Where to from metformin?

13 December 2023
GP Vertical Integration

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Acknowledgement of Country

I acknowledge the Traditional Custodians of country throughout Australia and recognise their continuing connection to land, waters and culture.

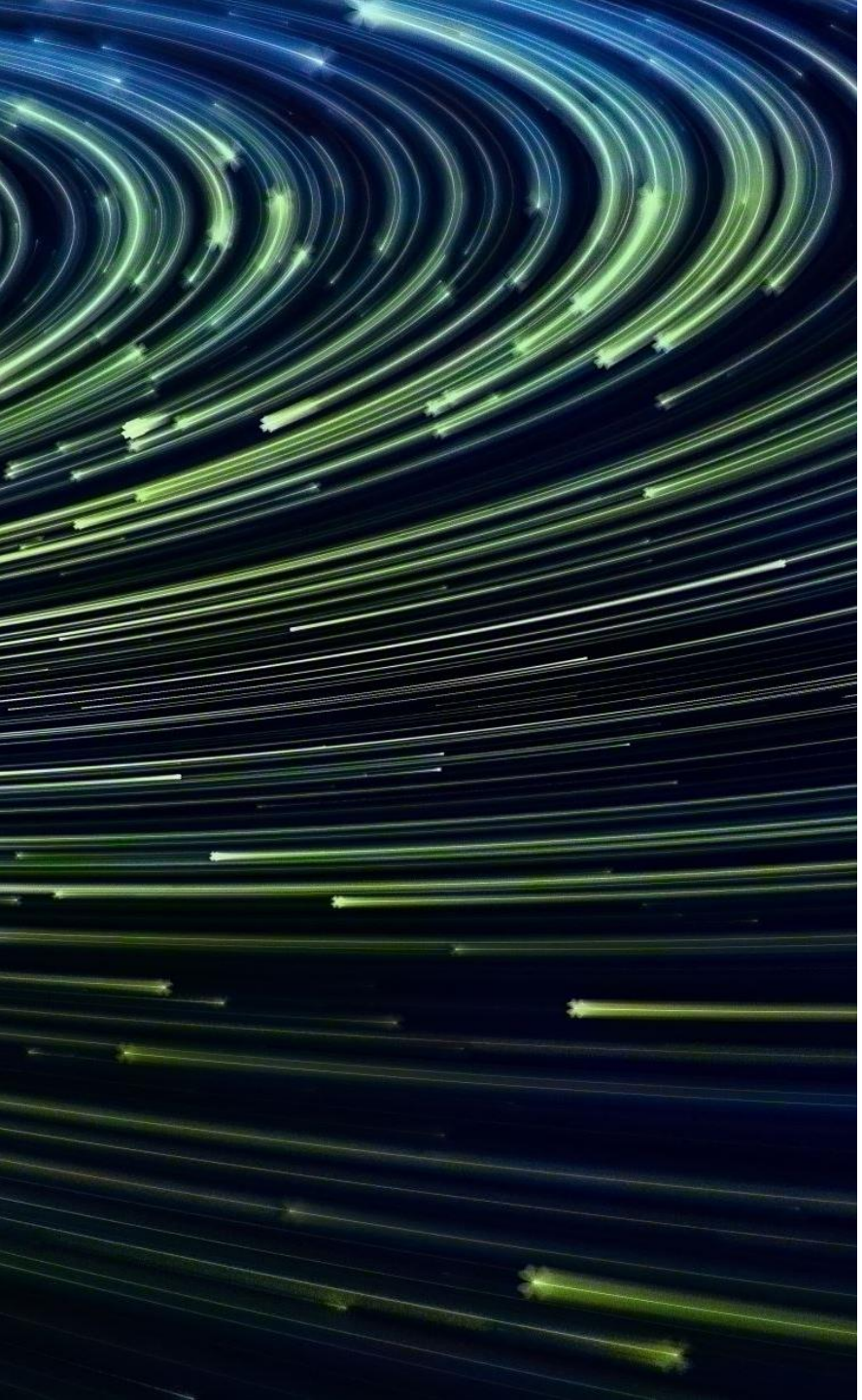
I pay my respects to their Elders past, present and emerging.

Disclosures

No conflicts of interest

Learning Objectives

- Identify non-insulin injectable treatment options for patients with type 2 diabetes, and their most appropriate use.
- Understand how to commence insulin for patients in the primary care setting.
- Gain confidence in the adjustment of insulin dosages
- Understand the limitations of the PBS for GPs when prescribing injectable therapies for patients type 2 diabetes.



Updated Terminology

BGL = blood glucose level *rather than BSL*

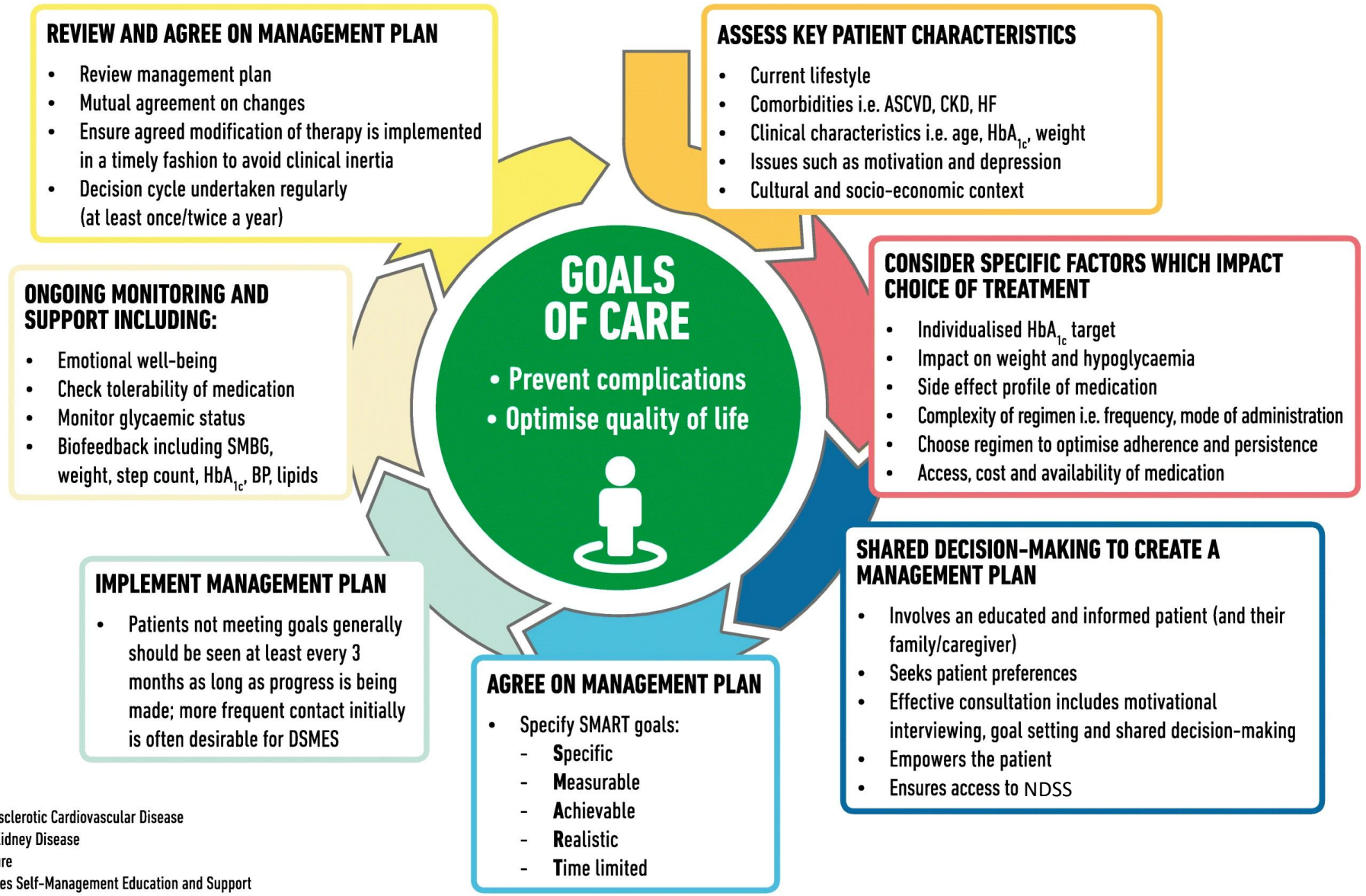
Oral diabetes medications/glucose lowering medications *rather than oral hypoglycaemic agents*

