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Side Effects of:

GLP-1 agonists
DPP-4 inhibitors
SGLT-2 inhibitors

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PharmD

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Objectives

- For each drug class:
  - Identify the overall place in therapy
  - Explain the mechanism of action
  - List the adverse effects
  - Provide recommendations when adverse effects occur

What are these agents?

GLP-1 agonists	DPP-4 inhibitors	SGLT-2 inhibitors
Albiglutide (Tanzeum)****	Alogliptin (Nesina)	Canagliflozin (Invokana)
Dulaglutide (Trulicity)	Linagliptin (Trajenta)	Dapagliflozin (Farxiga)
Exenatide (Byetta)	Saxagliptin (Onglyza)	Empagliflozin (Jardiance)
Exenatide ER (Bydureon pen/Bcise)	Sitagliptin (Januvia)	Ertugliflozin (Steglatro)
Liraglutide (Victoza)		
Lixisenatide (Adlyxin)		
Semaglutide (Ozempic)		

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Place in therapy

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Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

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

If A1C target not achieved after approximately 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- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

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COSTS*	low	low	high	high	high	high

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TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
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Combination Injectable Therapy (See Figure 8.2)

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A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

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COSTS*	low	low	high	high	high	high

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Triple Therapy — Metformin + — Lifestyle Management

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or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
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Combination Injectable Therapy (See Figure 8.2)

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Place in therapy

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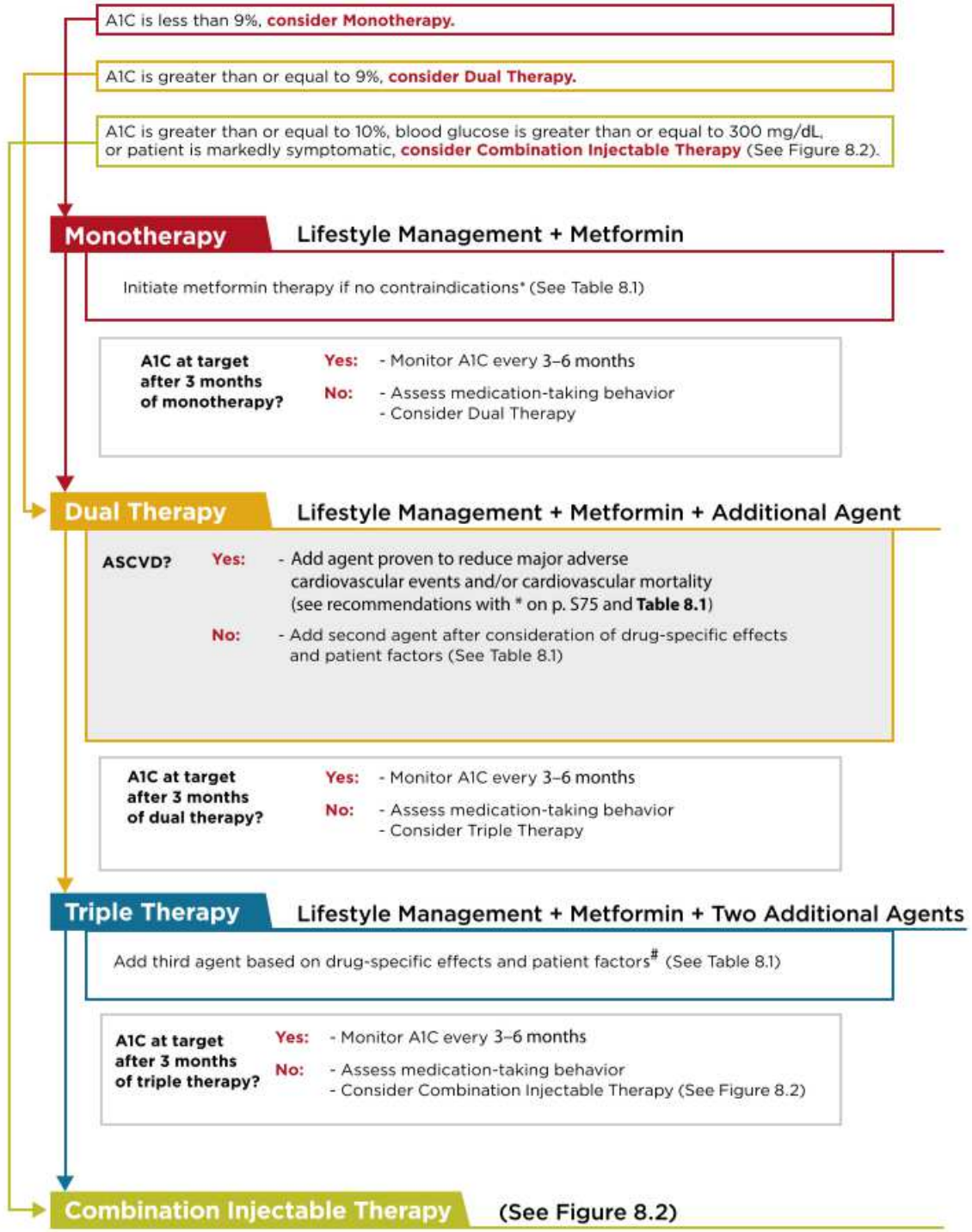
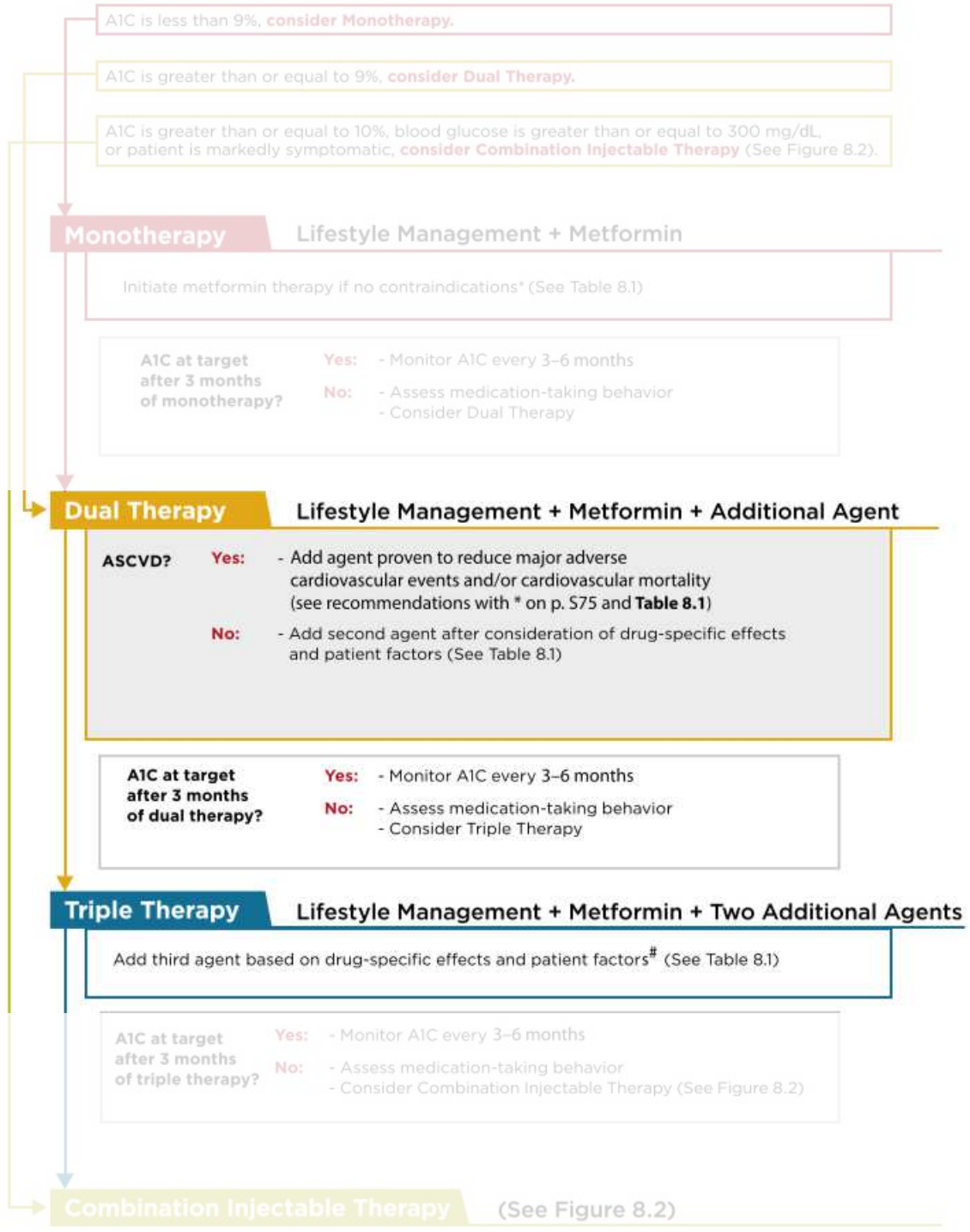

