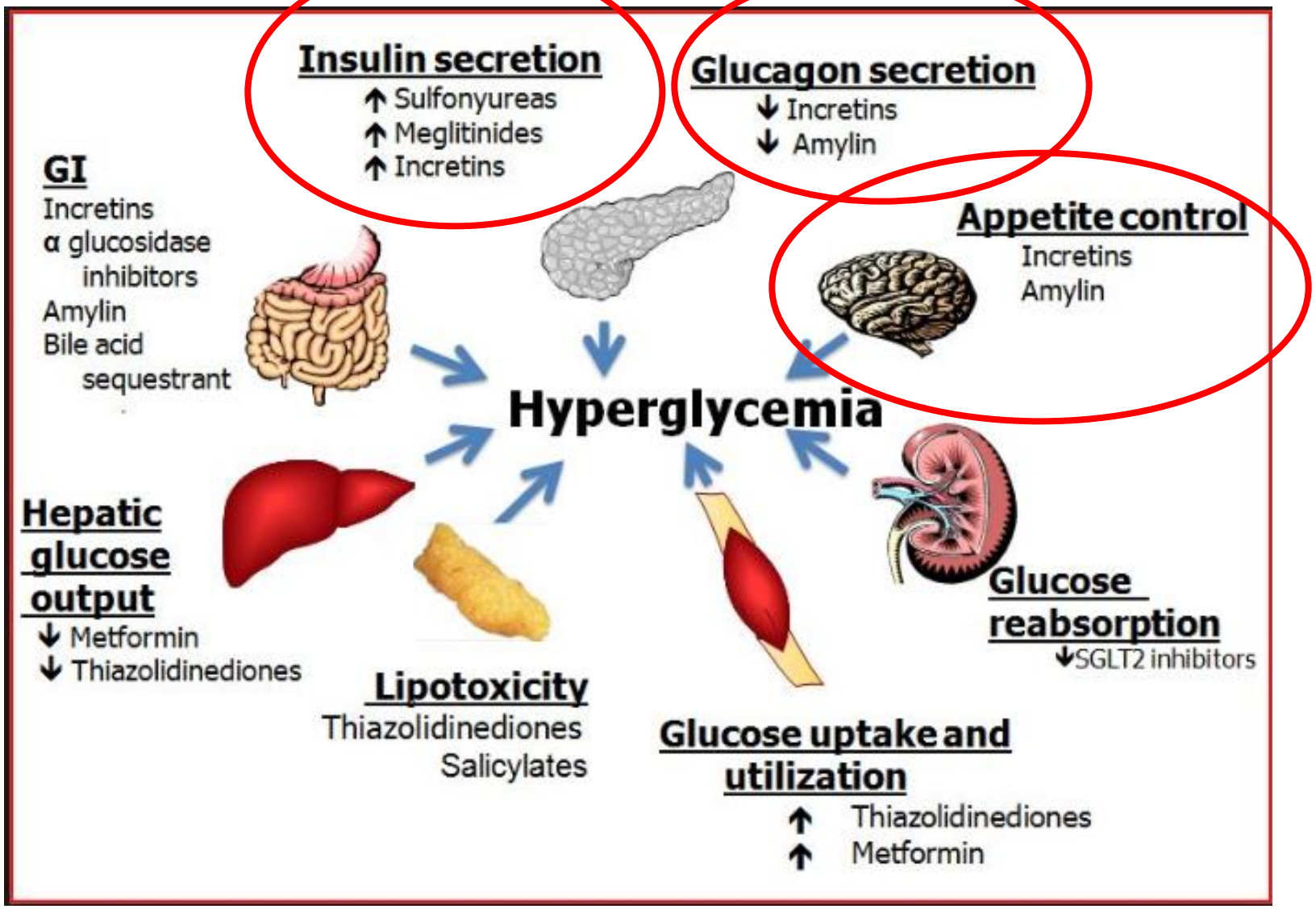
α-Glucosidase Inhibitors



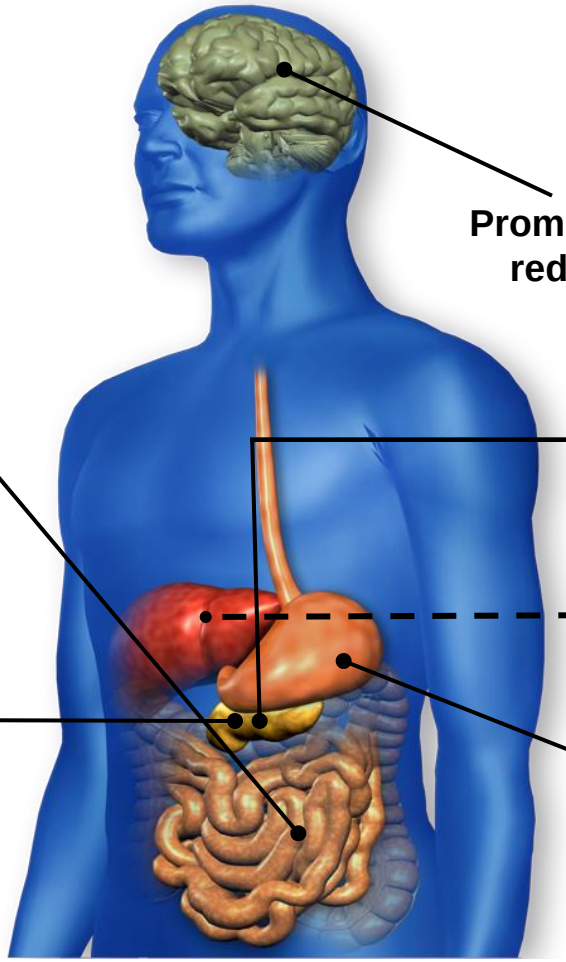
Thiazolidinediones (TZD)



Incretin based therapy- GLP1- RA/ DPP4- inhibitor



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

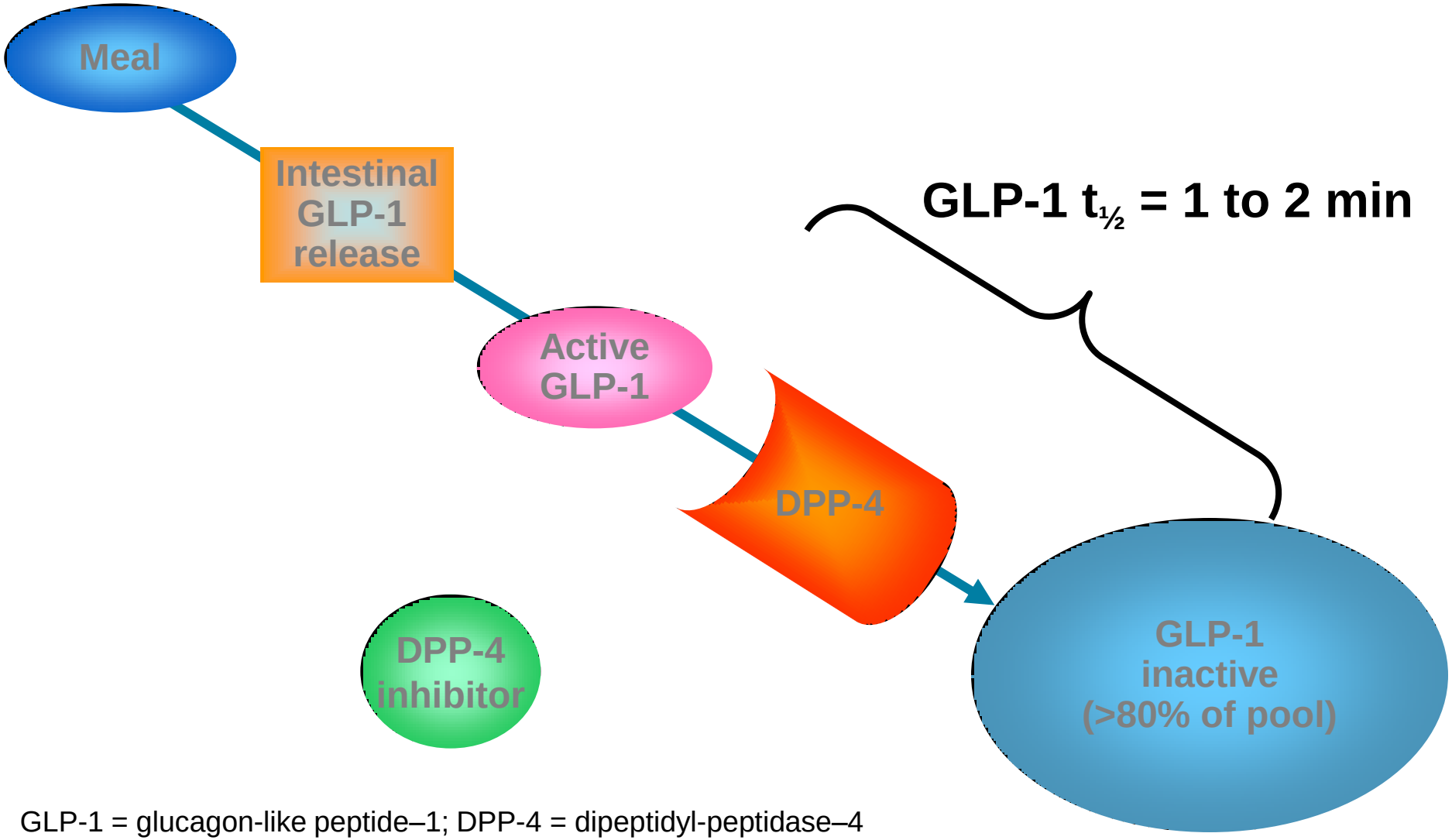
Liver: ↓ Glucagon reduces hepatic glucose output

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.

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.

Two classes of agents act via incretin effect

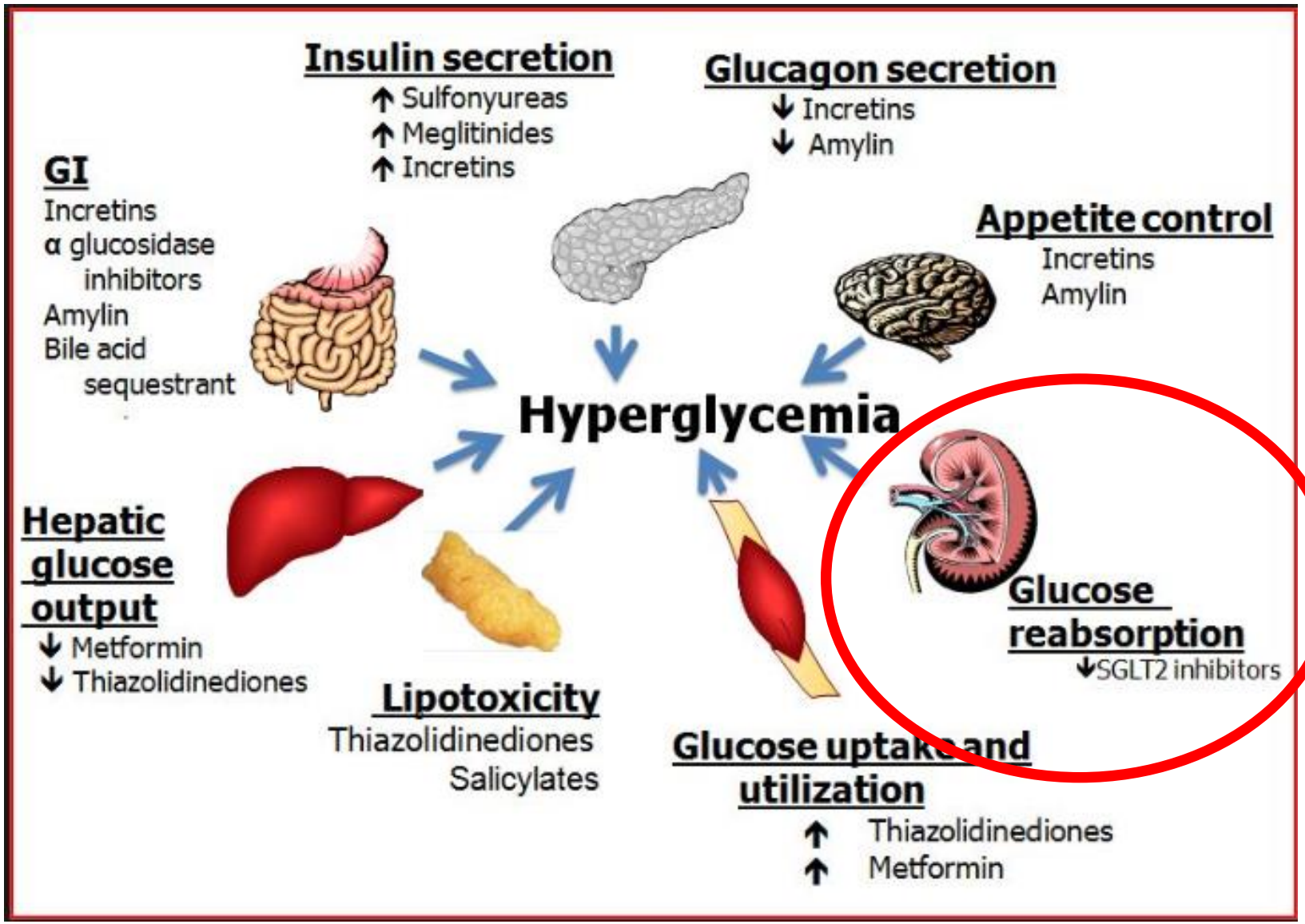
- GLP-1 receptor agonist

  Resistant to rapid proteolytics cleavage by DPP-4

- DPP4- inhibitors

  Limit the proteolytic cleavage by DPP-4.

SGLT2- inhibitor



Glucose Treatment

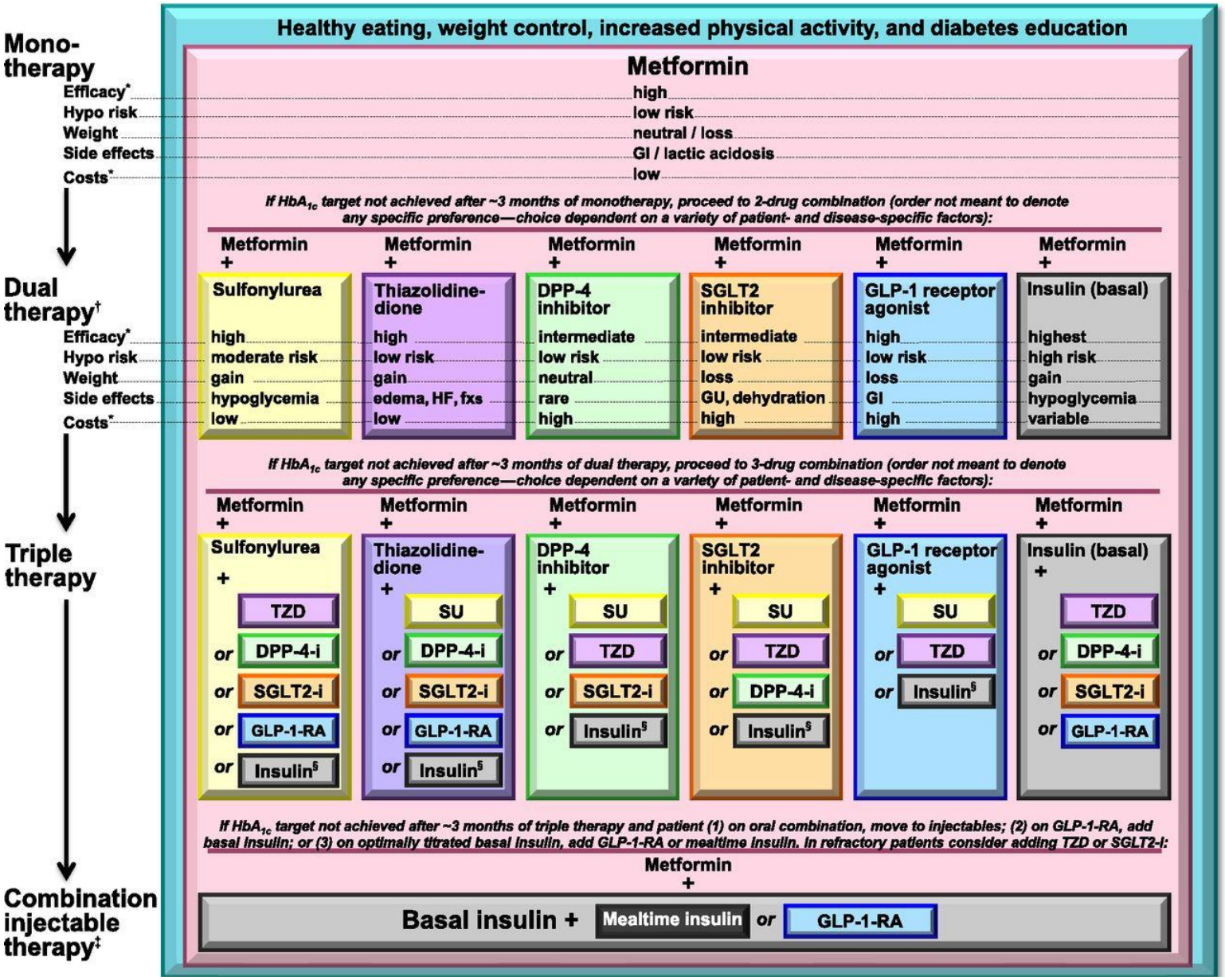
Anti-hyperglycemic intervention	**≈ A1c (%)*
Metformin	1.5-2.0
Sulfonylureas (SU)	1.5-2.0
Non-SU secretagogues	1.0-1.5
α-Glucosidase inhibitors	0.5-1.0
Thiazolidinediones (TZDs)	0.75-2.0
Insulin	N/A
Exenatide (GLP-1mimetics)	0.5-1.0
Dipeptidyl peptidase-4 (DPP-4) inhibitors	0.6-0.8
Pramlinitide (Amylin mimetic)	0.4-0.6
Cannabinoid-1 receptor blockade (Rimonabant)	0.6

***≈ A1c is directly proportional to baseline A1c value**

Comparison of anti-diabetic drug classes

	Class	Blood pressure	Body weight	Hypoglcaemia risk	Insulin mechanism
Oral	**Metformin**		↓	-	sensitizer
	SU		↑	↑	secretion
	TZD	↓	↑	-	sensitizer
	DPP4 i		-	-	secretion
	SGLT2 i	↓	↓	-	Independent
Injection	**GLP1 RA**	↓	↓	-	secretion
	Insulin		↑	↑	replacement

Antihyperglycemic therapy in type 2 diabetes: general recommendations.