PWD = patients/persons with diabetes *rather than type 1/2 diabetic*

SMBG = self-monitoring of blood glucose

Type 1 or Type 2 diabetes (T1D/T2D) *instead of insulin dependent diabetes mellitus (IDDM)*

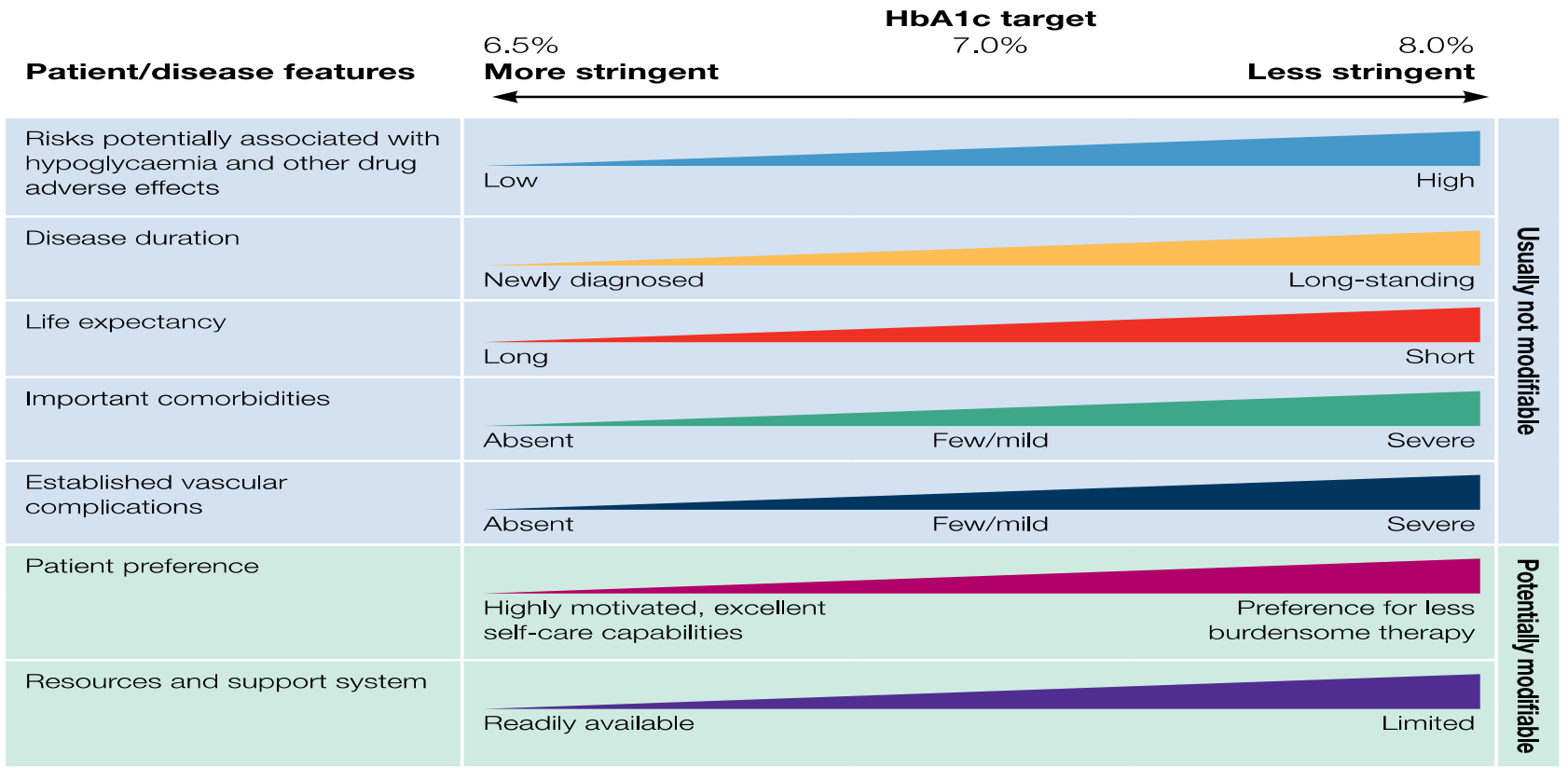
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Davies, M.J., D'Alessio, D.A., Fradkin, J. *et al.* Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* **61,** 2461–2498 (2018).