A1C is less than 9%, consider Monotherapy.
A1C is greater than or equal to 9%, consider Dual Therapy.
A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).
Monotherapy
Lifestyle Management + Metformin
Initiate metformin therapy if no contraindications* (See Table 8.1)
A1C at target after 3 months of monotherapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Dual Therapy
Dual Therapy
Lifestyle Management + Metformin + Additional Agent
ASCVD?
Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)
No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)
A1C at target after 3 months of dual therapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Triple Therapy
Triple Therapy
Lifestyle Management + Metformin + Two Additional Agents
Add third agent based on drug-specific effects and patient factors# (See Table 8.1)
A1C at target after 3 months of triple therapy?
Yes: - Monitor A1C every 3–6 months
No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)
Combination Injectable Therapy
(See Figure 8.2)



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Dual Therapy | **Lifestyle Management + Metformin + Additional Agent**

ASCVD?	**Yes:**	- Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)
	No:	- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

ASCVD: atherosclerotic cardiovascular disease

- Acute coronary syndromes
- Coronary or other revascularization
- Ischemic stroke or transient ischemic attack
- Atherosclerotic peripheral arterial disease

Recommendations: **liraglutide** (GLP-1) and **empagliflozin** (SGLT-2) [A]

- FDA indications for CV benefit in those with CV disease

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Glucagon-like peptide-1 receptor agonist

GLP-1 agonists
Albiglutide (Tanzeum)****
Dulaglutide (Trulicity)
Exenatide (Byetta)
Exenatide ER (Bydureon pen/Bcise)
Liraglutide (Victoza)
Lixisenatide (Adlyxin)
Semaglutide (Ozempic)