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Silvio E. Inzucchi et al. Dia Care 2015;38:140-149

American Diabetes Association.

Case 1

- Mr. Chan, 56 years old, construction site worker
- Chronic smoker, ND

- Good past health
- Family history: mother has T2DM at the age of 65

- Referred for high blood glucose on body check-up

- P/E:
  BP 152/94 P 72bpm
  BW 89kg Height 163cm BMI 33.5

  CVS, chest, abd: unremarkable

Case 1

- Investigations

  normal cbc, LRFT

  random glucose 14.0

  VBG: no metabolic acidosis

  urine ketone –ve

  HbA1c 8.4 Fasting glucose 9.5

  Na/ K 135/4.2 Ur/Cr 3.5/57 eGFR 62

Case 1: How to manage this patient?

- Advise to quit smoking
- Lifestyle modification
- T2DM- ???

Case 1: What medication should be used for DM control in Mr. Chan?

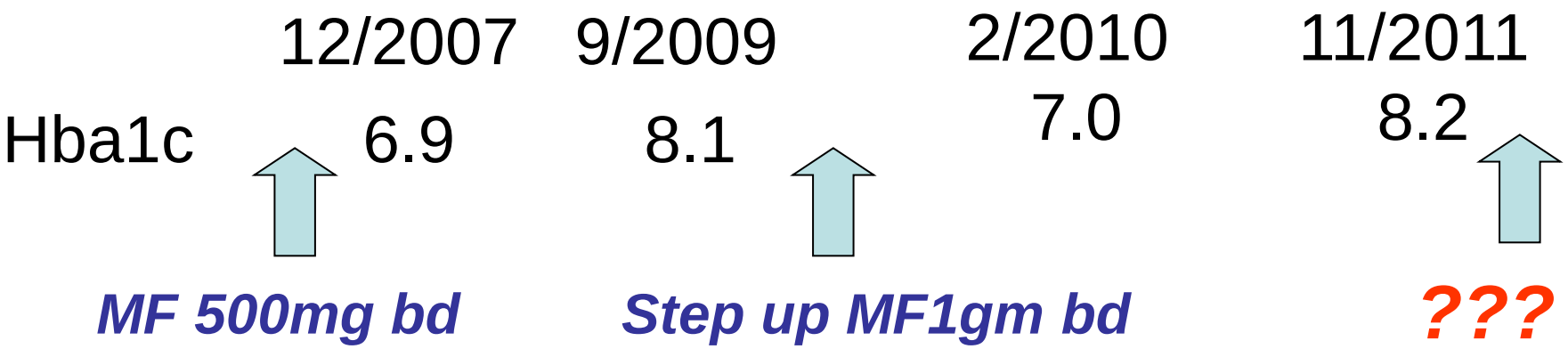
1. Metformin
2. Sulfonylurea
3. DPP4 inhibitor
4. SGLT2 inhibitor
5. Insulin

Metformin

- Recommended as a **first-line therapy** in newly diagnosed individuals.
- Decreases HbA1c by 1.5-2.0% **(very potent agent)**
- **No hypoglycaemia** if used alone
- Often leads to **modest weight reduction or weight stabilization**
- **Cardiovascular protection**. In the United Kingdom Prospective Diabetes Study (UKPDS), obese patients who were assigned initially to receive metformin rather than sulfonylurea or insulin therapy had a decreased risk of the aggregate diabetes-related endpoint (endpoints included both macrovascular and microvascular complications) and all-cause mortality.

Case 1

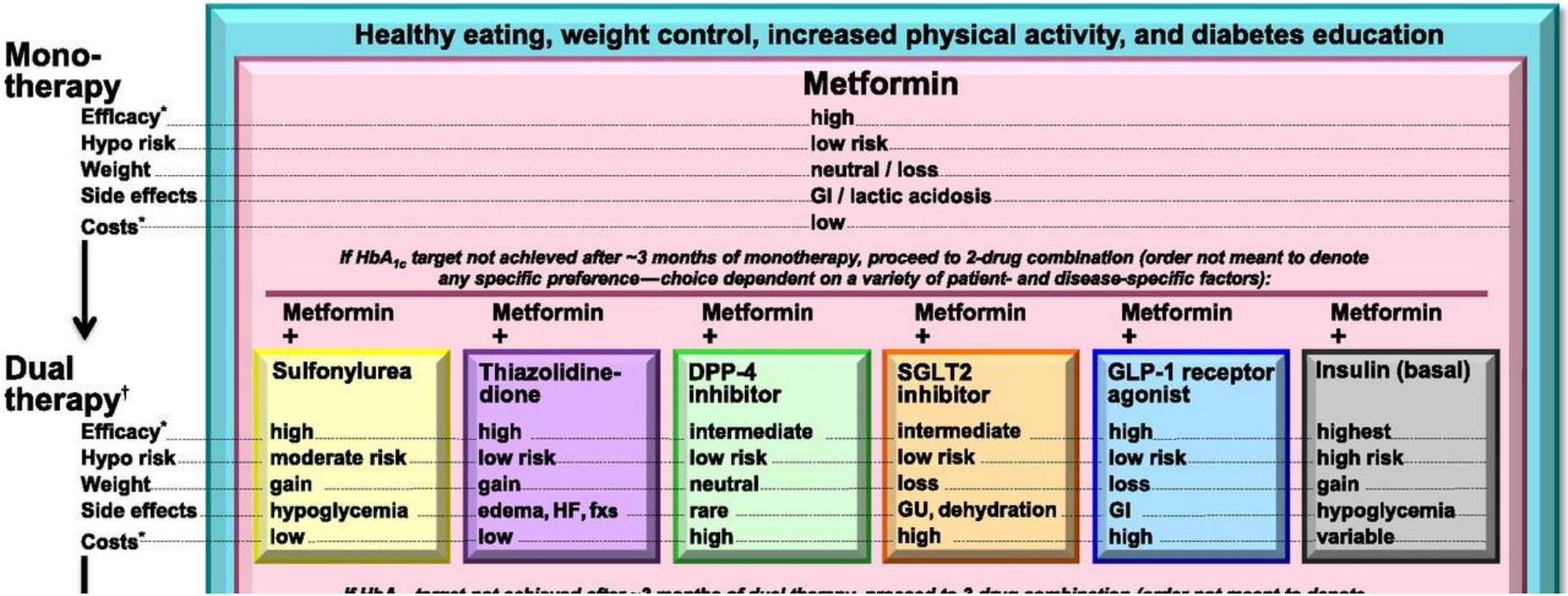
- Mr. Chan was put on
  metformin 500mg po bd
  zestril 5mg po daily



Case 1: How would you manage Mr. Chan?

1. Off metformin, and try another agent
2. Metformin + SGLT2 inhibitor
3. Metformin + Sulphonylurea
4. Metformin + DPP4 inhibitor
5. Metformin + GLP1- RA

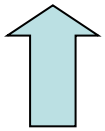
Algorithm of management of T2DM



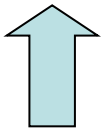
Case 1

- Mr. Chan preferred adding sulphonylurea as he could not afford SFI items and refused injection.

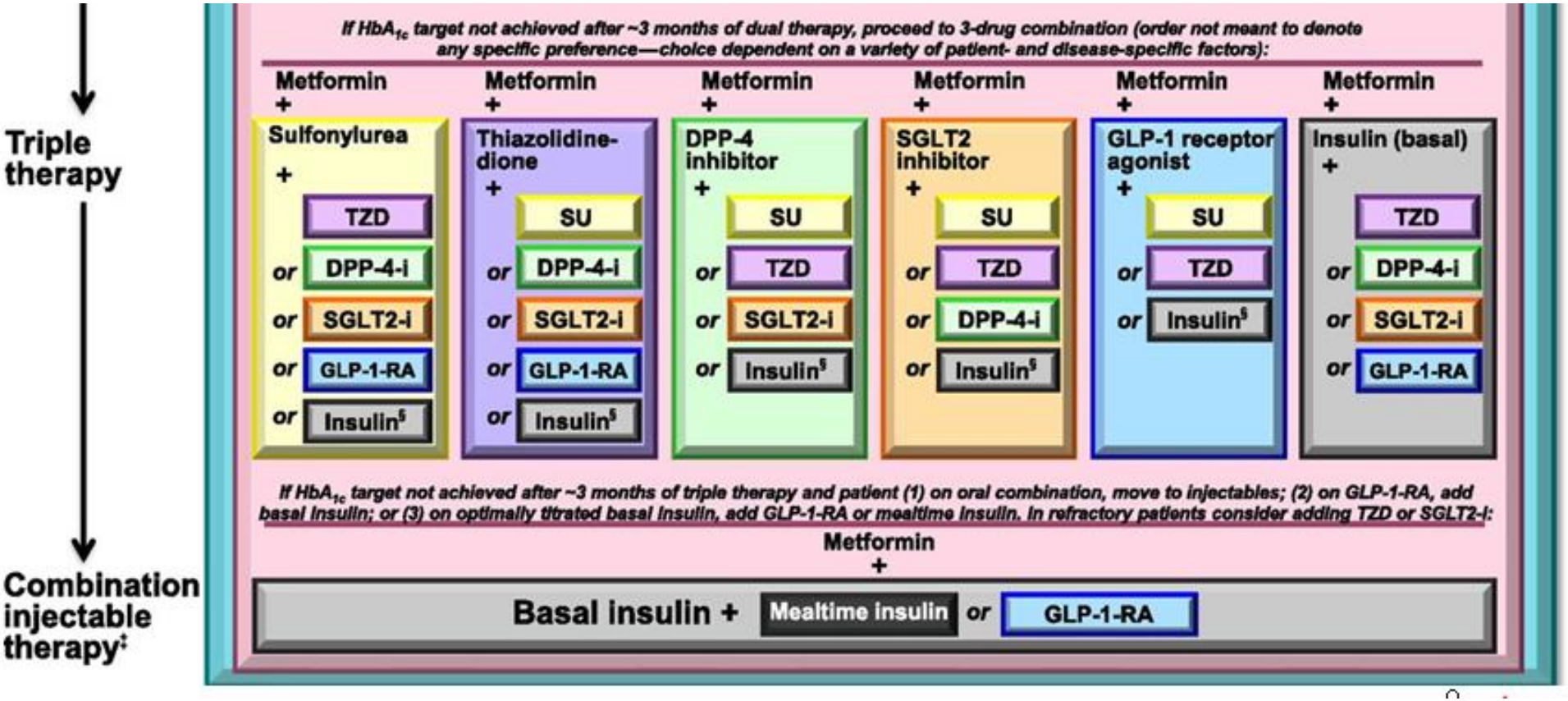
	11/2011	3/2012	12/2013
HbA1c	8.2	7.2	8.6



diamicron

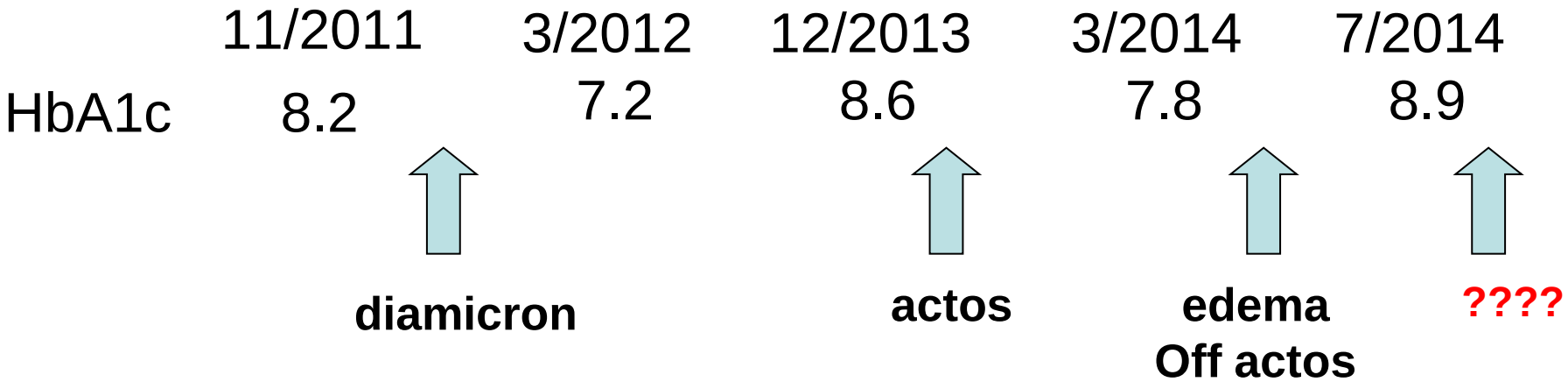


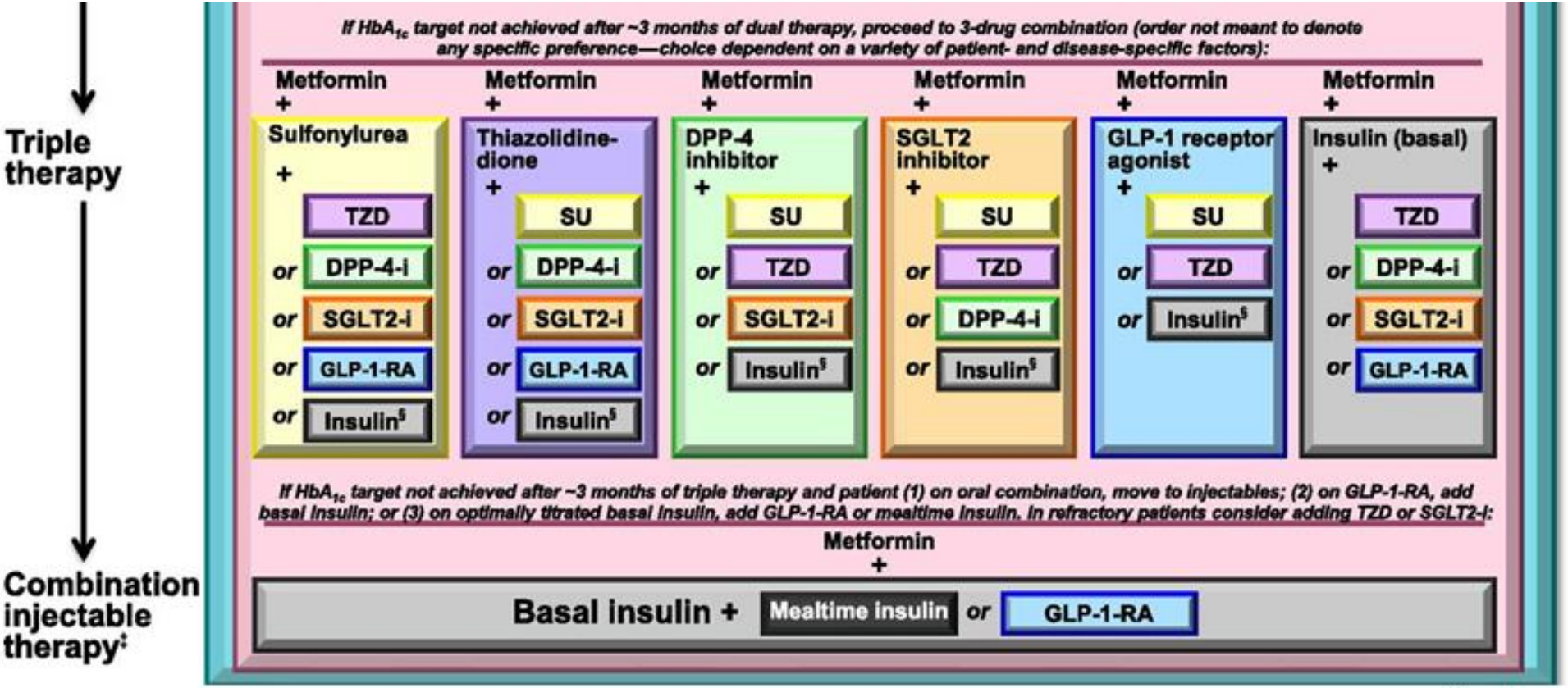
????


Triple therapy
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
Combination injectable therapy‡
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Case 1

- Different treatment options was discussed with Mr. Chan. As he could not SFI items and refuse insulin therapy, so actos was added to him.