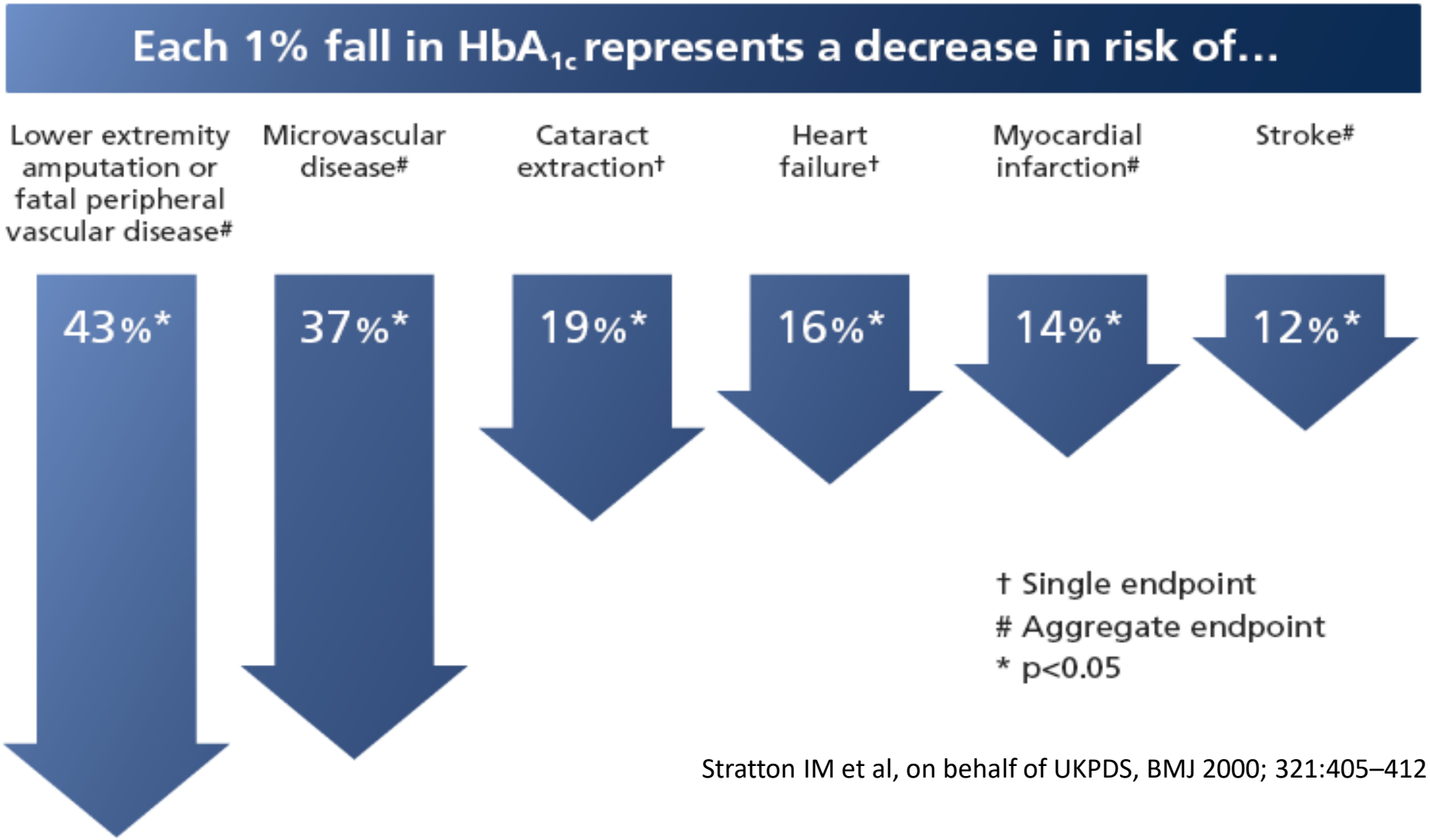
Figure 1. Approach to individualising HbA1c targets



Some important patient characteristics to consider when individualising HbA1c targets are listed on the left. More stringent efforts to lower HbA1c are justified for people who fall to the left of the range; those toward the right may have other priorities and require less stringent efforts.

Source: Adapted from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38(1):140–49, with permission of the American Diabetes Association.

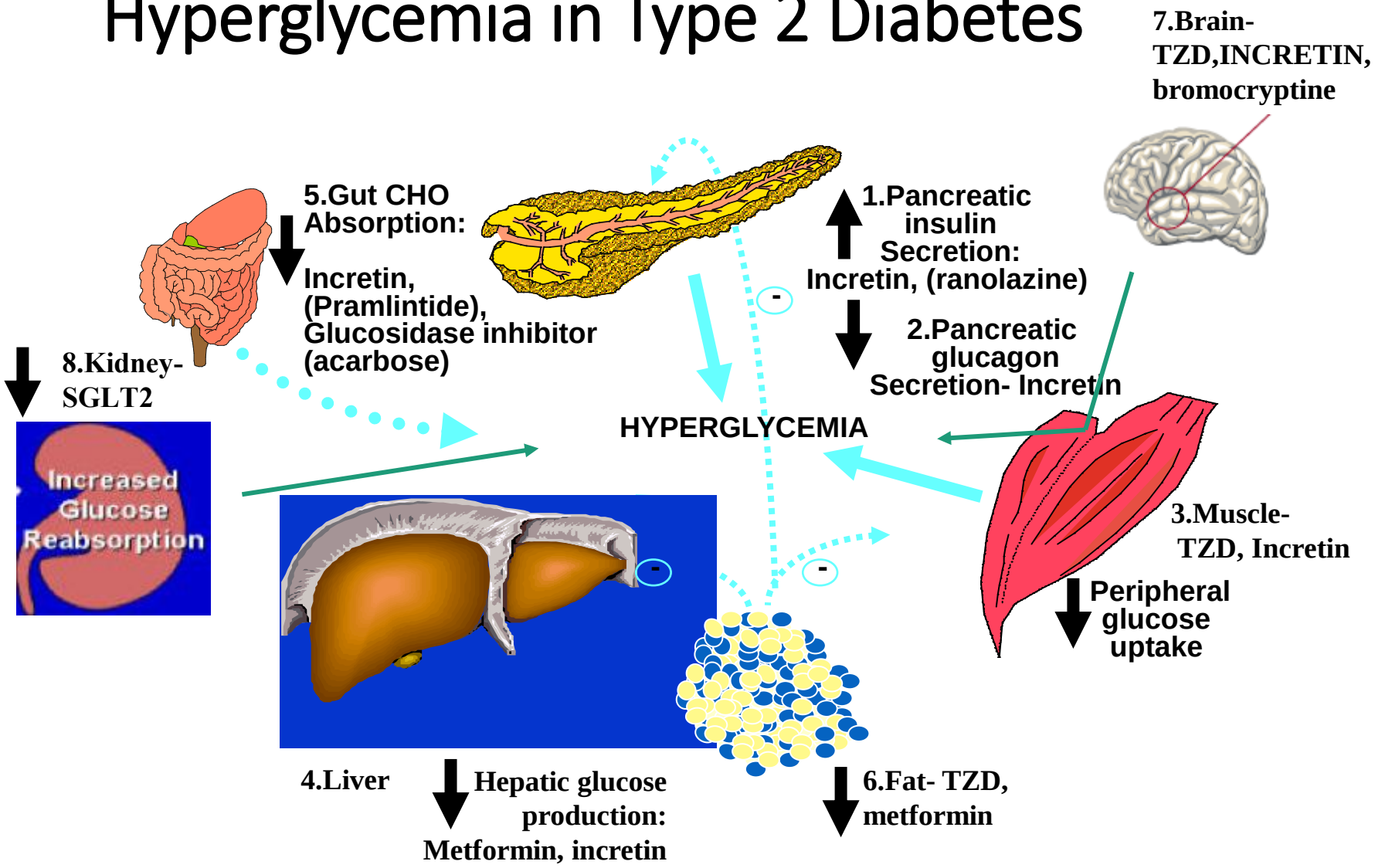
Association between mean HbA1c and complications