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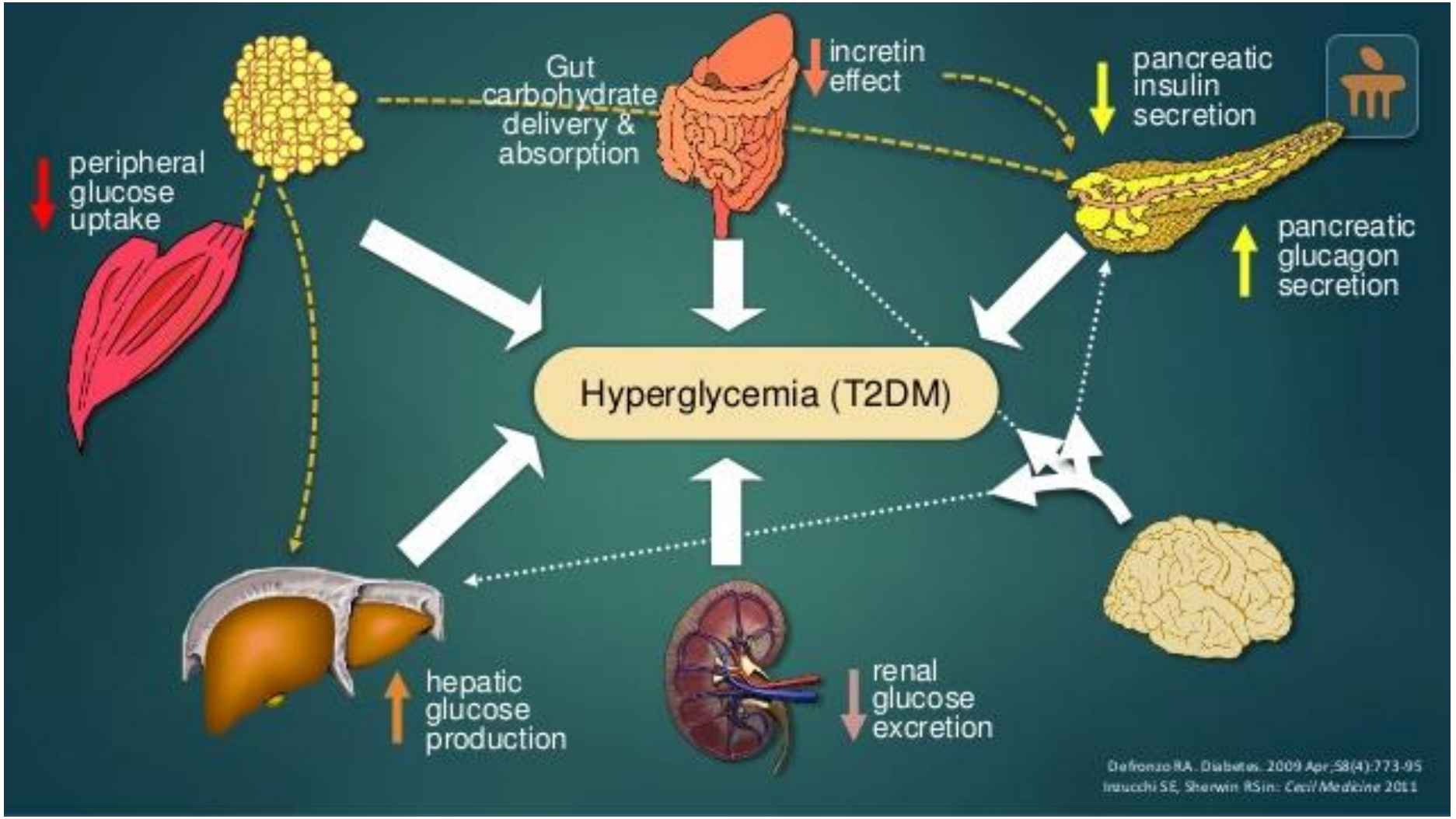
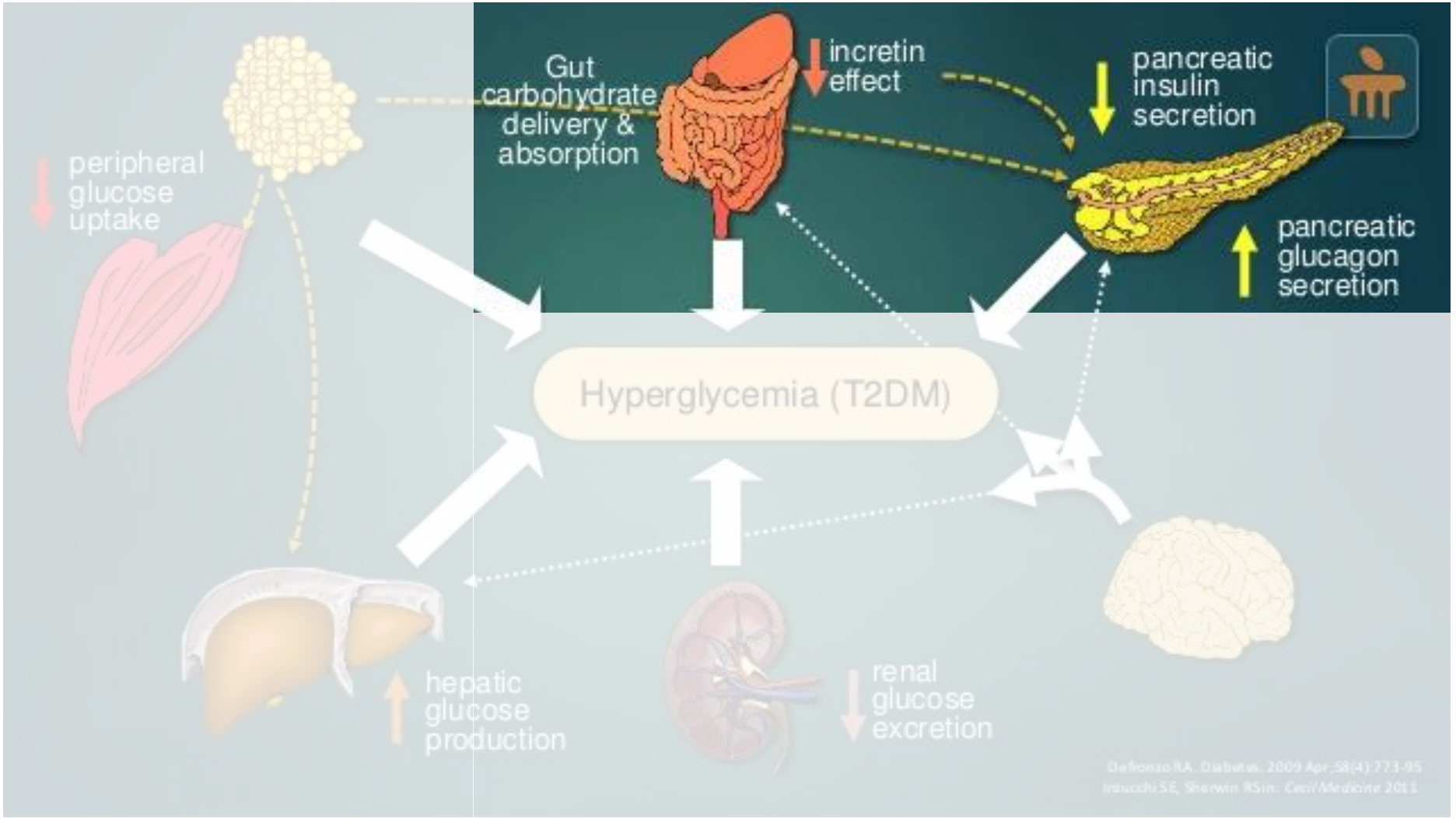
Hyperglycemia

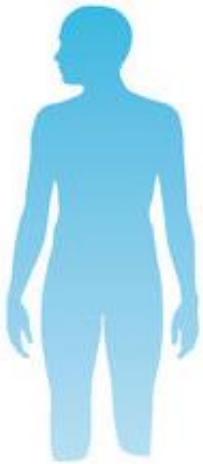


Hyperglycemia

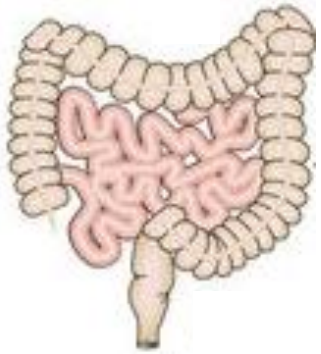


Incretins (gut hormones)