Triple therapy
Combination injectable therapy‡
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidinedione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Case 1

- Mr. Chan finally agreed insulin therapy

- Current medication
  metformin 1gm bd diamicron 160mg bd
  protaphane HM 10 unit sc

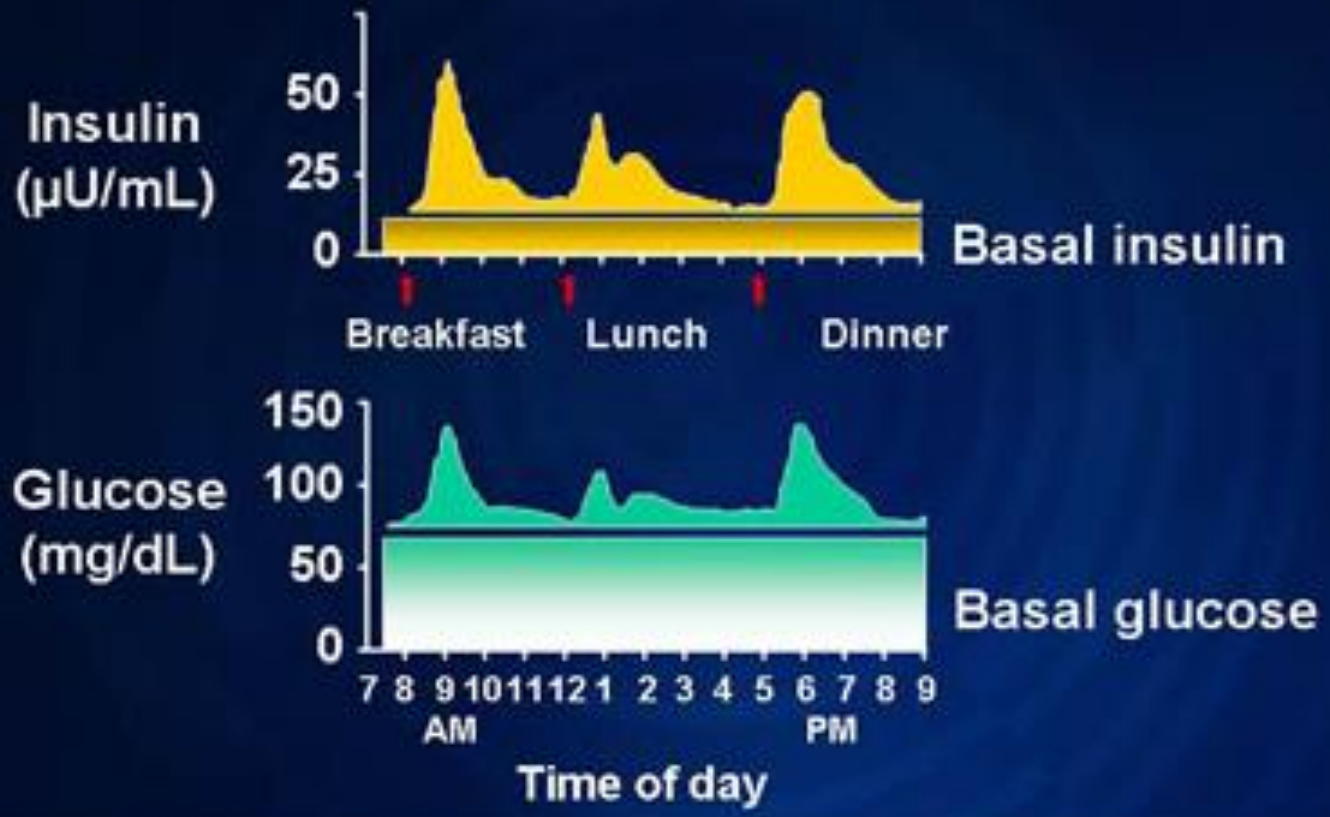
SMBG

(fasting) 4.2- 6.8
(post- breakfast) 9.8 -15.8
(pre-lunch) 4.7- 5.9
(post-lunch) 7.9-13.5
(pre-dinner) 6.2 -6.9
(post- dinner) 10.2-16.3

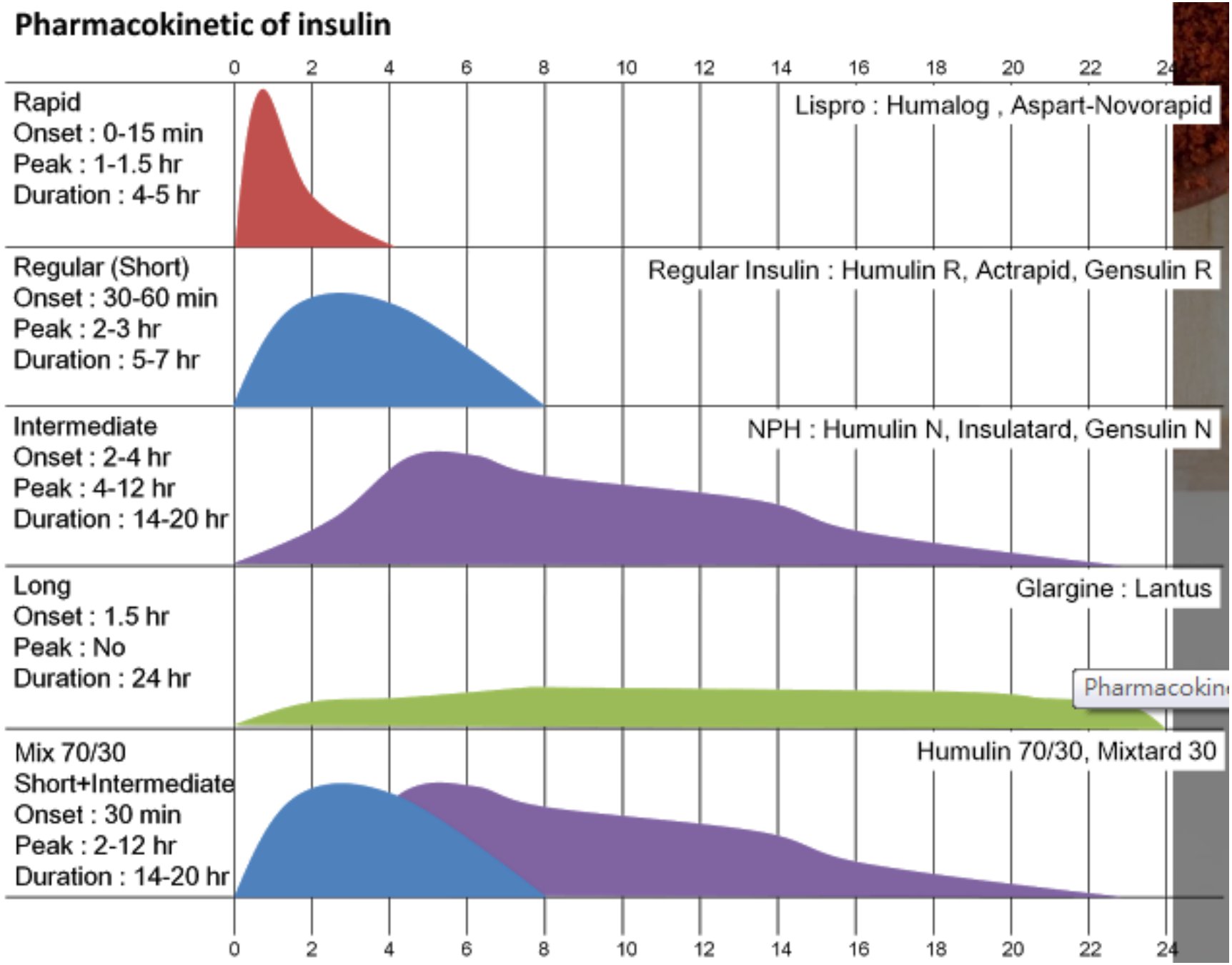
Satisfactory fasting glucose, but high post-prandial glucose…

What to do???

Physiologic Insulin Secretion: 24-hour Profile



Joslin Diabetes Center


Pharmacokinetic of insulin
0 2 4 6 8 10 12 14 16 18 20 22 24
Rapid
Onset : 0-15 min
Peak : 1-1.5 hr
Duration : 4-5 hr
Lispro : Humalog , Aspart-Novorapid
Regular (Short)
Onset : 30-60 min
Peak : 2-3 hr
Duration : 5-7 hr
Regular Insulin : Humulin R, Actrapid, Gensulin R
Intermediate
Onset : 2-4 hr
Peak : 4-12 hr
Duration : 14-20 hr
NPH : Humulin N, Insulatard, Gensulin N
Long
Onset : 1.5 hr
Peak : No
Duration : 24 hr
Glargine : Lantus
Mix 70/30
Short+Intermediate
Onset : 30 min
Peak : 2-12 hr
Duration : 14-20 hr
Humulin 70/30, Mixtard 30
0 2 4 6 8 10 12 14 16 18 20 22 24

Insulin preparation

- **Human vs analog**

  Human- e.g. protaphane/ actrapid, humulin R/ humulin N

  Analog- modification of insulin molecules was made to alter their pharmacokinetics

  e.g. lantus/ apidra, humalog, novorapid/ levemir

- **Efficacy**

  The newer rapid-acting insulin analogs may have a minor glycemic advantage over short-acting (regular) insulin in patients with type 1 diabetes, but not in patients with type 2 diabetes.

  The long-acting insulins, glargine and detemir causes less symptomatic and nocturnal hypoglycemia when compared with NPH

  In type 1 diabetes, insulin glargine may have a slight glycemic advantage

Insulin preparation- basal vs bolus

- **Basal insulin**

  - Suppress hepatic glucose production and maintain glucose control in fasting states.

  - E.g. once or twice daily intermediate – acting insulin (protaphane HM/ humulin N) or once daily long-acting insulin (lantus)

- **Bolus insulin**

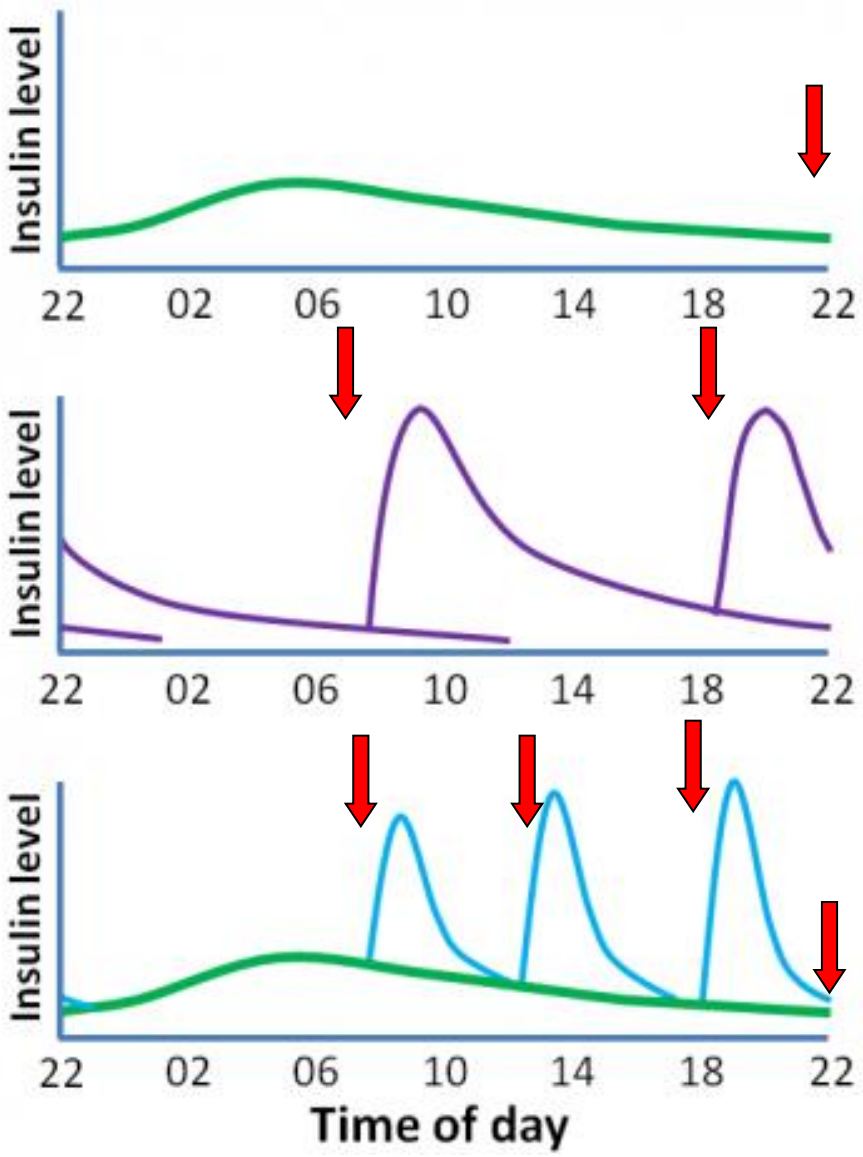
  - Cover extra requirements after food is absorbed.

  - E.g. short-acting (actrapid HN/ humulin R) or rapid-acting (novorapid/ humalog) insulin

Insulin therapy in T2DM

In type 2 diabetes, insulin is generally provided in several ways.

- As a ***basal supplement*** with an intermediate- to long-acting preparation for control of fasting glucose
- ***Twice daily regimen*** with intermediate-acting insulin, particularly helpful when pre-dinner BG are above goals.
- ***Basal bolus regimen*** - addition of a premeal (prandial) bolus dose of short-acting (regular) or rapid-acting (lispro, aspart, glulisine) insulin on top of basal insulin to cover the extra requirements after food is absorbed.
- As a premixed combination of intermediate-acting and short-acting or rapid-acting insulin



Once-daily basal insulin

Twice-daily mix-insulin

Basal-bolus therapy

Case 1: What are the treatment options in Mr. Chan ?

- Basal bolus regimen (adding pre-breakfast+ pre-lunch+ pre-dinner bolus insulin on top of basal insulin).

Advantage: Most physiological, Most flexible for titration, highest efficacy
Drawbacks: Inconvenience, frequent injection, and weight gain

- Twice daily regimen (with intermediate insulin or pre-mix insulin)

fewer injections, modest efficacy

- GLP1 RA + basal insulin

Less weight gain
GI side effects and cost

Insulin therapy – side effects

- Weight gain
- Hypoglycaemia
- Injection site pain
- Lipodystrophy

Figure 1: (a) Lipohypertrophy (b) Lipoatrophy



Case 1

- Suggested basal bolus therapy (i.e. 3+1 injection) in view of high post-prandial glucose after each meal (breakfast, lunch and dinner).

- However because of inconvenience, he preferred twice injection. Pre-mix injection bd (before breakfast and dinner) was added.

Case 2

- Mr. Lee, 56 years old, NSND
- PMH: HT, hyperlipidaemia. On zestril and zocor
- Admitted through AED for fatigue, weight loss of 20lb within 2 months, polyuria and polydipsia
- P/E:

  BP 134/72 P 72 BW 54kg Height 165cm BMI 19.8

  Slightly dehydrated

  CVS, chest, abd: unremarkable

Case 2

- Investigations

normal cbc
Na/ K 145/4.7 Ur/ Cr 9.2/ 101
RG 19.4 FG 15.1 HbA1c 11.2
VBG: no metabolic acidosis
urine ketone –ve
MSU C/ST: no growth
CXR: clear

Case 2: How would you manage this patient?

1. Metformin monotherapy
2. SU monotherapy
3. Dual therapy: metformin+ SU
4. Dual therapy: metformin + DPP4-inhibitor
5. Dual therapy: metformin + insulin

Case 2

- Consider initiating therapy with a dual combination when HbA_{1c} is ≥9% to more expeditiously achieve target.
- Insulin should be considered a part of any combination regimen when hyperglycemia is severe, especially if the patient is symptomatic or if any catabolic features (weight loss, any ketosis) are evident.
- Consider initiating combination therapy with insulin when blood glucose is ≥16.7and/or HbA_{1c} ≥10. Potentially, as the patient's glucose toxicity resolves, the regimen can be subsequently simplified.

Case 3

- Mrs. Wong, 69 year old
- PMH: T2DM for 20 years, HT, hyperlipidaemia, CHF

- Usual medication
  metformin 500 mg bd
  zocor 10mg nocte
  norvacs 10mg daily
  betaloc 50mg po bd

- Defaulted FU since 2012, and come back today for FU…

  Investigation:
  HbA1c 8.9% FG 12.3
  Ur/ Cr 15.2/ 295 (normal back in 2014) eGFR 22

Case 3: What would you do?

i) Step up metformin

ii) Stop metformin and start insulin therapy

iii) Stop metformin and start DPP4- inhibitor

iv) Stop metformin and start low dose actos

v) Stop metformin and start SGLT2-inhibitor

Management of DM in patients with renal impairment

- Chronic kidney disease (CKD) is associated with insulin resistance and, in advanced CKD, decreased insulin degradation. The latter can lead to a marked decrease in oral hypoglycaemic agents/ insulin requirement or even the cessation of therapy in patients with type 2 diabetes.

- The choice of initial agent depends upon glycemic goals and the risk of medication-associated adverse events.

Metformin

- Primarily excreted unchanged in urine.
- Patients with kidney dysfunction are more susceptible to drug accumulation and ***lactic acidosis***
- No definite cut-off of when not to use metformin

  2012 Kidney Disease Outcomes Quality Initiative (K/DOQI)

eGFR <30 mL/min	**X**
eGFR 30- 44mL/min	left up to the discretion of the clinician
eGFR ≥ 45 mL/min	√

Lactic acidosis

- Rare (3 cases per 100,000 patient-years)
- Should be suspected in any diabetic patient with metabolic acidosis without ketoacidosis (ketonuria and ketonemia)
- Characterized by elevated blood lactate levels (>5 mmol/L), metabolic acidosis with increased anion gap

- Non-specific symptoms (nausea, vomiting, abdominal pain, lethargy, hyperventilation, and hypotension)
- Medical emergency with high mortality rate if untreated
- Predisposed by conditions associated with hypoperfusion and hypoxemia

Contraindications

Metformin is contraindicated in patients with factors predisposing to lactic acidosis.

- Impaired renal function (eGFR< 30ml/min)
- Concurrent liver disease or alcohol abuse
- Unstable or acute heart failure at risk of hypoperfusion and hypoxemia
- Past history of lactic acidosis
- Decreased tissue perfusion or hemodynamic instability due to infection or other causes

Metformin

Remarks:

Patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) or undergo a surgical procedure (with potential compromise of circulation) should have metformin held until stable renal function can be established (normal urine output, normal serum creatinine, and no physical exam evidence of fluid overload or circulatory compromise).

Serum creatinine is typically assessed two to three days after contrast administration.