Stratton IM et al, on behalf of UKPDS, BMJ 2000; 321:405–412

(Newer) Treatments before insulin

Non-Insulin Therapy for Hyperglycemia in Type 2 Diabetes



Source: http://www.diabetesincontrol.com/diabetes-mellitus-101-for-medical-professionals-part-9-of-9/

Case 1 - Joe

- 49M
- Busy lifestyle – 3 kids, fulltime office work
- Gained weight – currently 110kg, BMI 34
- Would like to lose some weight, hard to find the time. Comes to see you for weight management and lethargy
- Type 2 diabetes for 5 years, on metformin alone
- HbA1c rising, currently 8%
- Non-smoker, no recreational drug use
- Drinks socially, sometimes 6 standard drinks or more in one night
- Family history of heart disease - father
- Normal renal function, had some chest pain recently while exercising, mildly deranged LFTs (small ↑ AST, ALT, GGT)
- What is your preferred second line treatment for Brett?

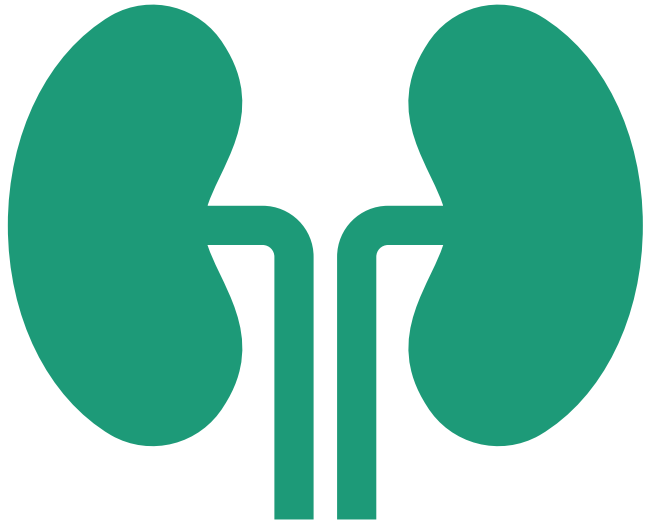
Joe's Treatment Options

a. Sulfonylurea
b. Sodium glucose co-transporter 2 inhibitor (SGLT-2 inhibitor)
c. GLP-1 agonist
d. DPP-IV inhibitor
e. Insulin e.g. glargine once daily

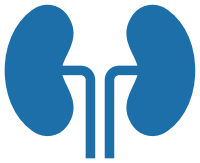
2nd Line Options

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors (Gliflozins)

- Phlorizin was isolated from the bark of the apple tree in 1835
- In 1990s, Tsujihara et al, working at Tanabe Seiyaku, a Japanese pharmaceutical company developed an oral form of SGLT2 inhibitor
- Inhibit renal sodium-glucose transporter to produce urinary glucose loss and decrease BGL
- Causes weight loss
- Reduced mortality, particularly in patients with heart failure
- Not recommended to be used in T1D patients
- Trade names: dapagliflozin (*Forxiga*), empagliflozin (*Jardiance*), ertugliflozin (*Steglatro*), [canagliflozin *Invokana* – discontinued in Australia, sotagliflozin (dual SGLT1/2) not approved]
- Fixed dose combinations with metformin (Xigduo, Jardiamet, Segluromet) or with gliptins (Glyxambi, Qtern, Steglujan)



SGLT2-i Disadvantages



Contraindicated: Diminished efficacy with renal impairment

eGFR< 45 ml/min/1.73m2 for empagliflozin and ertugliflozin

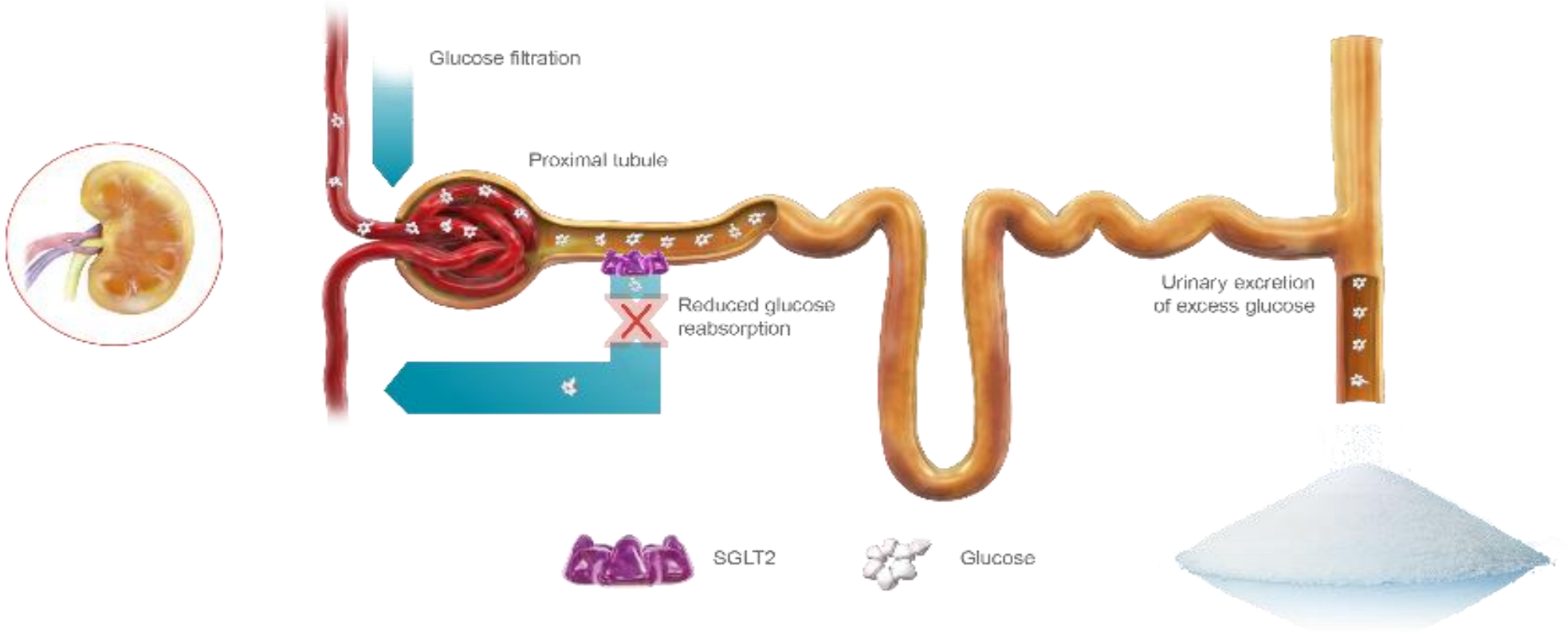
eGFR< 25 ml/min/1.73m2 for dapagliflozin