“Incretin effect”

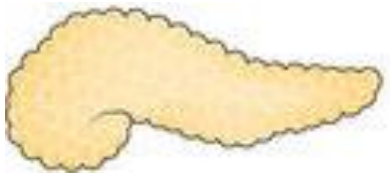


L cells



GLP-1 (glucagon-like peptide 1)
GIP (gastric inhibitory peptide)

- Minor role



Insulin secretion

Stimulates insulin secretion in response to oral glucose load

“glucose-dependent”

Incretins (gut hormones)

- Responsible for > 90% of insulin secreted by pancreas in response to an oral glucose load
- GLP-1 glucose-dependent insulin secretion when BG > 90

- In diabetes:
  - GLP-1 levels are low but patients remain sensitive to GLP-1
  - Incretin effect is blunted
  - Only about 50% insulin secreted compared to nondiabetic

- GLP-1 is rapidly inactivated by the enzyme DPP-4

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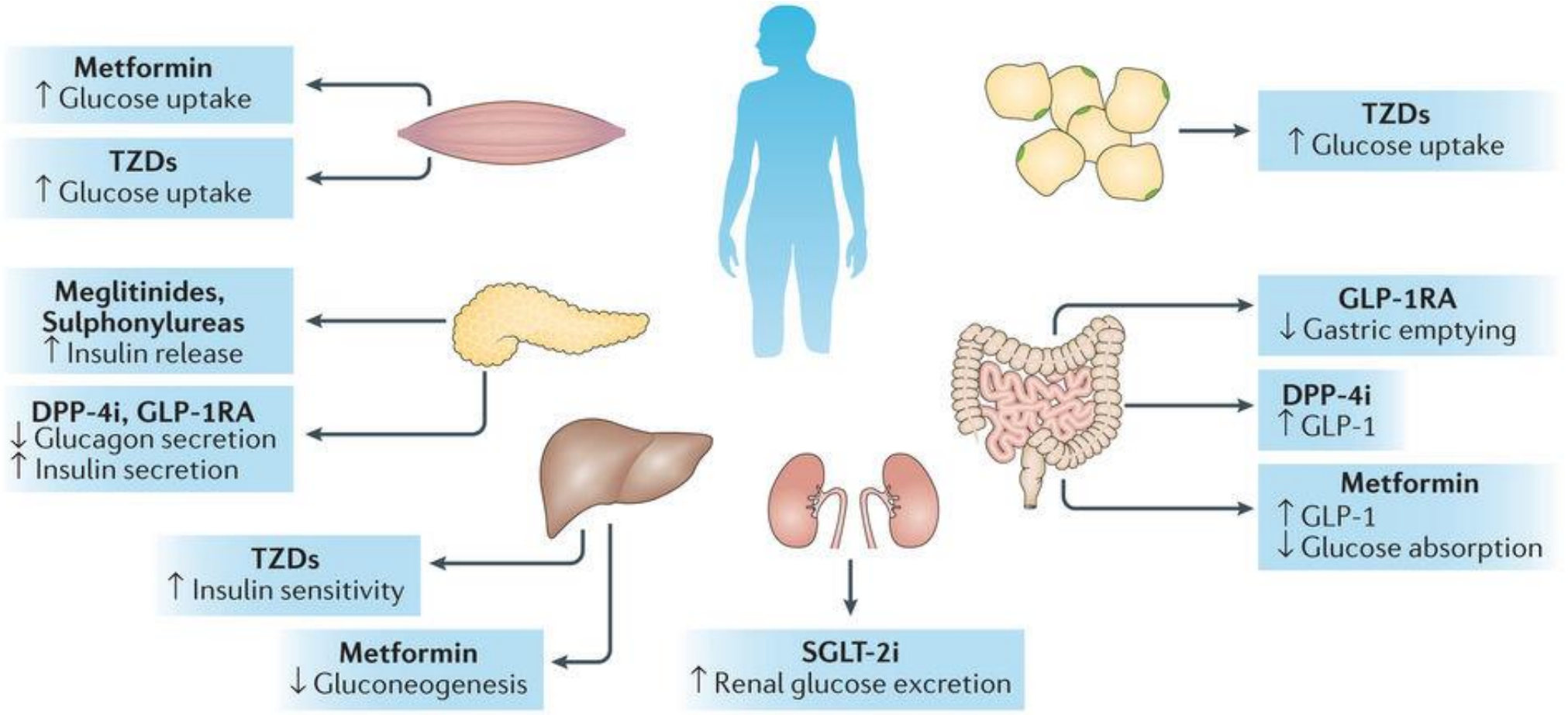
Mechanism of action