Sulfonylureas

- Insulin secretogogues - control blood glucose levels by directly stimulating insulin secretion in the pancreatic β cells.

- First generation
  - Tobutamide
  - Chlorpropamide

- Second generation
  - Glipizide (glucotrol)
  - Gliclazide (diamicron)
  - Glibenclamide (daonil)

- Third generation
  - Glimepiride (amaryl)

Sulfonylureas

- If an oral agent is used, the short-acting sulfonylurea, glipizide, is the preferred agent among patients with eGFR<30 mL/min/1.73.

- The dose for glipizide is 2.5 to 10 mg/day.

- Glibenclamide and other long-acting sulfonylureas are generally not recommended in any CKD patient with type 2 diabetes, because of the risk of hypoglycemia.

Thiazolidinediones (TZD)

- Medications in this class:
  Pioglitazone (Actos®)
  rosiglitazone (Avandia®)

- In 2010, the European Medicines Agency suspended sales of rosiglitazone, owing to concern regarding cardiovascular safety and the availability of alternative therapies.

- In HK, all drug containing rosiglitazone were withdrawn from market since September 2010

Thiazolidinediones (TZD)

- Given the risk of edema formation and heart failure, thiazolidinediones should be avoided in patients with advanced CKD, especially if they have pre-existing heart failure.

- Increased risks for urinary bladder cancer with the use pioglitazone – avoid its use in patients with active / past history of bladder cancer /haematuria with unknown cause.

α-Glucosidase Inhibitors

- Metabolism: extensively degraded in the intestine by bacterial and digestive enzymes
- 34 % as inactive metabolites are excreted by kidney
- Contraindicated in patients with inflammatory bowel disease, cirrhosis, or elevated plasma creatinine (>177 μmol/l)

DPP4-inhibitors

	Sitagliptin	Saxagliptin	Vildagliptin	Linagliptin	Alogliptin
Dosage	100 mg qd	5 mg qd	50 mg bid	5 mg qd	25 mg qd
Earliest approval*	2005	2009	2007	2011	2010
Approximate half-life	12 hours	2 hours	3 hours	>120 hours	21 hours
Elimination	Renal clearance (75%)	Hepatic metabolism to active metabolite (half as potent) Renal excretion (12%-29% unchanged parent and 21%-52% as metabolite)	Renal metabolism and renal clearance (55% as unchanged parent and approximately 26% as metabolite)	Entero-hepatic Eliminated unchanged in feces via biliary excretion (85%)	Renal clearance (63%)
Important drug interactions	Low clinically meaningful interactions	Low clinically meaningful interactions	Low clinically meaningful interactions	Efficacy may be limited in patients receiving concurrent inducers of CYP3A4 or P-gp (eg, rifampicin)	Low clinically meaningful interactions

DPP4 inhibitor

Summary of Dose Reductions Recommended in Patients With Renal Impairment

	Sitagliptin	Saxagliptin	Vildagliptin	Linagliptin	Alogliptin
Usual dose	100 mg qd	5 mg qd	50 mg bid	5 mg qd	25 mg qd
CrCl ≥50 mL/min	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
CrCl ≥30 to <50 mL/min	Dose reduction to 50 mg/day	Dose reduction to 2.5 mg	Not recommended	No dose adjustment required	Dose reduction to 12.5 mg/day
CrCl <30 mL/min	Dose reduction to 25 mg/day	Dose reduction to 2.5 mg	Not recommended	No dose adjustment required	Dose reduction to 6.25 mg/day
End-stage renal disease	Dose reduction to 25 mg/day	2.5 mg administered following dialysis	Not recommended	No dose adjustment required	Dose reduction to 6.25 mg/day
Peritoneal dialysis	Dose reduction to 25 mg/day	No data available	Not recommended	No dose adjustment required	Dose reduction to 6.25 mg/day

GLP-1 RA

- Exenatide (Byetta) –The first GLP-1 RA (exenatide twice daily) approved in Europe in 2006. SC, bd, 5mcg/ 10mcg



- Liraglutide (Victoza) – the second GLP-1 RA marketed in Europe in 2009. SC, daily, 0.6mg/1.2mg/1.8mg



- Lixisenatide (lyxumia) – marketed in 2013. SC, daily, 10mcg/20mcg



GLP-1 RA

- Used with caution in patients with moderate CKD (CrCl 30-50ml/min) and not at all in patients with severe CKD (CrCl <30ml/min)

SGLT2 inhibitor

Dapagliflozin

- Contraindicated in patients with eGFR <60mL/min

Empagliflozin

- Contraindicated in patients with eGFR <45ml/min

Insulin

- the starting dose of insulin may need to be lower than would ordinarily be used for patients with normal kidney function.

- CKD is associated with decreased renal and ultimately hepatic metabolism of insulin

CKD patients with type 2 diabetes

- May be treated with an oral agent, although many patients end up on insulin therapy because it is more effective.

- Preferred oral agents in patients with eGFR <30 mL/min/1.73 : short-acting sulfonylurea, e.g. glipizide or meglitinide repaglinide.

Case 3: What would you do?

i) Step up metformin ✗

ii) Stop metformin and start insulin therapy √

iii) Stop metformin and start DPP4- inhibitor

modest HbA1c lowering effect

iv) Stop metformin and start low dose actos

Risk of fluid overload, CHF symptoms

v) Stop metformin and start SGLT2-inhibitor

Contraindicated in eGFR <60mL/min

Case 4

- Mrs. Cheung 79 years old
- NSND

- PMH: T2DM for 25 years, HT, renal impairment, AF, history of stroke and IHD

- Current medications

  warfarin 2mg nocte

  betaloc 100mg bd norvasc 10mg daily

  zestril 10mg daily

  Humulin R 8 unit sc before dinner

  Humulin N 12 unit sc bedtime

  diamicron 80mg bd

Case 4

- Investigations (latest FU)
  wcc 4.3 Hb 10.3 plt 247
  Na/ K 136/ 4.9 Ur/ Cr 12.1/ 231
  HbA1c 7.8 FG 12.1

-> stepped up insulin dosage because of optimal glycaemic control

- Admitted through AED for hypoglycaemic symptoms, with H'stix 2.3 checked by ambulance man.
  Patient has URTI symptoms and poor appetite x2/7

Hypoglycaemia in patients with DM

Hypoglycaemia is defined by the ***Whipple's triad***

1) The development of autonomic or neuroglycopenic symptoms consistent of hypoglycaemia.

2) Presence of low plasma or blood glucose concentration, and

3) Resolution of the symptoms after the glucose concentration is raised.

	Typical Symptoms	**Plasma Glucose Concentration**
Documented symptomatic hypoglycaemia	Yes	≤ 3.9 mmol/L
Probable symptomatic hypoglycaemia	Yes	Not proven (presumably ≤ 3.9 mmol/L)
Asymptomatic hypoglycaemia	No	≤ 3.9 mmol/L
Severe hypoglycaemia	Assistance of another person is required	Mostly not available during this event
Pseudohypoglycaemia	Yes	≥ 4.0 mmol/L

Symptoms of hypoglycaemia

- *Neurogenic (autonomic) symptoms*

- Resulted form activation of autonomic nervous symptoms
- Tremor, palpitation, anxiety, sweating, hunger, and paresthesia

- *Neuroglycopenic symptoms*

- Resulted from reduced brain sugar
- Weakness, fatigue, difficult thinking, confusion, behavioral changes, seizure, coma

Counterregulatory defenses against hypoglycaemia

1. **Decrease insulin secretion** – favors ↑ hepatic (& renal) glucose production ↓ glucose utilization by insulin-sensitive tissue e.g. muscle

2. **Increase glucagon secretion** – stimulates hepatic glycogenolysis and hepatic gluconeogenesis

3. **Increase epinephrine secretion** – stimulate hepatic glycogenolysis and gluconeogenesis (& renal gluconeogenesis)

Impaired defenses in T1DM and advanced T2DM patients.

Hypoglycaemic unawareness

- Result of reduced sympathoadrenal responses & the resultant reduced neurogenic symptom responses to a given level of hypoglycaemia.

Hypoglycaemia- associated autonomic failure

- Vicious cycle of recurrent hypoglycaemia
- Recent antecedent iatrogenic hypoglycaemia causes both defective gluc counterregulation (reducing the epinephrine response) and HU.

Consequences of hypoglycaemia

- Preventing the maintenance of euglycemia over a lifetime.
- Morbidity
- In the ADVANCE and ACCORD trials, severe hypoglycaemia was associated with a significant increase risk of major cardiovascular events and a 1.4 to 3- fold higher risk of mortality.
- According to Hong Kong Diabetes Registry, type 2 diabetic patients with severe hypoglycaemia have a higher incidence of all site cancer and mortality compared to their counterpart.

BMJ 2010;340:b4909
N Engl J Med 2010;363:1410-1418

Risk factors for hypoglycaemia

1. Duration of insulin therapy & loss of endogenous insulin
2. Past history of severe hypoglycamaemia / hypoglycaemia unawareness
3. Tight glycaemic control
4. Old age
5. Cognitive dysfunction
6. Presence of renal impairment or macroalbuminuria
7. Alcohol
8. Exercise (prolonged duration, intensity, inadequate energy supply)

- Insulin and insulin secretagogues (sulfonylurea, esp long-acting drug, such as glibencladmide, and meglitinides) are the most common drugs associated with hypoglycemia.

- Agents that do not cause unregulated hyperinsulinemia, such as metformin, alpha glucosidase inhibitors, thiazolidinediones, GLP1-RA , DPP4 inhibitors and SGLT2 inhibitors probably do not cause hypoglycemia. However, they increase the risk if used with insulin or an insulin secretagogues.

- Other drugs that are often prescribed for people with diabetes and that possibly increase the risk of hypoglycemia are ACEI, ARB and non-selective beta2-adrenergic antagonists.

Strategies to prevent hypoglycamia

1. Patient education and empowerment

   Early recognition of S/S of hypoglycaemia
   Prevention and treatment of hypoglycaemia

2. Frequent self-monitoring of blood glucose (SMBG)

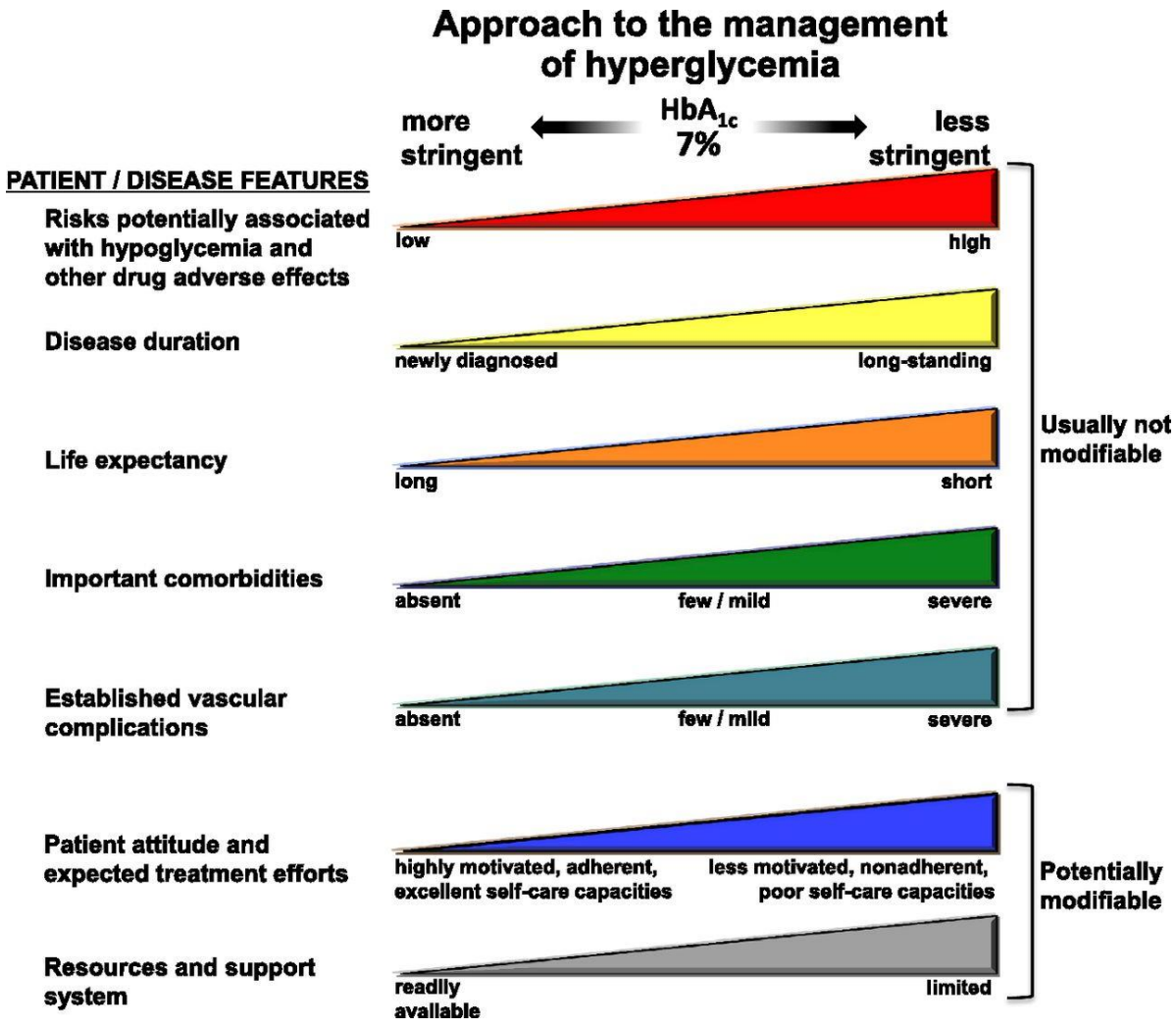
   Use of long-acting insulin anaglog (e.g. glargine and determir) as basal insulin and rapid-acting insulin analogs (e.g. lispro, aspart) as the pre-meal bolus insulin

3. Flexible and rational insulin (and other drug) regimens

4. Individualized glycemic goals, and

5. Ongoing professional guidance and support

Modulation of the intensiveness of glucose lowering in type 2 diabetes.



Silvio E. Inzucchi et al. Dia Care 2015;38:140-149

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American Diabetes Association.

Treatment of hypoglycaemia

- Acute treatment should include quick acting carbohydrate, followed by long acting carbohydrate to prevent subsequent hypoglycaemia recurrence.

- ***Rule 15:***

  - Consume 15-20 grams of glucose or simple carbohydrates.
  - Recheck your blood glucose after 15 minutes. If hypoglycemia continues, repeat.
  - Once blood glucose returns to normal, eat a small snack if your next planned meal or snack is more than an hour or two away.

Example of 15gm Simple Carbohydrates	Examples of Long-acting Carbohydrates
Glucose tablets	Two biscuits
Gel Tube	One slice of bread / toast
4 ounces (1/2 cup) of juice or regular soda (not diet)	200 – 300ml glass of milk (not soya)
1 tablespoon sugar, honey or corn syrup	Normal meal if due (must contain carbohydrates)
8 ounces of nonfat or 1% milk	
Hard candies, jellybeans, or gumdrops	

Glucagon kit*: 1mg given SC or IMI produces a significant increase in blood glucose, which usually leading recovery of consciousness within 10 to 15 minutes. It acts onliver glycogen and converts it to glucose. It may be followed by marked nausea or even vomiting. Patients given glucagon require a larger portion of long acting CHO to replenish glycogen stores.*

Case 4

- Mrs.Cheung **79** years old
- NSND

- PMH: T2DM for **25 years**, HT, **renal impairment**, AF, history of stroke and **IHD**

- Current medications

  warfarin 2mg nocte

  betaloc 100mg bd norvasc 10mg daily

  zestril 10mg daily

  Humulin R 8 unit sc before dinner

  Humulin N 12 unit sc bedtime

  diamicron 80mg bd

Case 4

- Investigations

  wcc 4.3 Hb 10.3 plt 247

  Na/ K 136/ 4.9 **Ur/ Cr 12.1/ 198**

  HbA1c **7.8** FG 10.1

- Admitted through AED for hypoglycaemic symptoms, with H'stix 2.3 checked by ambulance man.
- Patient has URTI symptoms and **poor appetite** x2/7

- Recently stepped up insulin dosage on last FU because of optimal glycaemic control

Case 5

- Mr. Ho 56 years old
- Chronic smoker and drinker

- PMH: T2DM for 8 years, HT, hyperlipidaemia

- Current medications
  metformin 750mg bd
  losartan 100mf daily
  zocor 10mg nocte

Case 5

- Admitted last month for acute myocardial infarction, with percutaneous coronary intervention performed.

- FU at clinic today

  Investigations

  Hba1c 8.2 FG 8.2

  Na/ K 137/3.9 Ur/ Cr 5.8/63 eGFR 67

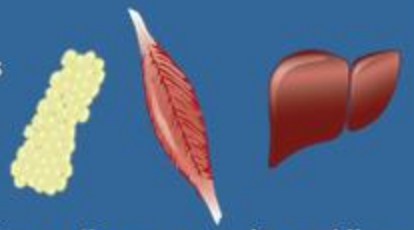
- He questioned whether there is any new DM medication that he ma benefit from.