Precautions: Avoid use with loop diuretics, very low carbohydrate intake, bowel preparation, perioperatively

Adverse effects: Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss

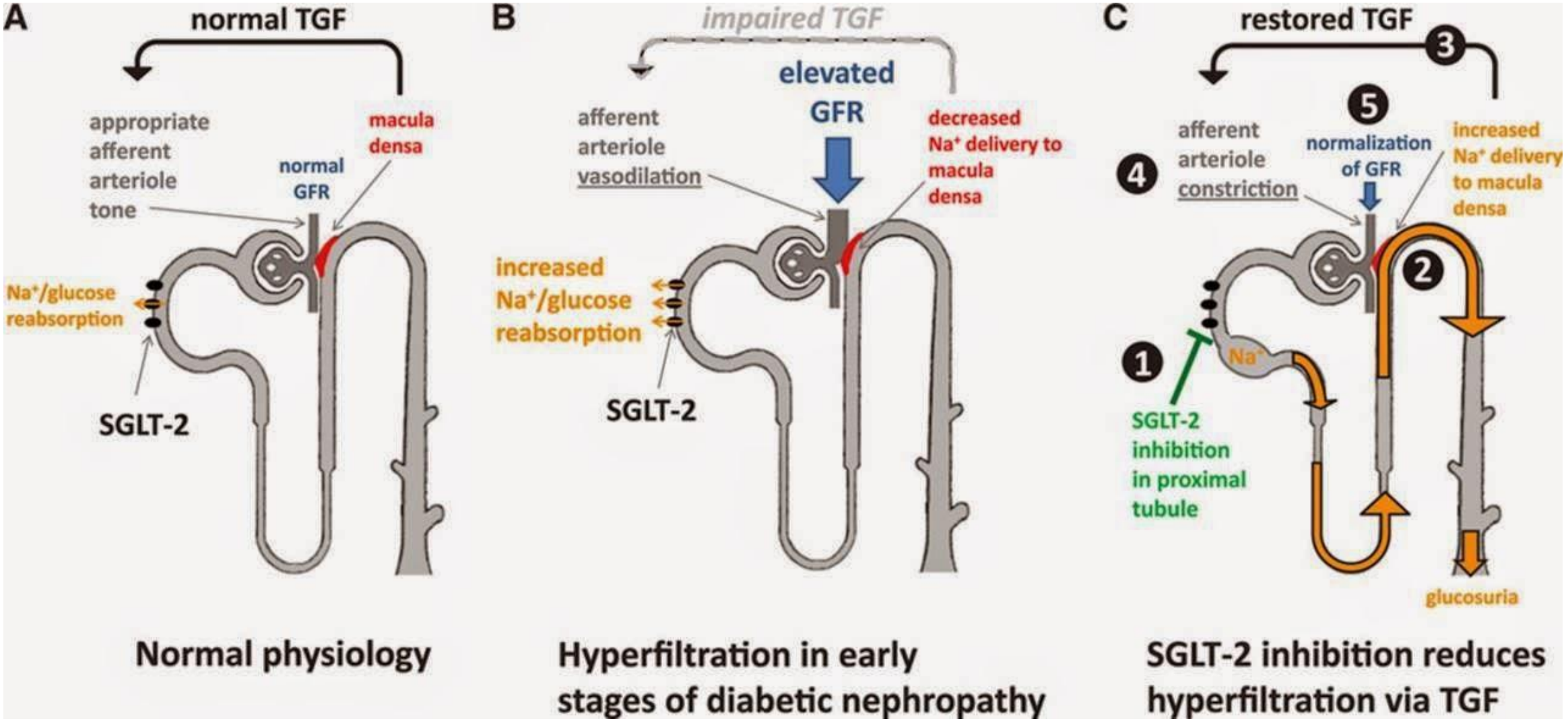
How does SGLT2i work to lower glucose levels?

- The kidney plays an important role in glucose balance, filtering approximately 180g of glucose/day
- Normally, up to 97% of the filtered glucose is re-absorbed at the proximal tubule by Sodium/glucose cotransporter 2 (SGLT2)