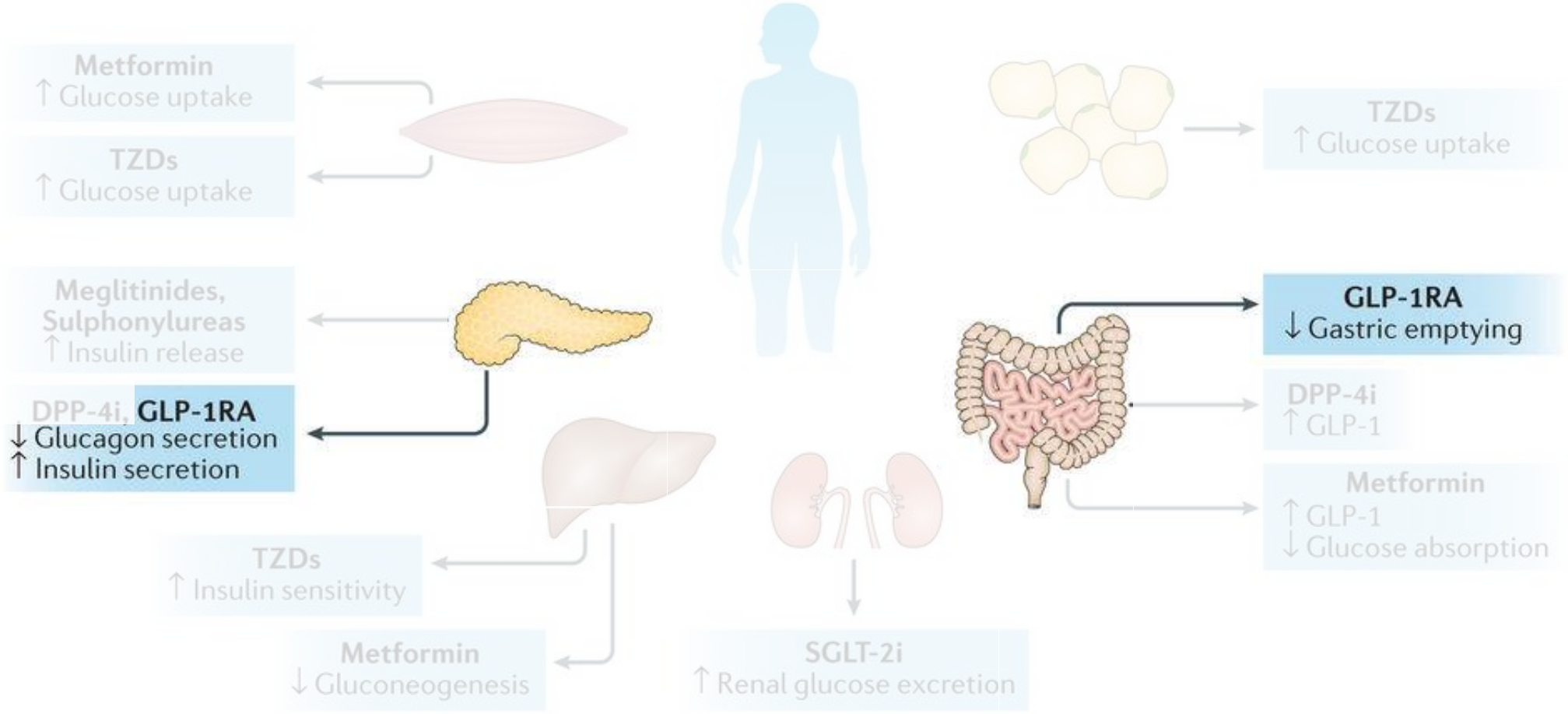
- ↑ glucose-dependent insulin secretion
- ↓ inappropriate high postprandial glucagon secretion
  - ↓ hepatic glucose production
- ↑ satiety
  - Promotes weight loss
- Slows gastric emptying
  - Slows the rate glucose enters plasma

- Does not stimulate insulin secretion during hypoglycemia
- Does not inhibit the release of glucagon

How do they work?



How do they work?



Contraindications = do not use

- Black box warning (not exenatide and lixisenatide)
  - Medullary thyroid carcinoma
  - History or family history of multiple endocrine neoplasia syndrome type-2
  - ↑ incidence of thyroid C-cell tumors in rats
- Contraindication
  - Hypersensitivity

Warnings/precautions

- Acute renal failure
  - Postmarketing reports; majority had nausea, vomiting, diarrhea, & dehydration
  - Monitor kidney function, d/c if occurs
- Acute pancreatitis
  - Postmarketing reports of fatal and nonfatal
  - Not recommended with pancreatitis history
  - Monitor s/s, d/c if occurs
- Acute gallbladder disease
  - Cholelithiasis and cholecystitis reported
  - Gallbladder studies if suspected
- Gastrointestinal disease
  - Gastroparesis reported
  - Not recommended with severe GI disease
  - Monitor s/s, d/c if occurs

Warnings/precautions

- Hypoglycemia
  - In combination with insulin and/or sulfonylureas
  - Lower dose before starting GLP-1 RA
- Immunogenicity
  - Antibodies against GLP-1 RA
  - Monitor for unexplained worsening glycemic control, change class if occurs
- Diabetic retinopathy complications (semaglutide)
  - Vitreous hemorrhage and blindness reported
  - Monitor for worsening diabetic retinopathy, change agent if occurs

Adverse Effects

- Nausea, vomiting, diarrhea
  - Dose-dependent
  - Often decreases over time, titrate slowly, change agent or class if intolerable
- Injection site
  - Mass, nodule, pruritus, and injection site reactions reported
  - Change agent, change class if severe
- Altered renal function
  - Postmarketing reports of ↑Scr and worsening CKD
  - Monitor renal function, d/c if worsening continues

Dipeptidyl peptidase-4 inhibitor

DPP-4 inhibitors
Alogliptin (Nesina)
Linagliptin (Trajenta)
Saxagliptin (Onglyza)
Sitagliptin (Januvia)