Novel diabetes therapy: SGLT2 inhibitor

Existing and Novel Mechanisms to Reduce Hyperglycemia in T2DM[a-d]

Insulin-dependent mechanisms

Insulin action
- Thiazolidinediones
- Metformin



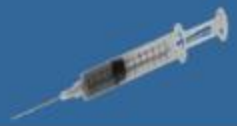
Adipose tissue, muscle, and liver

Insulin release
- Sulphonylureas
- GLP-1 RAs*
- DPP-4 inhibitors*
- Meglitinides



Pancreas

Insulin replacement
- Insulin



Glucose utilization

Insulin-independent mechanism

SGLT2 inhibition



Glucose excretion/caloric loss

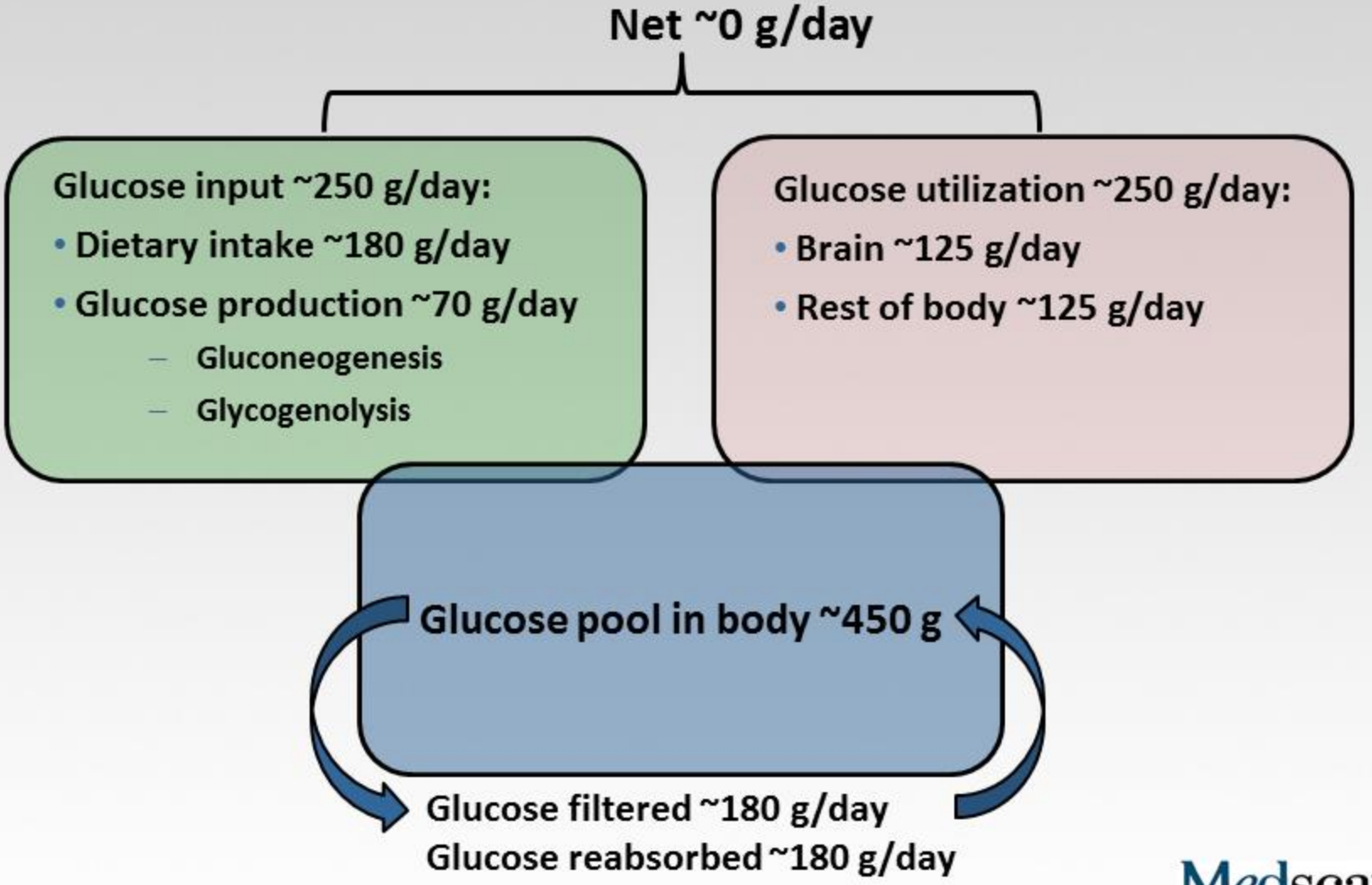
*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1 RAs and DPP-4 inhibitors also act to decrease glucagon secretion.

DDP-4, dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter 2; T2DM = type 2 diabetes mellitus

a. Washburn WN. *J Med Chem*. 2009;52:1785-1794; b. Bailey CJ. *Curr Diab Rep*. 2009;9:360-367;
c. Srinivasan BT, et al. *Postgrad Med*. 2008;84:524-531; d. Rajesh R, et al. *Int J Pharma Sci Res*. 2010;1:139-147.

Medscape EDUCATION

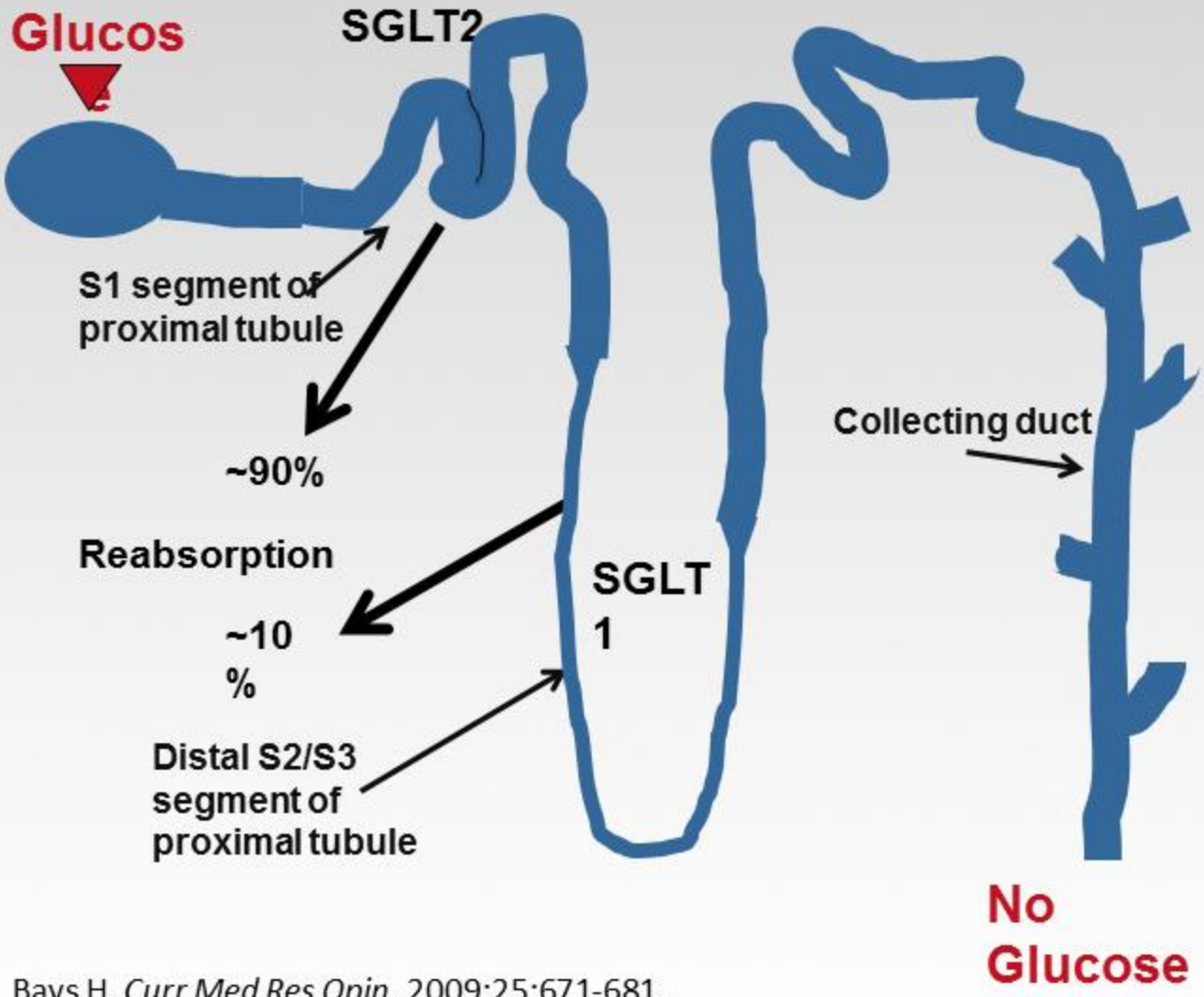
The Kidney Filters and Reabsorbs a Large Proportion of the Glucose Present in the Body



Medscape EDUCATION

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

Glucose Transporters in the Renal Proximal Tubule in Normal Individuals

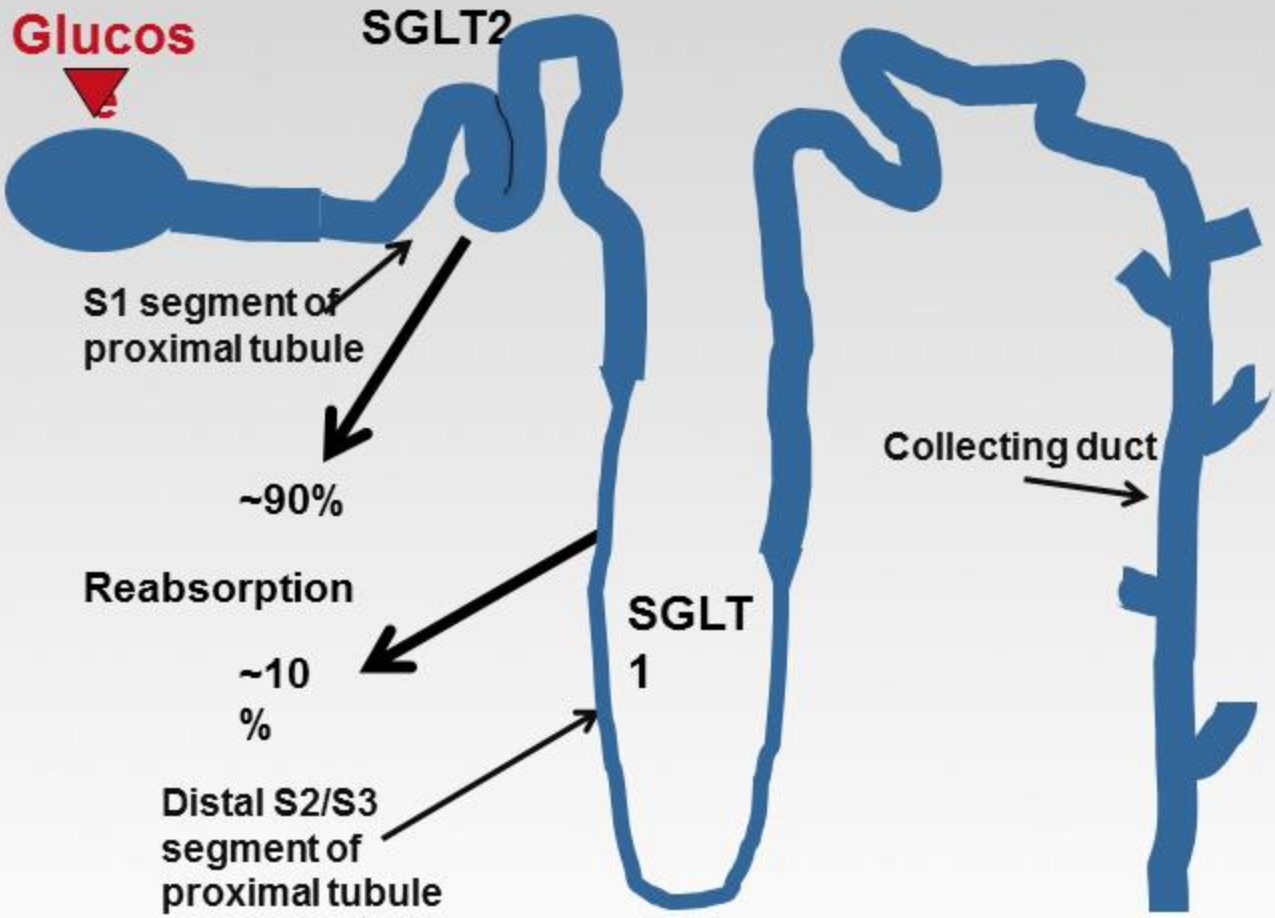


- SGLTs 1 – 6 – active energy dependent glucose transporters
- SGLT 1 – low capacity/high affinity: Intestine
- SGLT 2 – high capacity/ low affinity : kidney
- SGLT 3 – widespread glucose sensor
- SGLTs 4 – 6 – roles to be defined

Bays H. *Curr Med Res Opin*. 2009;25:671-681.

Medscape EDUCATION

Glucose Transporters in the Renal Proximal Tubule in Type 2 Diabetes

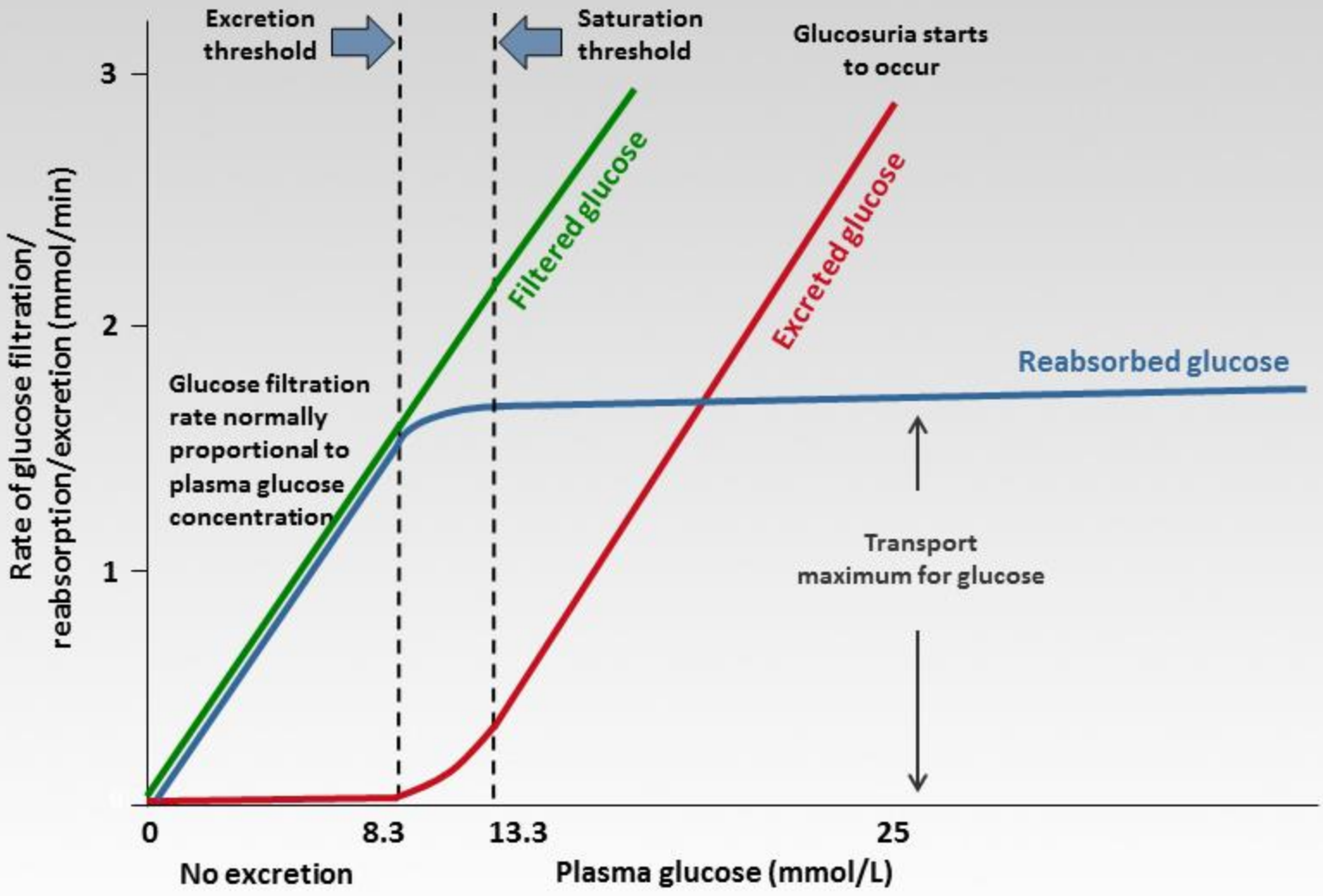


- Hyperglycemia increases SGLT2 expression and absorption capacity

Bays H. *Curr Med Res Opin*. 2009;25:671-681.