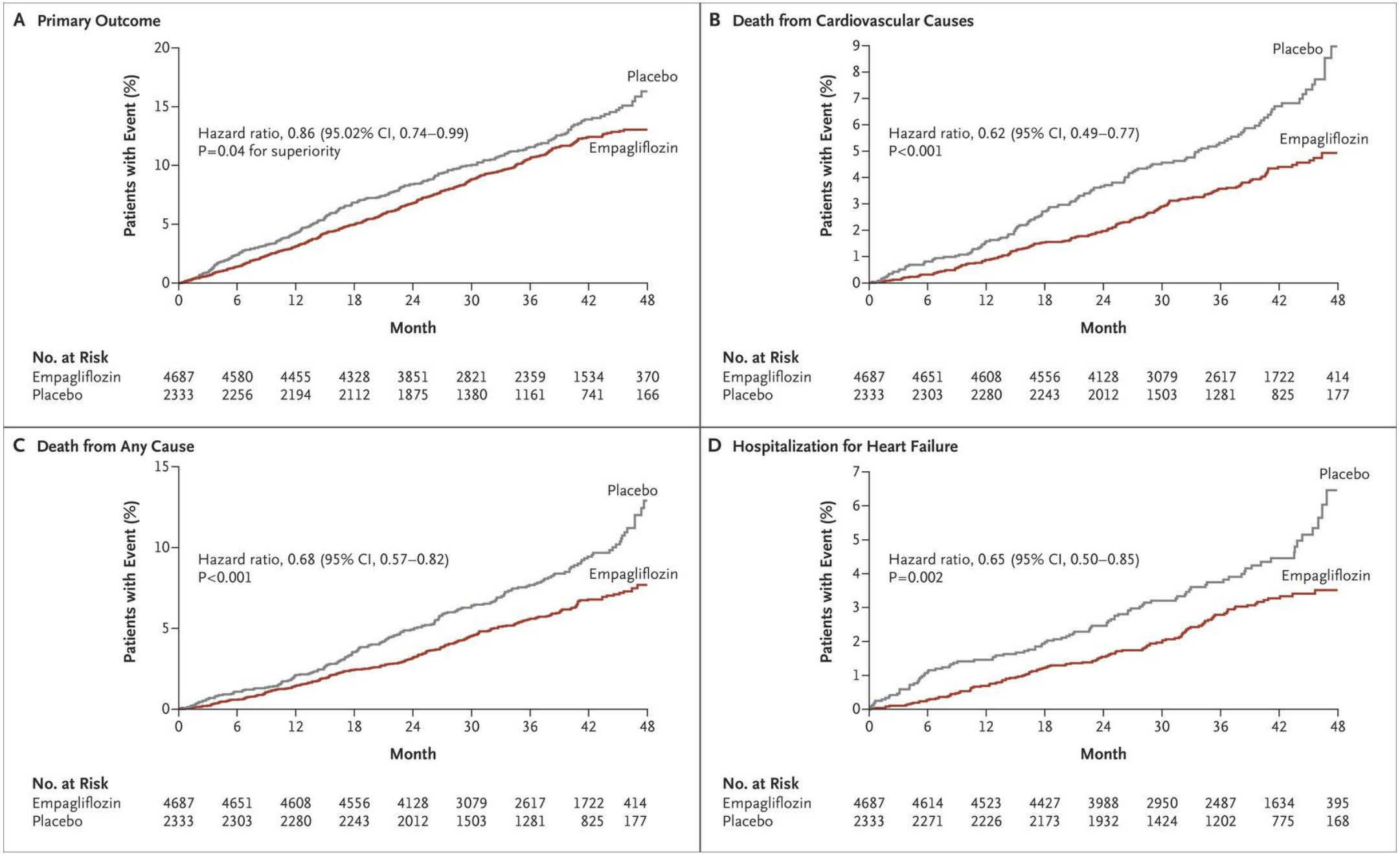


1. FORXIGA® Approved Product Information; **2.** XIGDUO® XR Approved Product Information; **3.** Saeed et al. *Drug Des Dev Ther* 2014;8:2493–2505; **4.** Wright EM *et al. J Int Med* 2007; 261:32–43; **5.** Idris I et al. *Diabetes Obes Metab* 2009; 11:79–88.