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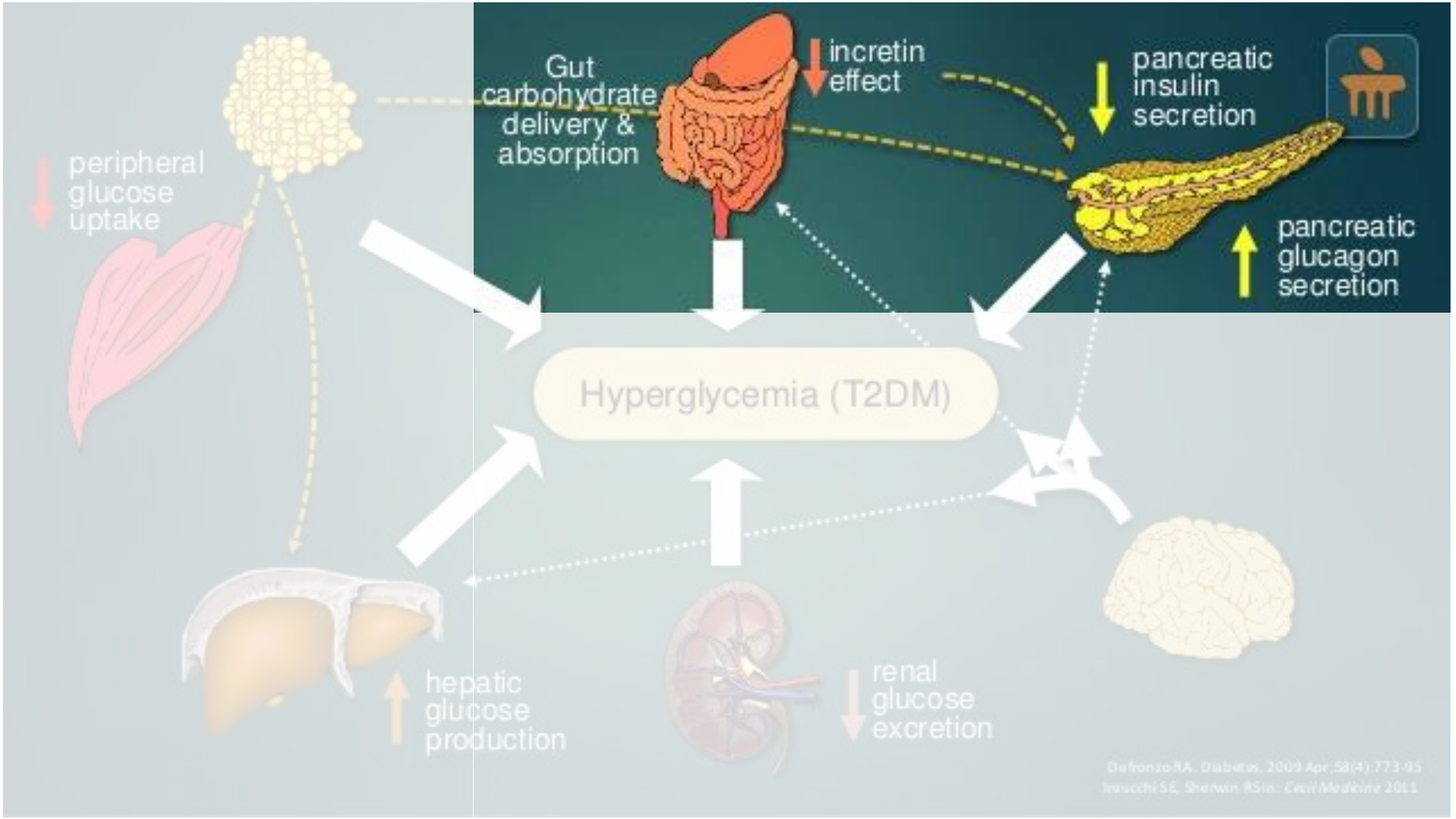
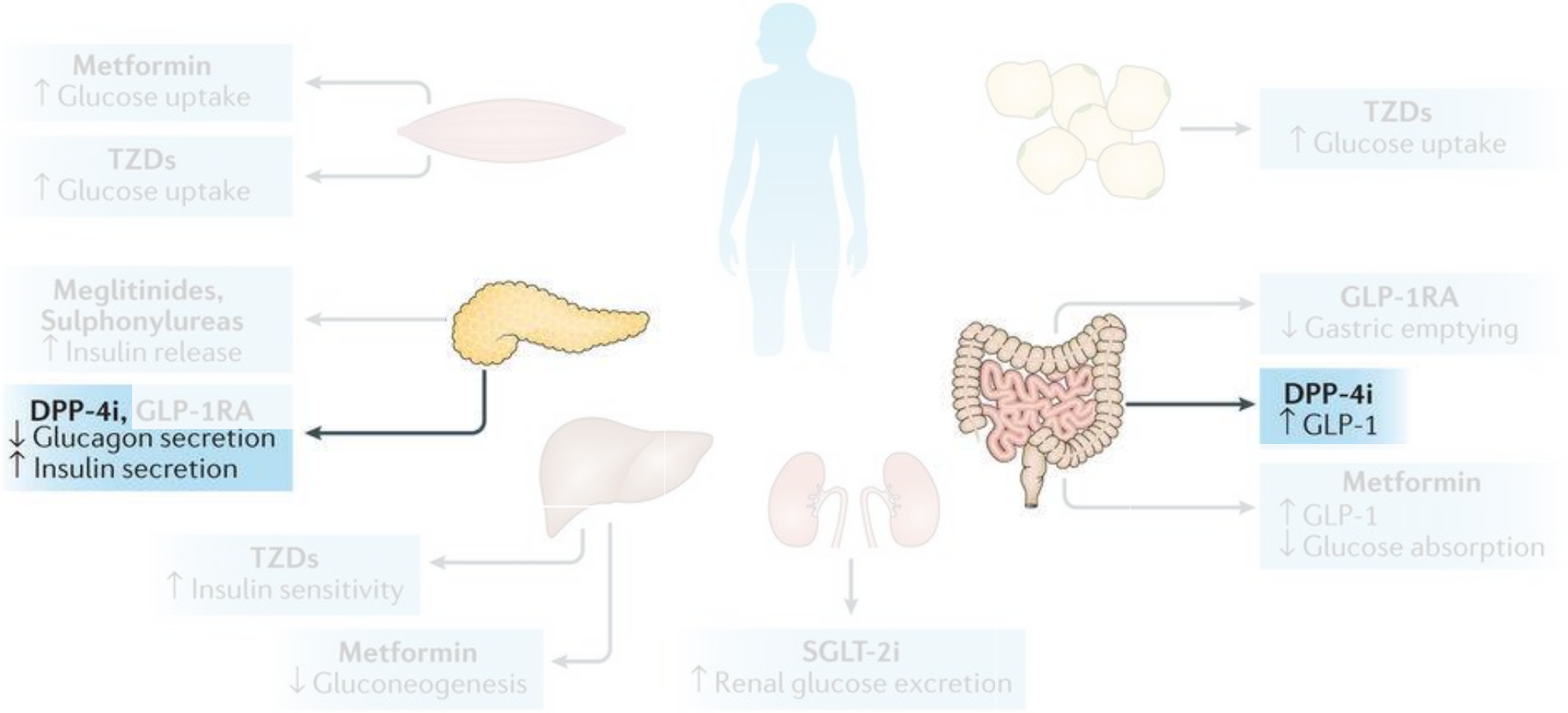
Hyperglycemia



Mechanism of action

- Blocks DPP-4 (nondiabetic levels of GLP-1 achieved)
  - ↑ glucose-dependent insulin secretion
  - ↓ inappropriate high postprandial glucagon secretion
  - Does not alter gastric emptying
  - Does not have significant satiety effects
    - Considered weight neutral

How do they work?