Medscape EDUCATION

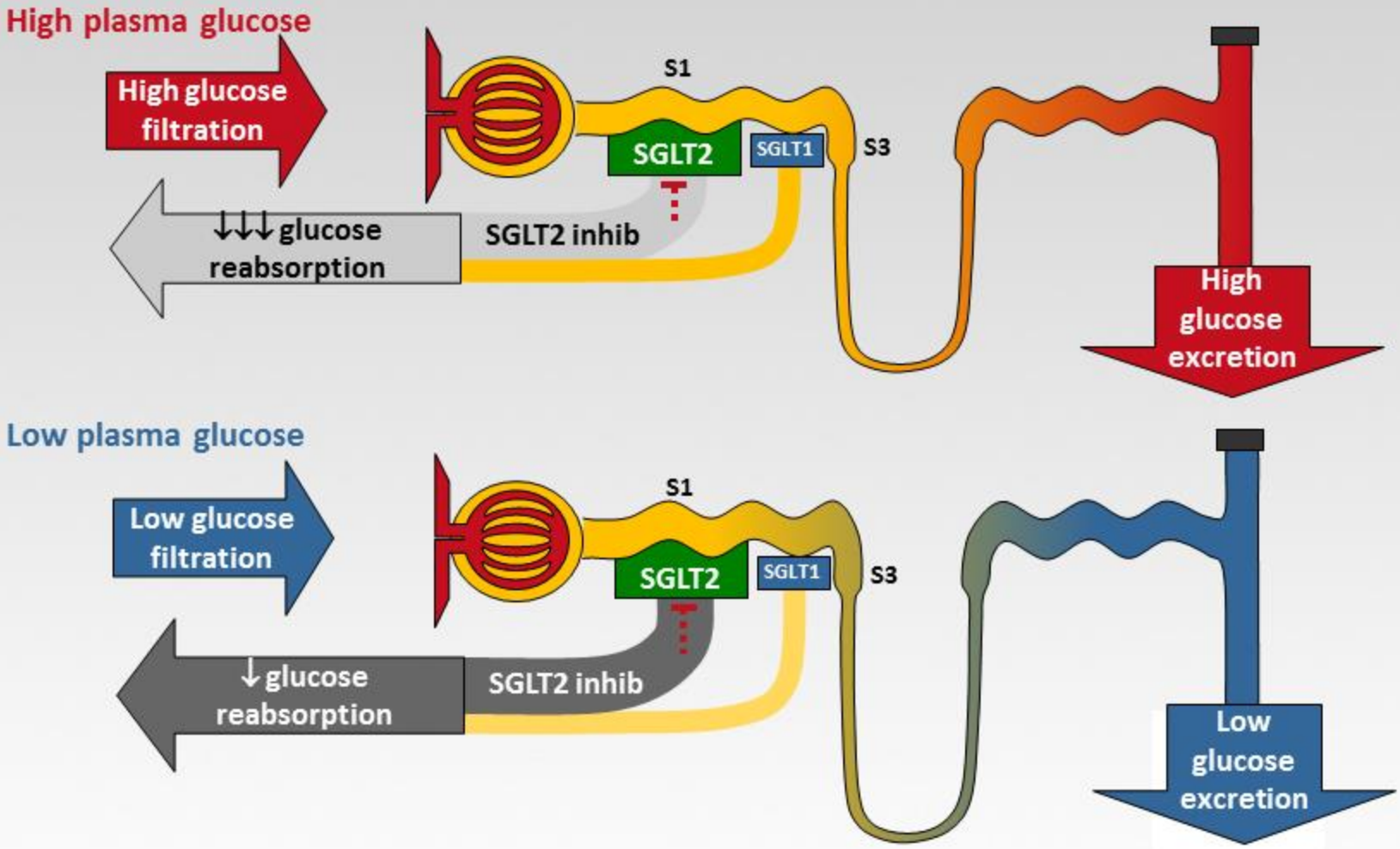
If Plasma Glucose Levels Get Too High, the Glucose Transporters Cannot Reabsorb All the Glucose, Leading to Glucosuria



a. Adapted from: Chao EC, et al. *Nat Rev Drug Discov* .2010;9:551-559;
b. Marsenic O. *Am J Kidney Dis.* 2009;53:875-883.

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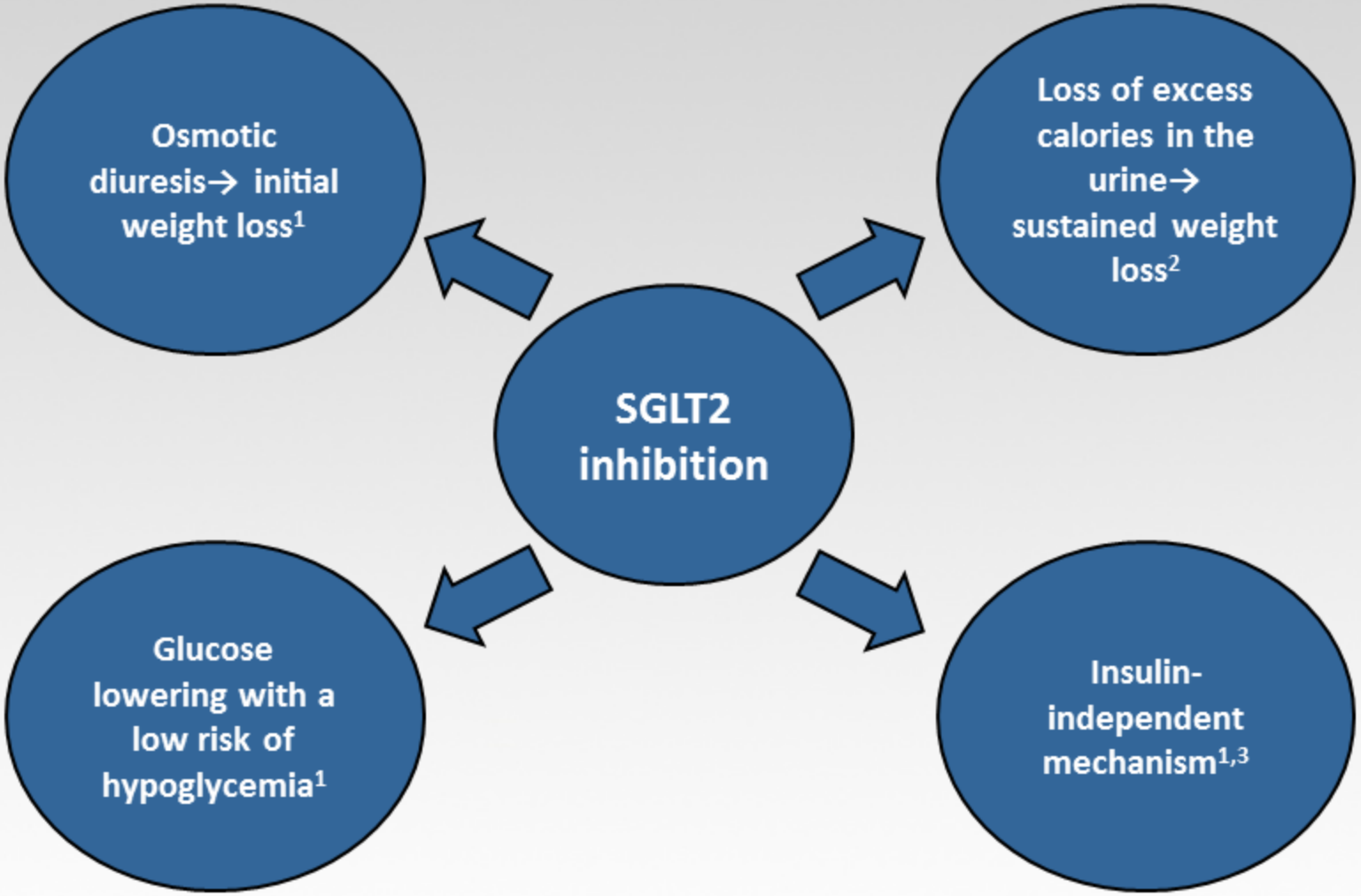
SGLT2 Inhibition Reduces Renal Glucose Reabsorption



Medscape EDUCATION

DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14.

SGLT2 Inhibition: Potential Clinical Benefits in T2DM



a. Neumiller JJ. *Drugs.* 2010;70:377-385; b. Bays H. *Curr Med Res Opin.* 2009;25:671-681;
c. Lo MC, et al. *Am J Ther.* 2010 doi: 10.1097/MJT.0b013e3181ec9eb2

Medscape EDUCATION

SGLT-2 inhibitor

- SGLT2 inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion
- their glycemic efficacy is dependent on blood glucose concentration and renal function.
- The mechanism of action of SGLT2 inhibitors is independent of insulin secretion ability or of the degree of insulin resistance.
- They can be used at any stage of T2DM and at any age, as long as renal function is sufficient.

SGLT-2 inhibitor

- Medications in this class

  dapagliflozin (forxiga)

  empagliflozin (jardiance)

- Efficacy: The reduction in HbA1c depends on the baseline HbA1c and renal function. Patients are "good responders" (decrease in HbA1c levels ranging from -0.84% to -1.87% when HbA1c is high >8% and renal function is good (eGFR >70 mL/min/1.73 m2).

Body Weight, Blood Pressure, or Lipid Benefits

Decrease in body weight of ~ 2-3 kg

- Osmotic diuresis- fluid loss and volume depletion and a short-term weight loss.
- loss of calories linked to glycosuria
- Loss of body fat- main contributor of weight loss. SGLT2 inhibitors increase fat oxidation and decrease waist size.

- SGLT2 inhibitors cause a reduction in systolic blood pressure (~3-4mmHg) and a small (~ 2 mm Hg) decrease in diastolic blood pressure, without a compensatory increase in heart rate.

- Increase HDL-C and decrease triglycerides.
- Increase low-density lipoprotein-cholesterol (LDL-C), but there is little or no change in the HDL-C/LDL-C ratio.

- The mechanisms underlying the change in lipids are unknown.

Cardiovascular safety trials with SGLT2 inhibitors -EMPA-REG outcome trial

- Investigated the effects of empagliflozin (10 or 25 mg) or placebo once daily, in addition to standard care, on cardiovascular morbidity and mortality in 7020 patients with T2DM with established CV disease.

- The primary outcome was: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (3-point major adverse cardiac event [MACE]) in both empagliflozin groups (pooled data) vs placebo

- The median duration of treatment was 2.6 years, and the median observation time was 3.1 years.

EMPA-REG outcome trial

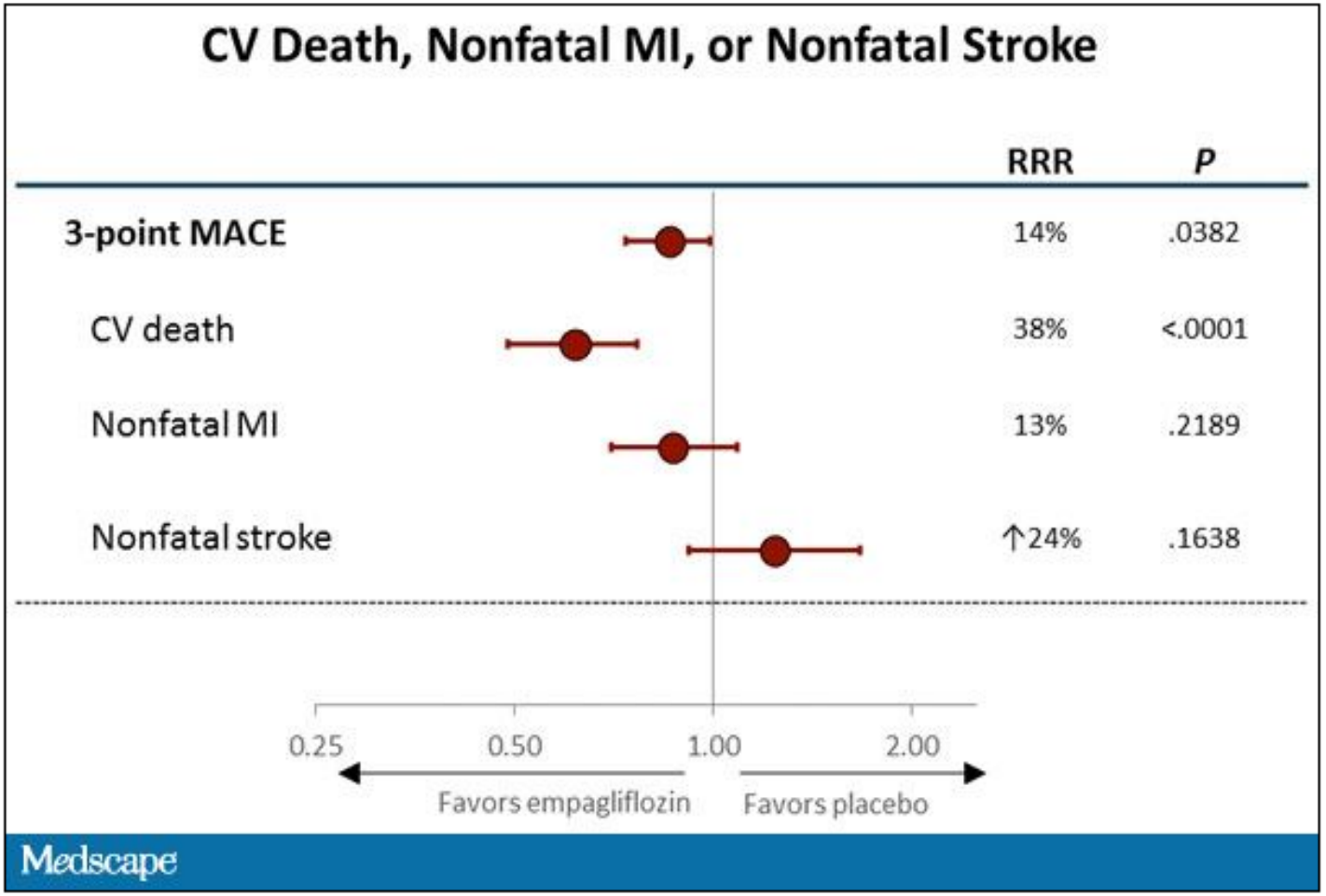


Figure 1. Individual components of the 3-point MACE. *CV = cardiovascular; MACE = major adverse cardiac event; MI = myocardial infarction; RRR = relative risk reduction*. Source: Zinman B, et al.[87]

EMPA-REG outcome trial

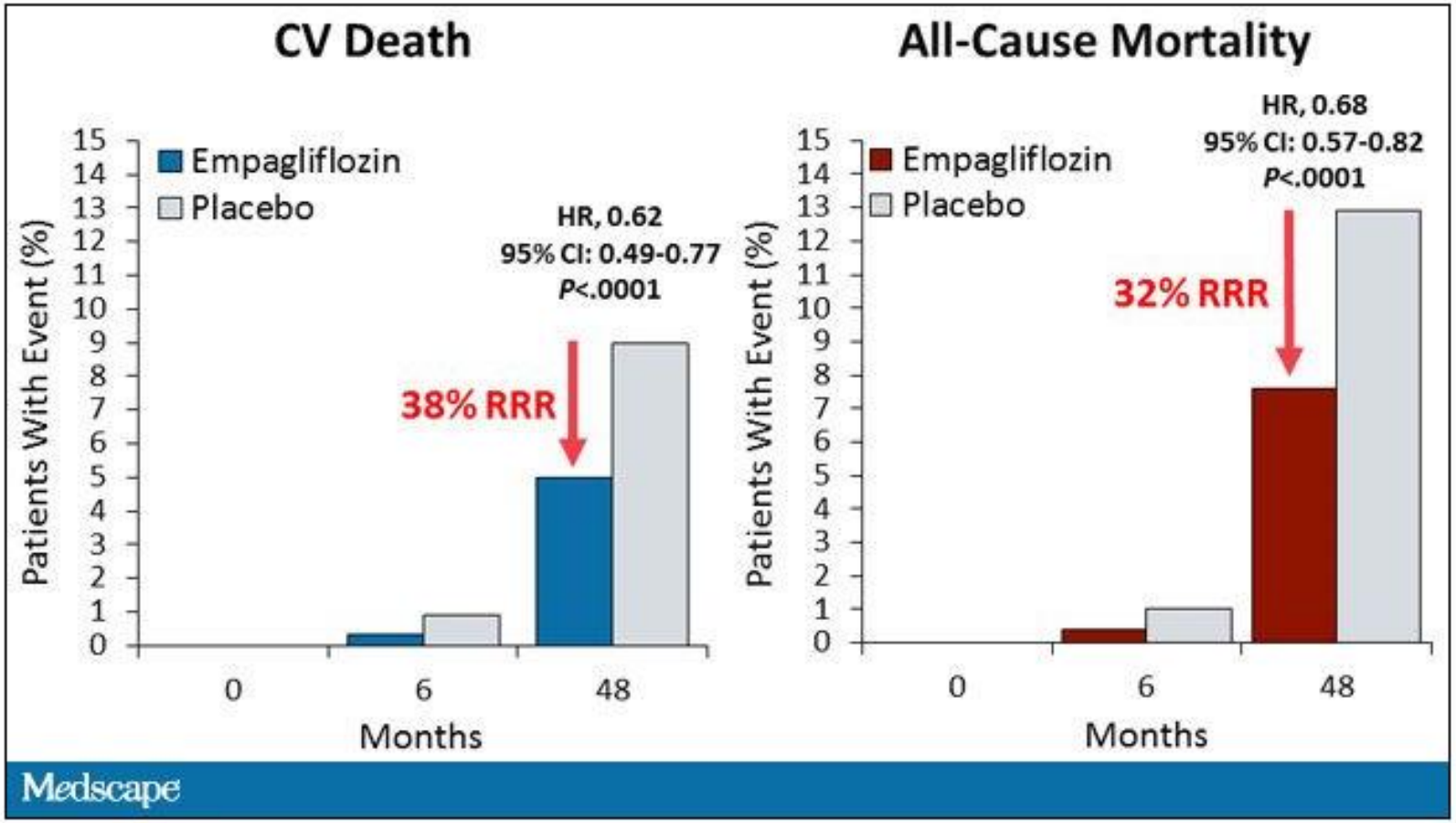


Figure 2. CV death and all-cause mortality with empagliflozin. *CI = confidence interval; CV = cardiovascular; RRR = relative risk reduction.* Source: Zinman B, et al.[87]

EMPA-REG outcome trial

- The mechanisms behind the cardiovascular benefits with empagliflozin are unknown but are unlikely to be due to glycemic control.

- Will the result from EMPA-REG outcome trial alter the treatment algorithm in T2DM especially in those with established CV disease??

Side effects

- Increase the risk for genital infections
  - more often in women (~10-15%) than men (1-4%)
  - occur within the first 4 months
  - mild, resolve with standard treatment.

- The diuretic effect of SGLT2 inhibitors may result in polyuria and volume depletion, which in turn can cause postural dizziness, hypotension, dehydration
  - should not be added to patients on loop diuretic

- Increase the risk of diabetic ketoacidosis

Case 6

- Mr. Lau, 69 years old
- NSND

- T2DM for 2 years, on metformin 500mg and diamicron 80mg po bd

- Noted high BP on follow-up
  BP 152/82 P 74bpm

- Investigation
  Hba1c 6.9 FG 4.2
  Normal cbc/ LRFT
  Lipid profile
  TC 5.9 TG 1.8
  LDL-C 3.6 HDL-C 0.9

Hyperglycaemia is not the only concern!!!!