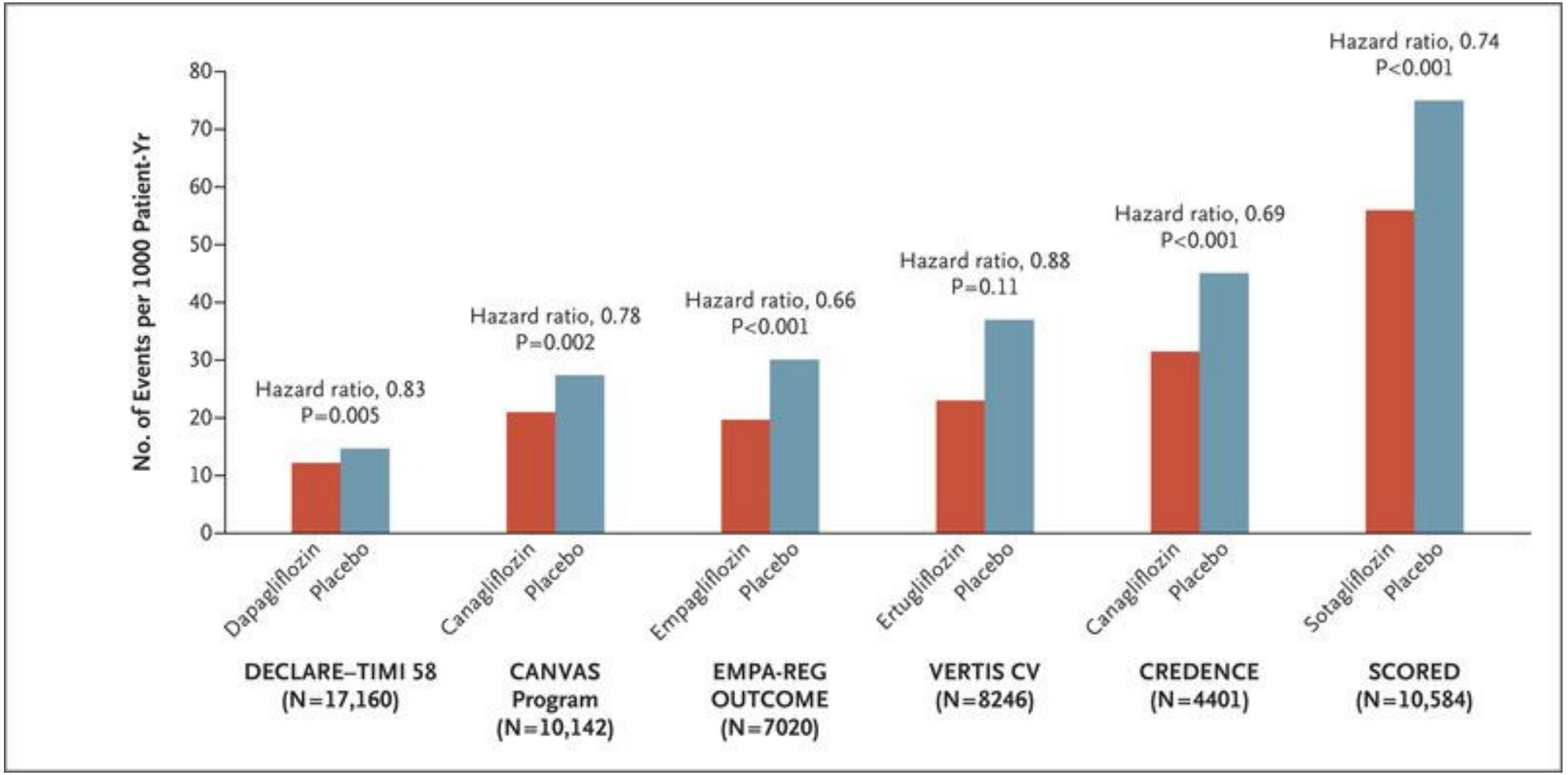
Mechanism of SGLT-2 inhibitors



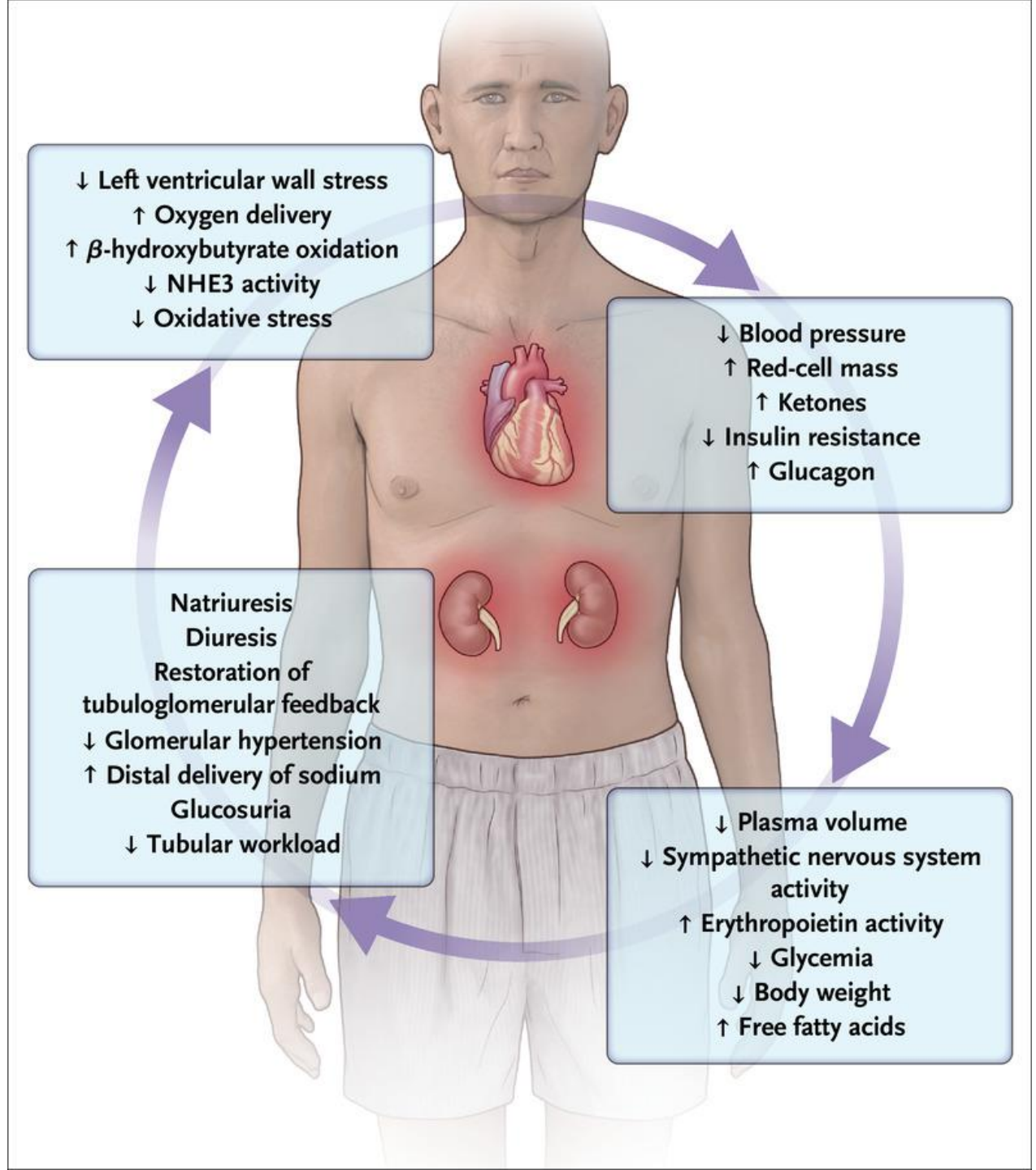
Source: Cherney et al. Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus. Circulation 2014



Source: Zinman et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, NEJM 2015