Contraindications = do not use

- Hypersensitivity

Warnings/precautions

- Acute pancreatitis
  - Postmarketing reports
  - Monitor s/s, d/c if occurs
- Arthralgia
  - Severe and disabling joint pain reported
  - d/c if occurs, may rechallenge
- Heart failure
  - Peripheral edema and HF hospitalization reported
  - Monitor new/worsening HF, d/c if occurs
- Hypoglycemia
  - In combination with insulin and/or sulfonylureas
  - Lower dose before starting DPP-4i

Warnings/precautions

- Acute renal failure (sitagliptin)
  - Postmarketing reports
  - Monitor renal function, d/c if occurs

- Hepatotoxicity (alogliptin)
  - Postmarketing reports of fatal and nonfatal hepatic failure
  - Monitor s/s and LFTs, d/c if confirmed alogliptin-induced, change agent
  - Never restart

Adverse effects

- Nasopharyngitis
- Upper respiratory tract infection
- Headache
- Urinary tract infection

- If recurrent or intolerable, change agent or class

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors
Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
Ertugliflozin (Steglatro)

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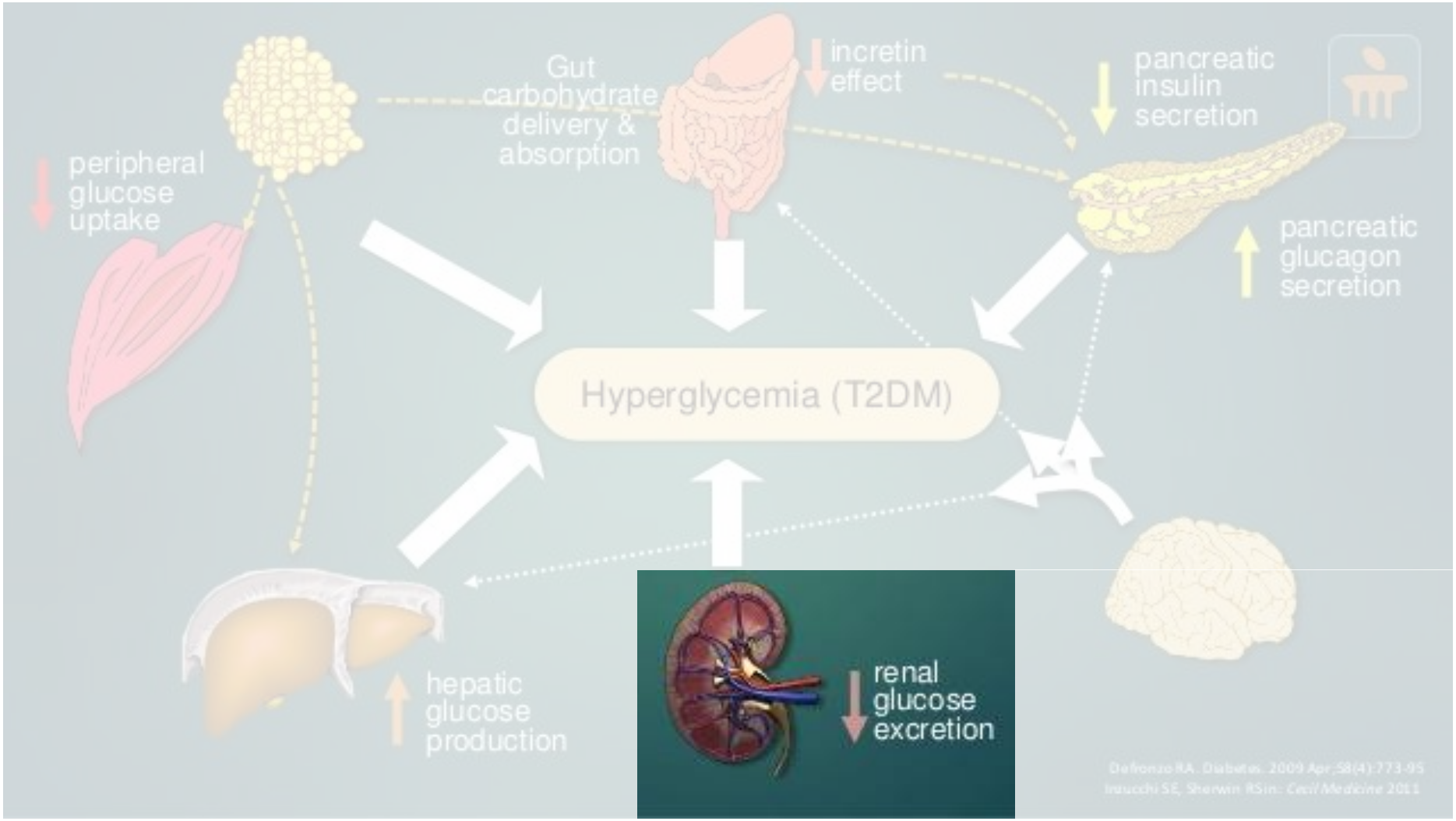
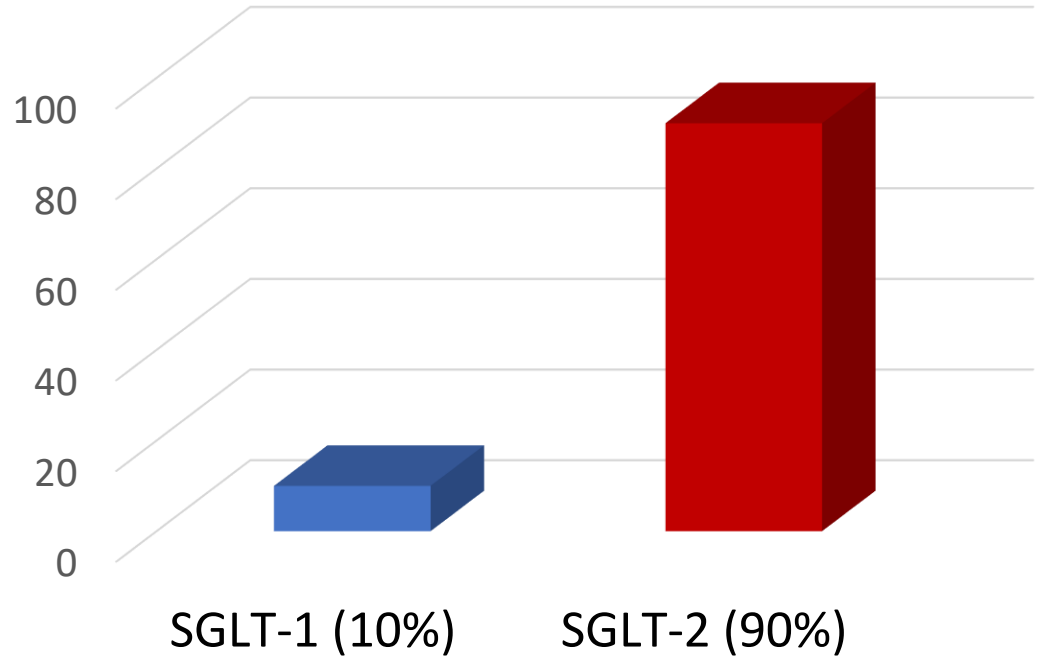
Hyperglycemia