- Hypertension is a common problem in patients with both type 1 and type 2 diabetes.

- Early treatment of hypertension is particularly important in diabetic patients both to prevent cardiovascular disease and to minimize progression of renal disease and diabetic retinopathy.

Antihypertensive Treatment in Diabetic Patients

- Nonpharmacological treatment

  low salt diet

  weight loss

  exercise and

  avoidance of smoking and excess alcohol ingestion

- Antihypertensive medications

Case 6: What medication should be used for BP control in Mr.Lau?

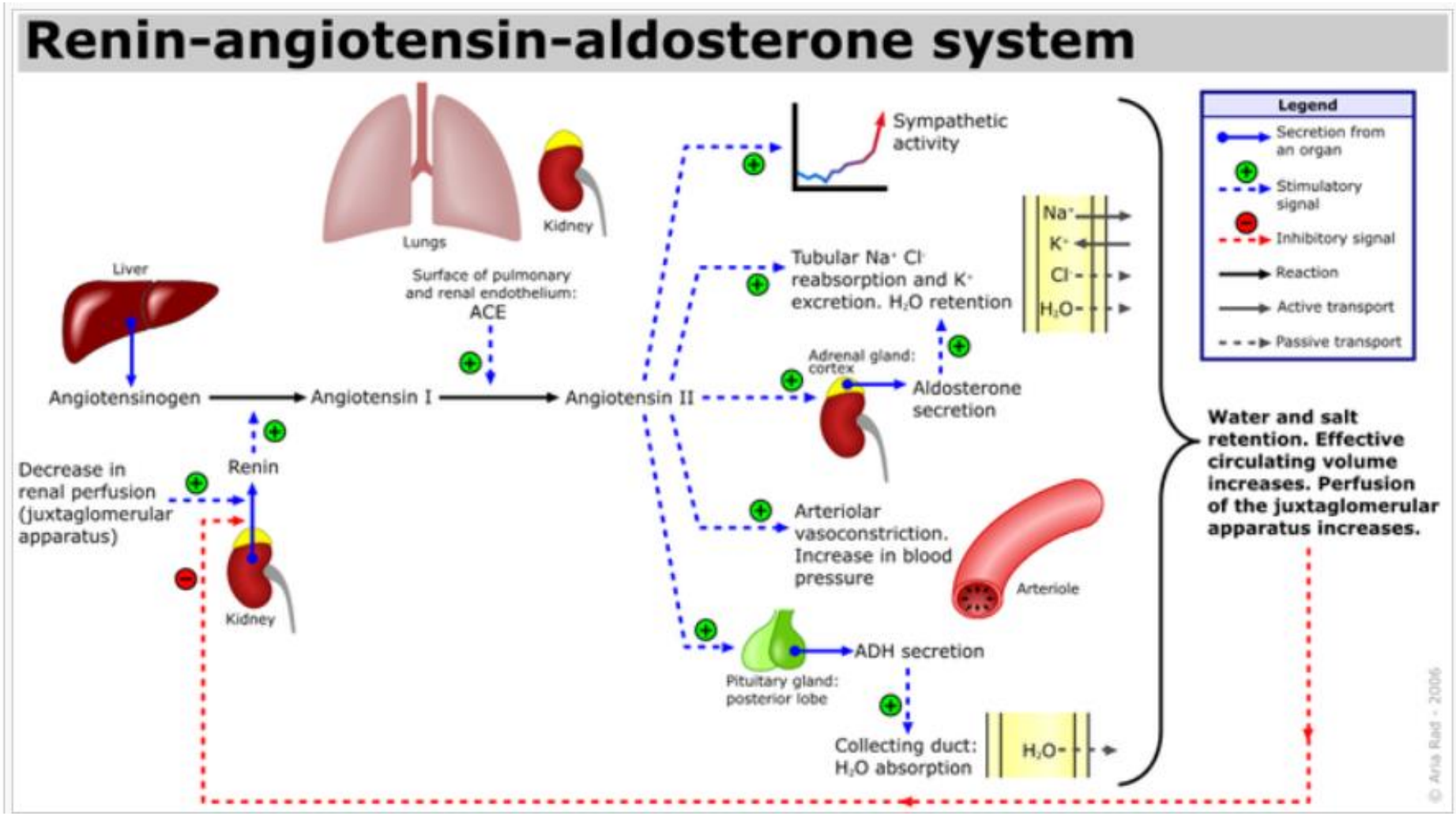
1. Beta-blocker, e.g. betaloc/ atenolol
2. Calcium channel blocker, e.g. adalat retard/ norvasc
3. Alpha- blocker, e.g. minipress
4. ACEI or ARB, e.g. zestril, losartan
5. Thiazide diuretic, e.g. Hydrochlorothiazide

Choice of antihypertensive drugs

Overall approach to selecting a therapy — The choice of antihypertensive agents in diabetic patients is based upon their ability to do the following:

- Prevent mortality
- Prevent adverse cardiovascular events, such as myocardial infarction, stroke, and heart failure
- Prevent the progression of renal disease, if present

RAS Blockers (ACEIs & ARBs)



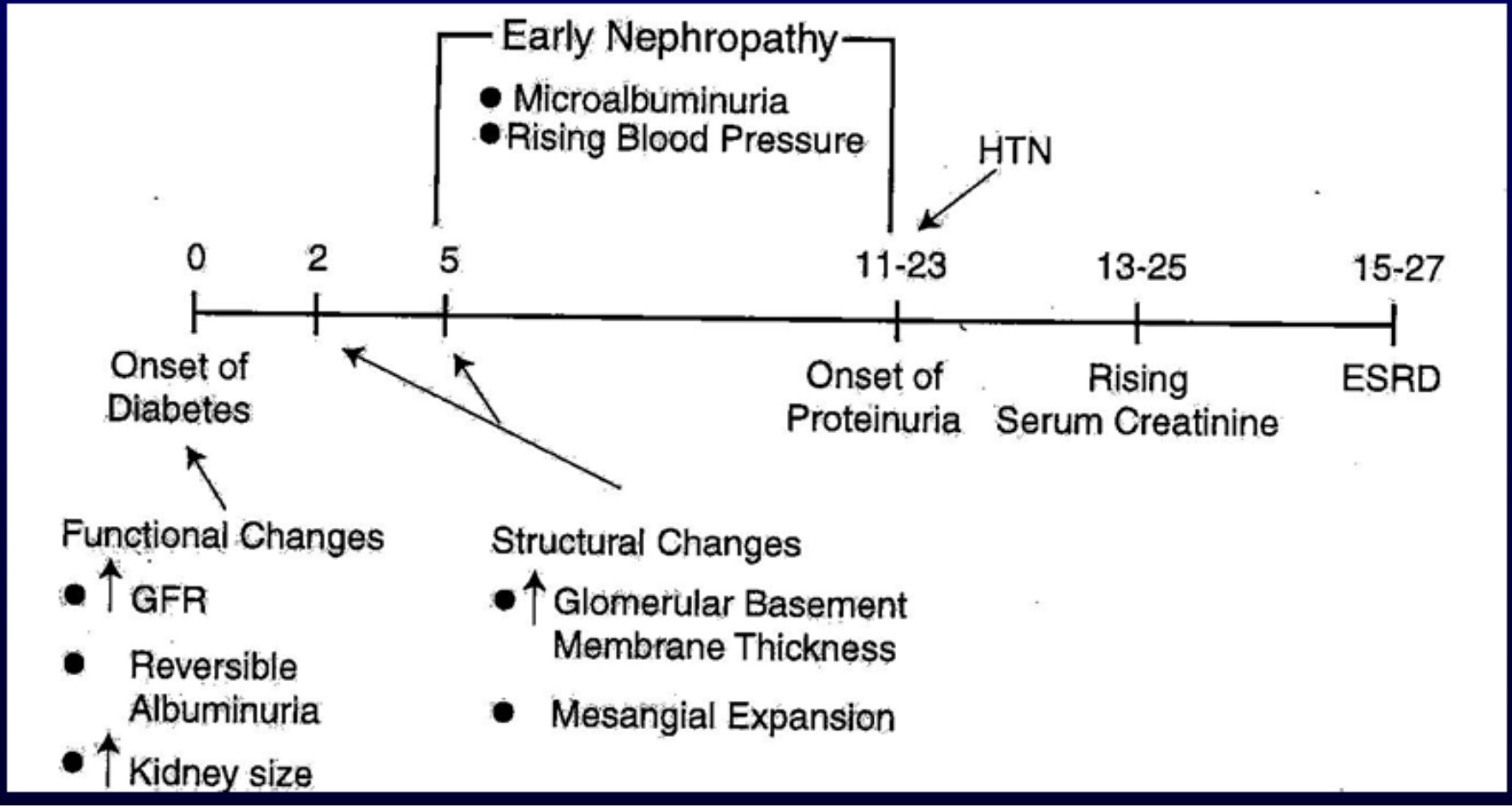
RAS Blockers (ACEis & ARBs)

- ACEIs block the conversion of angiotensin I into angiotensin II by inhibition of ACE, while ARBs block angiotensin II Type I receptors.

- The reduced levels of angiotensin II lead not only to vasodilatation and a fall in BP but also to a reduction of potential harmful effects of angiotensin II on the cardiorenovascular system, such as structural damage to the heart, blood vessels and kidneys.

- RAS blockers prevent progression from microalbuminuria to overt diabetic nephropathy.

Natural History



Microalbuminuria & Proteinuria

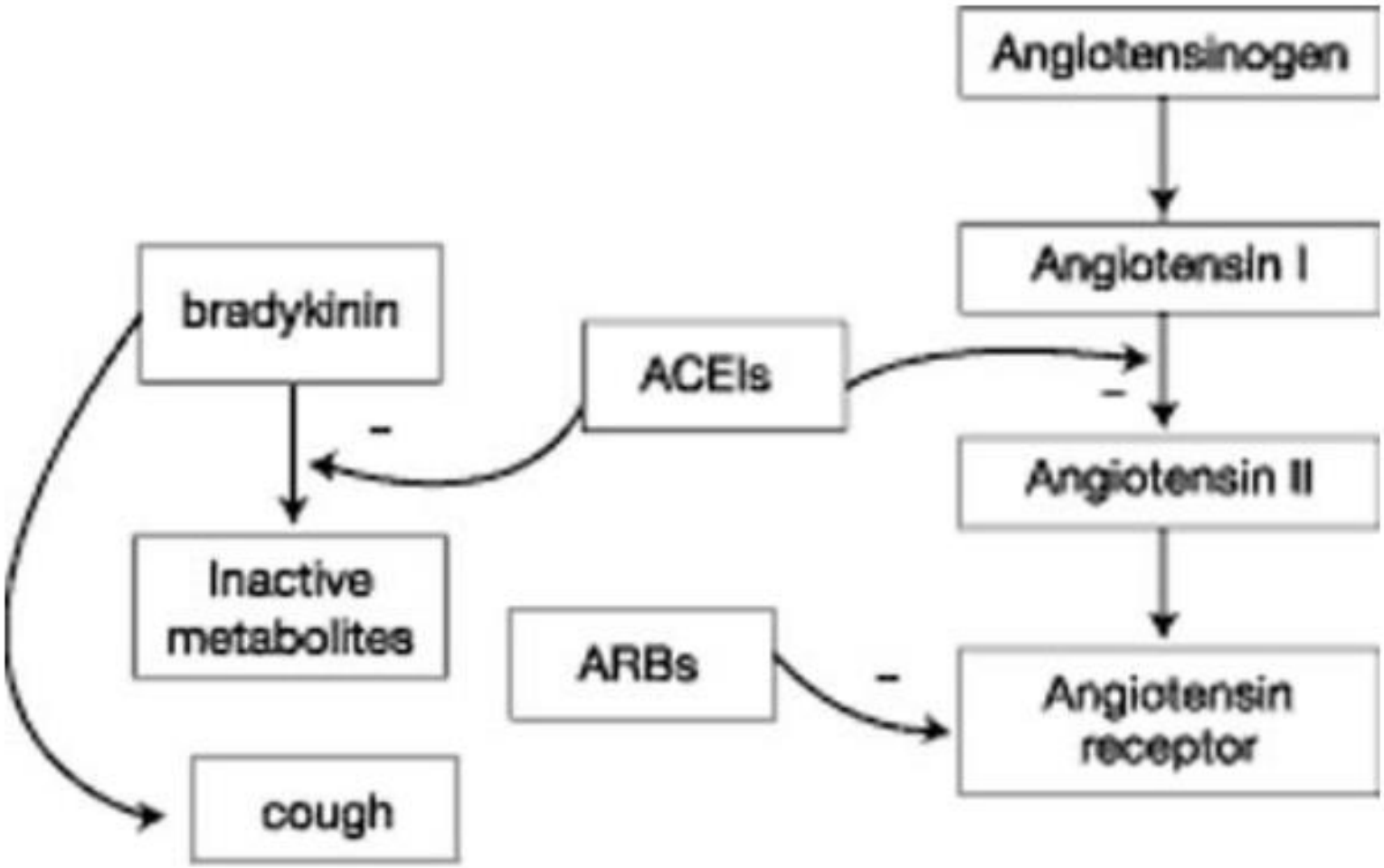
	Normal		Microalbuminuria		Overt proteinuria
	F	M	F	M	
Albumin/creatinine ratio (mg/mmol)	<3.5	<2.5	>3.5	>2.5	>30
Equivalent Albumen excretion (mg/day)	<30		30-300		300

- Diagnosis of microalbuminuria based on 2 out of 3 urine samples in absence of UTI
- After 5 years of Dx in T1DM & than annually.
- At the time of diagnosis in T2DM.

Side effects of ACEI/ ARB

- Acute renal failure (especially in bilateral renal artery stenosis)
- Hyperkalemia
- Dry cough, angioedema (for ACEI, mediated by bradykinin)




Angiotensinogen
Angiotensin I
Angiotensin II
Angiotensin receptor
ACEIs
ARBs
bradykinin
Inactive metabolites
cough
-
-
-

Thiazide diuretics

- Effective in hypertensive diabetic patients, acting at least in part by reversing the underlying tendency for volume expansion.
- A combination of thiazide and a RAS blocker is particularly effective as mild fluid loss increases the antihypertensive effect of RAS blocker.
- also may minimize or prevent some of the metabolic complications associated with diuretic therapy, such as hypokalemia, hyperlipidemia, and hyperuricemia
- In high doses may worsen glycemic control by impairing insulin secretion and decreasing peripheral insulin sensitivity.

Calcium channel blocker

- Efficient and well tolerated.
- No adverse effects on lipid or carbohydrate metabolism.
- In ACCOMPLISH study, hypertensive patients (60% with DM) assigned to combination therapy consisting with benaepril plus amlodipine have fewer cardiovascular events than those assigned to benazepril plus low dose hydrochlorothiazide (8.8% vs 11%, hazard ratio 0.79%)

β-blockers

- Increase the risk of developing new-onset diabetes mellitus, particularly when combined with thiazide diuretics.
- Modest worsening of glycemic control seen with metoprolol.
- Concerns about masking of hypoglycemic symptoms.
- It is still a useful add-on antihypertensive agent, especially in patients with coronary artery disease, and heart failure

Alpha blockers

- Not widely used as primary therapy in diabetes because of side effects such as orthostatic hypotension.

- Useful as add-on therapy, particularly in older men with symptomatic prostatism.

Overall approach in diabetic patients who require antihypertensive therapy is as follows:

- In patients with severely increased albuminuria (formerly called "macroalbuminuria") or moderately increased albuminuria (formerly called "microalbuminuria")

  ACE inhibitor or ARB should be used

- In patients without increased albuminuria, initial monotherapy can consist of an ACE inhibitor, ARB, thiazide diuretic, or calcium channel blocker. However, because angiotensin inhibitors can prevent albuminuria, many experts will choose an **ACEI or ARB**.

- In patients who require more than one drug to control their blood pressure, a **combination of an ACE inhibitor (or ARB if unable to take an ACE inhibitor) and a dihydropyridine calcium channel blocker** (eg, amlodipine) should be used

糖尿**ABC**

Control of ABC

- “A” - HbA1c </= 7.0
- “B” – Blood pressure 130/80
- “C” – cholesterol, LDL-C < 2.6mmol/L

- 糖尿併發症在五至七年內的病發率可減五成。

Case 7

- Mrs. Chan 45 years old
- NSND, married with 2 children

- PMH: T2DM for 6 years, HT, hyperlipidaemia, gout and OSA on CPAP

- Current medications

  metformin 1gm bd

  lixisenatide 20mcg sc daily

  lantus 28unit sc nocte

  zocor 20mg nocte

  zestril 20mg daily norvasc 10mg daily

  allopurinol 300mg daily

Case 7

- P/E
  BP 138/73 P67bpm
  BW 106kg Height 160cm BMI 41.4
  CVS, chest, abd: unremarkable

- Investigation
  normal cbc/ LRFT
  HbA1c 9.2 FG 12.3
  Lipid profile
  TC 6.4 TG 2.5
  LDL-C 3.2 HDL-C 1.1

Case 7: Is Mrs. Chan suffering from metabolic syndrome?

- MES is a collection of heart disease risk factors that increase your chance of developing heart disease, stroke and diabetes.
- It is also associated with premature mortality.
- Recent study estimates that the prevalence of MES in Hong Kong Chinese population is around 17%.

- **New MES Definition by International Diabetes Federation (IDF)**
  國際糖尿聯盟最新提出的標準

Mandatory component:

Central obesity – waist circ. ethnicity-specific

- Europid ≥94cm men, ≥80cm women
- **Asian (not Japanese) ≥90cm men, ≥80cm women**
- Japanese ≥85cm men, ≥90cm women

Plus two or more of other criteria:

Triglycerides >1.7mmol/L or on specific treatment
HDL cholesterol <1.03mmol/L in men, <1.29 in women or on specific treatment
Blood Pressure ≥130/85 or on treatment
FBG ≥5.6mmol/L or previously diagnosed T2DM

我是中央肥胖嗎?



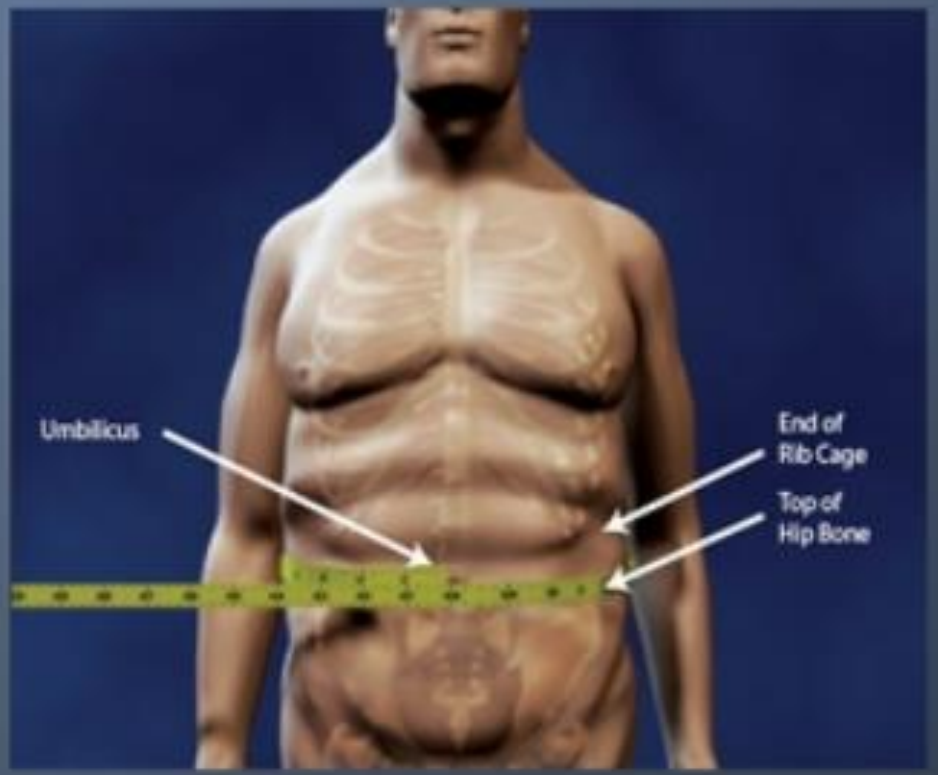
- 量度腰圍是最簡單而有效的方法
- 可反映腹內脂肪的積存

	男士	女士
歐洲人	>94厘米 (37.0吋)	>80厘米(31.5吋)
南亞裔人	>90厘米(35.4吋)	>80厘米(31.5吋)
中國人	>90厘米(35.4吋)	>80厘米(31.5吋)
日本人	>85厘米(33.5吋)	>90厘米(35.4吋)

International Diabetes Federation (2005)

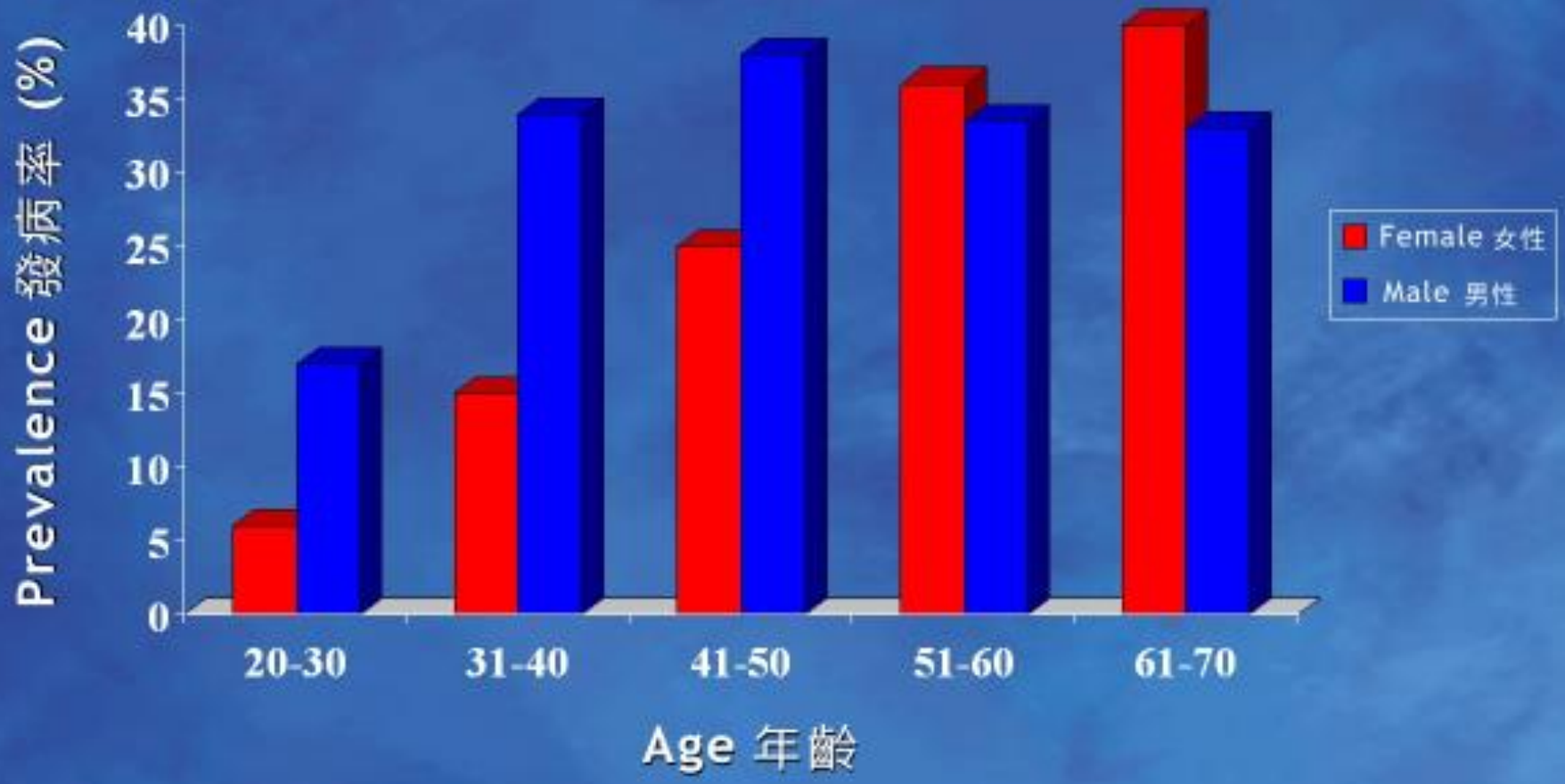
正確量度腰圍的方法

- 用軟尺圍著腹部
- 放在肋骨與盆骨兩者中間
- 在呼氣後測量
- 注意尺不要太鬆或太緊，及與地面平衡



Prevalence of obesity in HK

香港肥胖症發病率 (BMI >25)



Ko GT et al. Asia Pac J Clin Nutr 2006

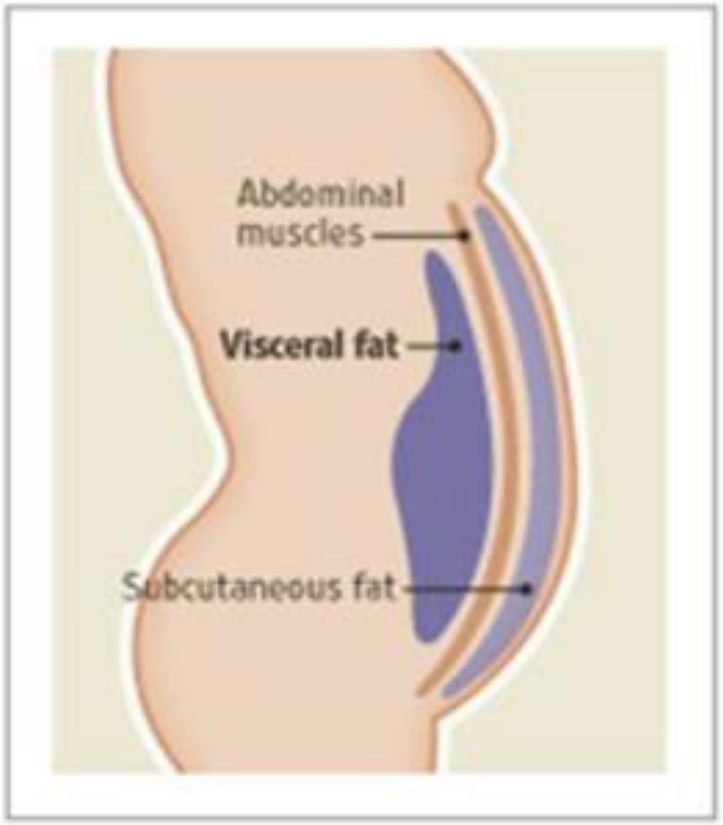
BMI cut-off for Caucasians

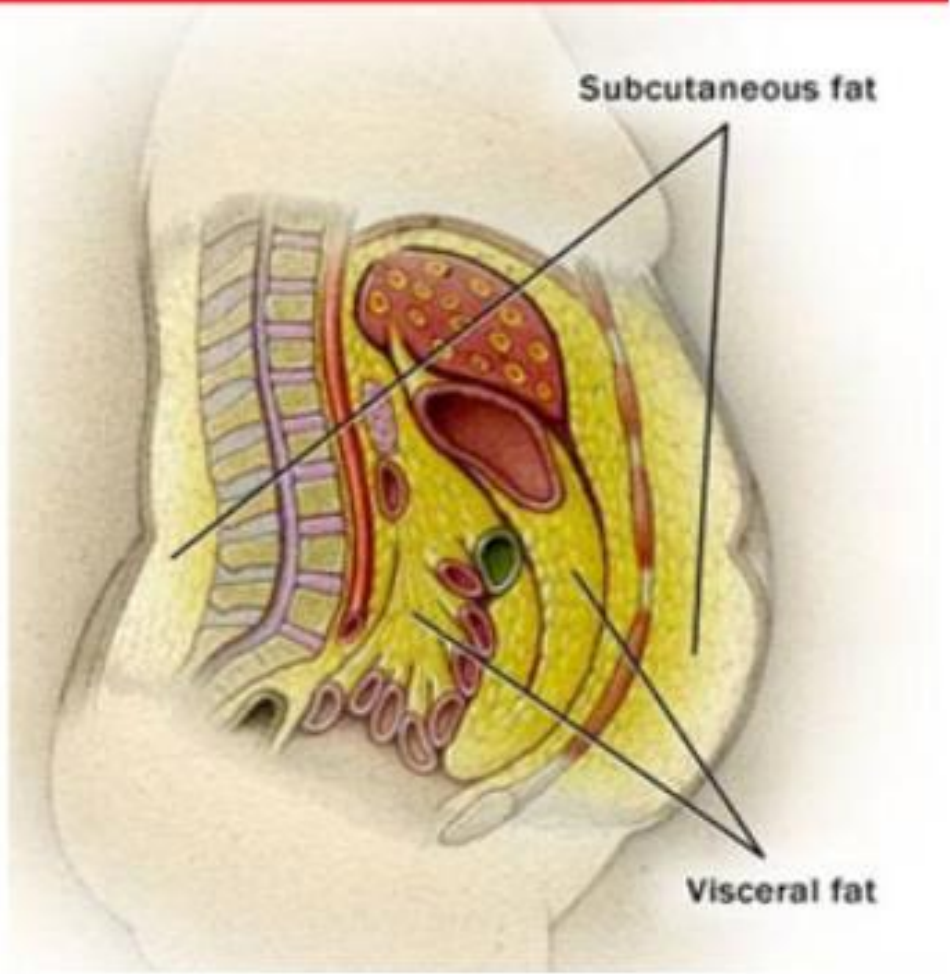
BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
≥ 40.0	class III obesity

The Hospital Authority of Hong Kong- BMI cut-off points

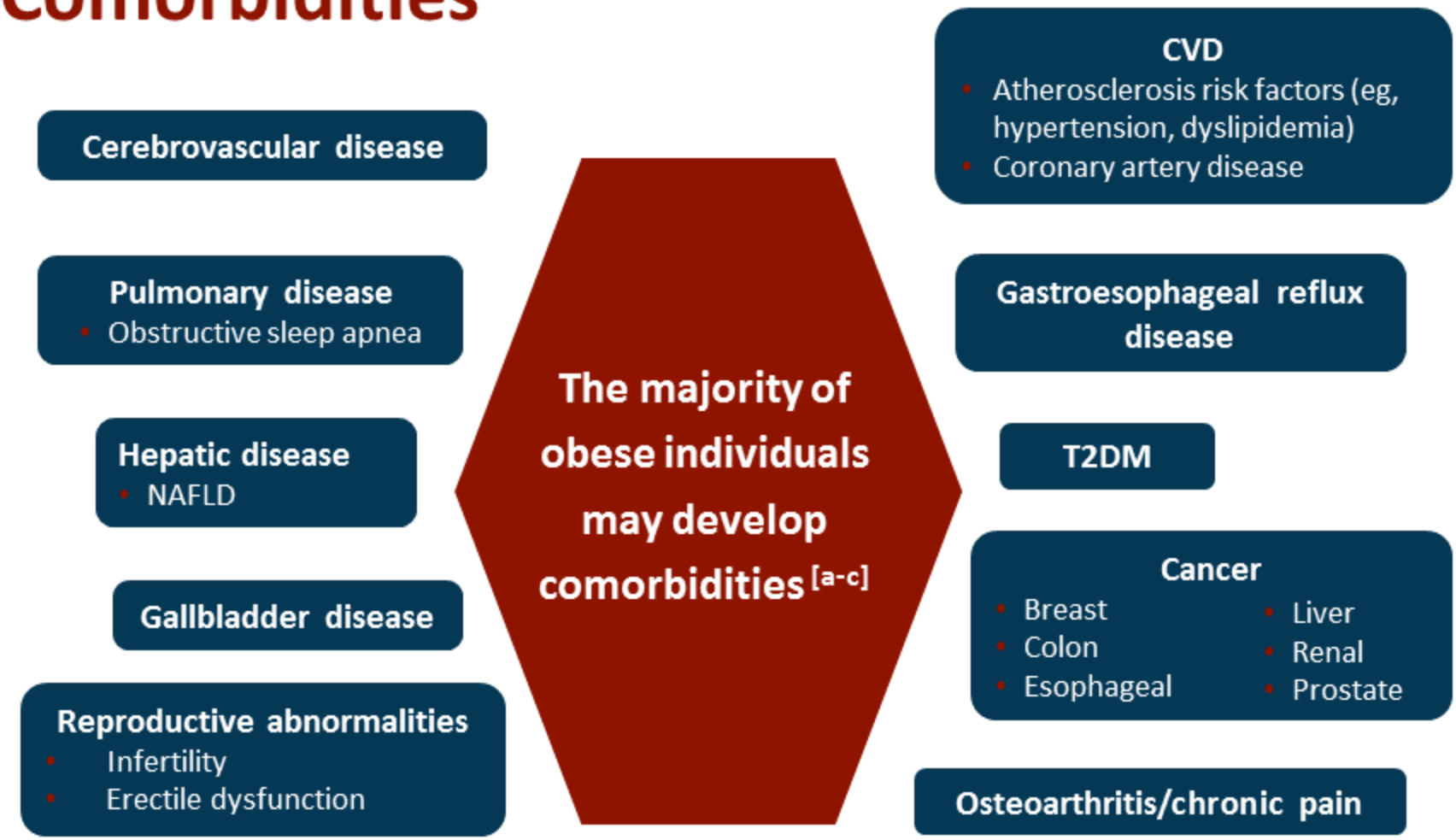
	BMI (kg/m2)
Normal weight	**18.2-22.9**
Overweight	**≧23.0**
At risk	**23.0-24.9**
Obese I	**25.0-29.9**
Obese II	**≧30.0**

Visceral Fat is the Culprit





Obesity Is Associated With Multiple Comorbidities



a. Catenacci VA et al. *Clin Chest Med*. 2009;30:415-444.
b. Calle EE et al. *N Engl J Med*. 2003;348:1625-1638.
c. Bluher M. *Exp Clin Endocrinol Diabetes.* 2009;117:241-250.

T2DM and obesity

Beyond pharmacological management…

Bariatric surgery



Summary of consensus definitions of diabetes remission by American Diabetes Association

Partial remission
Hyperglycaemia below diagnostic thresholds for diabetes (HbA1c <6.5%, FG 5.6-6.9mmol/L) **At least 1 year's duration** **No active pharmacologic therapy or ongoing procedures**
Complete remission
Normal glycaemic measures(HbA1c <6.5%, FG 5.6-6.9mmol/L) **At least 1 year's duration** **No active pharmacologic therapy or ongoing procedures**
Prolonged remission
Complete remission of at least 5 years' duration

Inclusion Criteria for Metabolic Surgery in Asians

IFSO-APC Consensus statements 2011:

- BMI ≥ 35 with or without co-morbidities: for treatment of obesity
- BMI ≥ 30: for treatment of inadequately controlled T2DM or metabolic syndrome
- BMI ≥ 27.5: may be considered as a non-primary alternative to treat inadequately controlled T2DM or metabolic syndrome

Inclusion Criteria for Metabolic Surgery in Asians

- Age 18-65
- Failure to lose weight with life-style changes and medical therapy
- Acceptable surgical risks with no major organ failure
- Compliant and motivated patients willing to accept the surgical risks and post-operative lifestyle changes

Thank you!