Sodium-glucose cotransporters

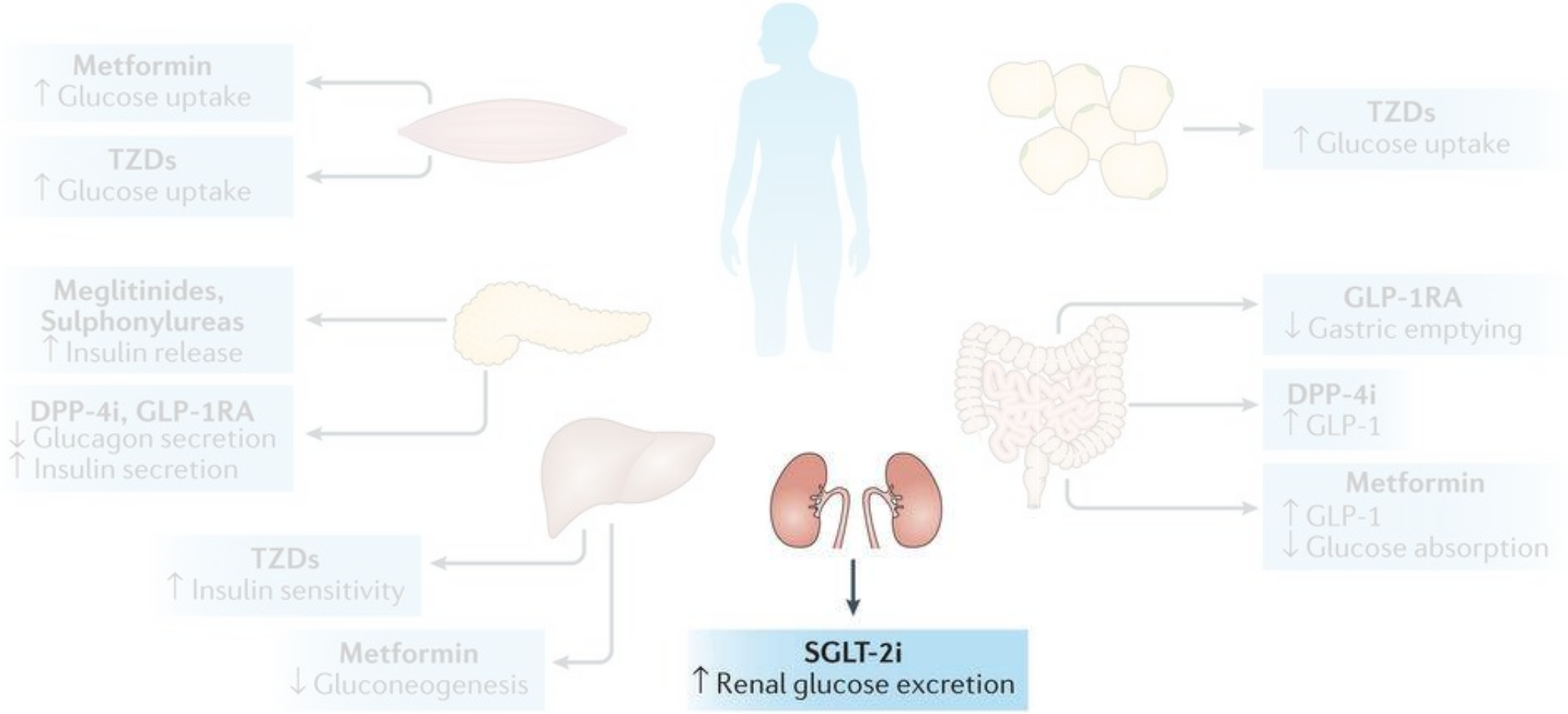
- Glucose is reabsorbed back into systemic circulation from the kidney
  - This occurs through SGLT-1 and SGLT-2 receptors



Mechanism of action

- Works in the kidney to block reabsorption of glucose
  - 50-80g of glucose/day may be passed into the urine with SGLT-2 receptor inhibition
  - Weight loss

How do they work?



Contraindications = do not use

- Black box warning (canagliflozin)
  - Lower limb amputation in those with diabetes and CVD
    - Monitor for infections or ulcers of lower limbs, d/c if occurs

- Contraindications
  - Hypersensitivity
  - Severe renal impairment (eGFR < 30)
  - End stage renal disease
  - Dialysis

Warnings/precautions

- Hypotension/volume depletion
  - Symptomatic hypotension
  - Monitor volume status and correct as needed, d/c if harm > benefit
- Ketoacidosis
  - Postmarketing reports of fatal and nonfatal
  - Monitor for metabolic acidosis regardless of glucose control
  - D/c if suspected, change class if confirmed SGLT-2i-induced
- Acute kidney injury
  - Postmarketing reports of AKI and impaired renal function
  - Monitor renal function and volume status, d/c if occurs
  - Temporarily d/c if fluid intake is reduced

Warnings/precautions

- Urosepsis and pyelonephritis
  - Postmarketing reports of hospitalizations
  - Monitor s/s, change agent or class if recurrent or intolerable
- Genital mycotic infections
  - Increased risk with genital mycotic infection history, uncircumcised males
  - Monitor s/s, change agent or class if recurrent or intolerable
- Hypoglycemia
  - In combination with insulin and/or sulfonylureas
  - Lower dose before starting SGLT-2i
- Increased LDL
  - Dose related
  - Monitor lipids, use lowest effective dose, change class if uncontrollable

Warnings/precautions

- Bone fracture (canagliflozin)
  - Change agent if occurs
- Hyperkalemia (canagliflozin)
  - In those with impaired renal function
  - Monitor potassium, change agent if uncontrollable
- Bladder cancer (dapagliflozin)
  - Higher incidence reported
  - Not recommended with active bladder cancer
  - Caution with bladder cancer history
- Lower limb amputation (ertugliflozin)
  - Higher incidence reported
  - Monitor for infection or ulcers of lower limbs, d/c if occurs

Adverse effects

- Female mycotic infections
- Urinary tract infections
- Nasopharyngitis
- Increased urination

- If recurrent or intolerable, change agent or class

References

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Questions?

Thank you everyone!