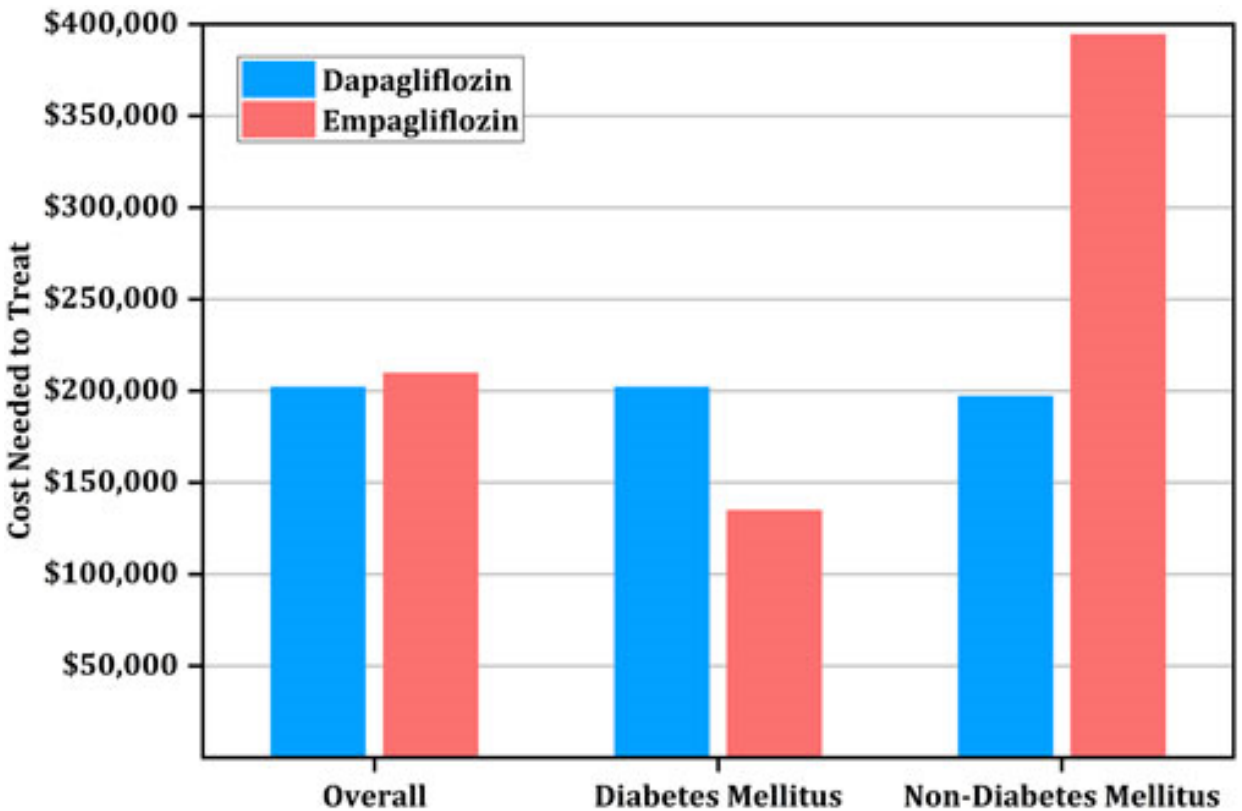
Braunwald, NEJM 2022

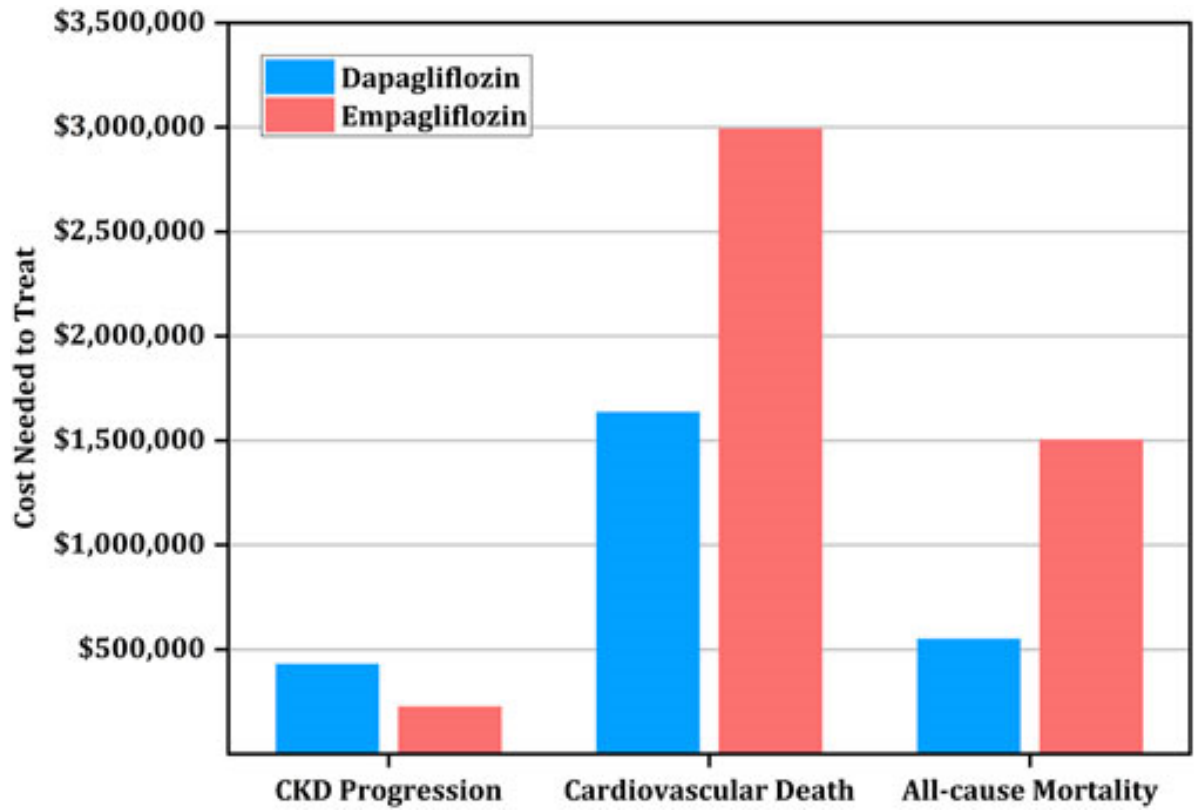

↓ Left ventricular wall stress
↑ Oxygen delivery
↑ β-hydroxybutyrate oxidation
↓ NHE3 activity
↓ Oxidative stress
↓ Blood pressure
↑ Red-cell mass
↑ Ketones
↓ Insulin resistance
↑ Glucagon
Natriuresis
Diuresis
Restoration of tubuloglomerular feedback
↓ Glomerular hypertension
↑ Distal delivery of sodium
Glucosuria
↓ Tubular workload
↓ Plasma volume
↓ Sympathetic nervous system activity
↑ Erythropoietin activity
↓ Glycemia
↓ Body weight
↑ Free fatty acids

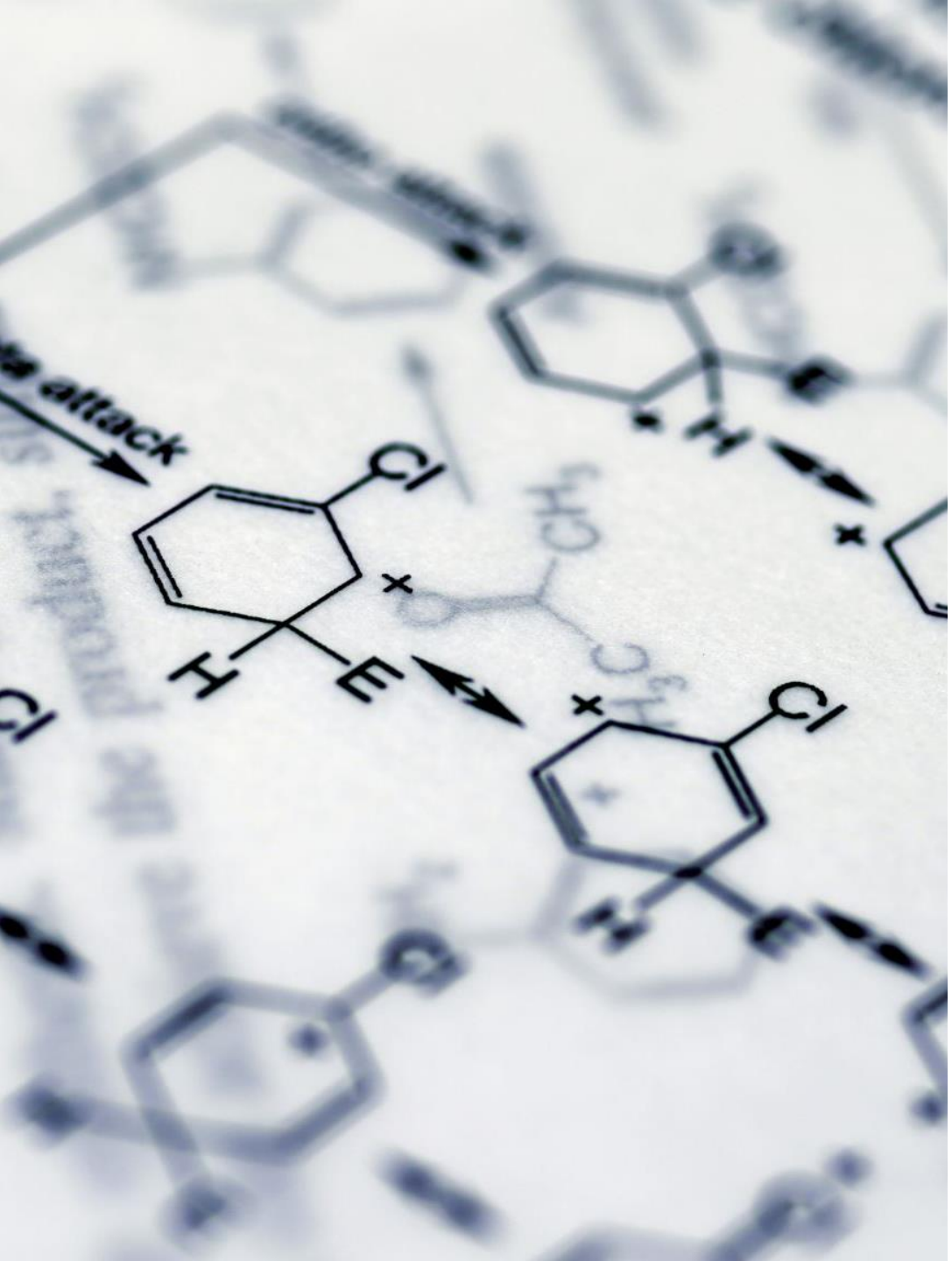
Dapagliflozin versus empagliflozin in patients with chronic kidney disease

Hilmi Alnsasra[1,2]*, Gal Tsaban[1,2], Adam Solomon[2], Fouad Khalil[3], Enis Aboalhasan[4], Abed N. Azab[1,5], Joseph Azuri[6,7], Ariel Hammerman[8] and Ronen Arbel[4]

Prevention of CKD







Sodium Glucose co-transporter-2 inhibitor (SGLT2i) Precautions

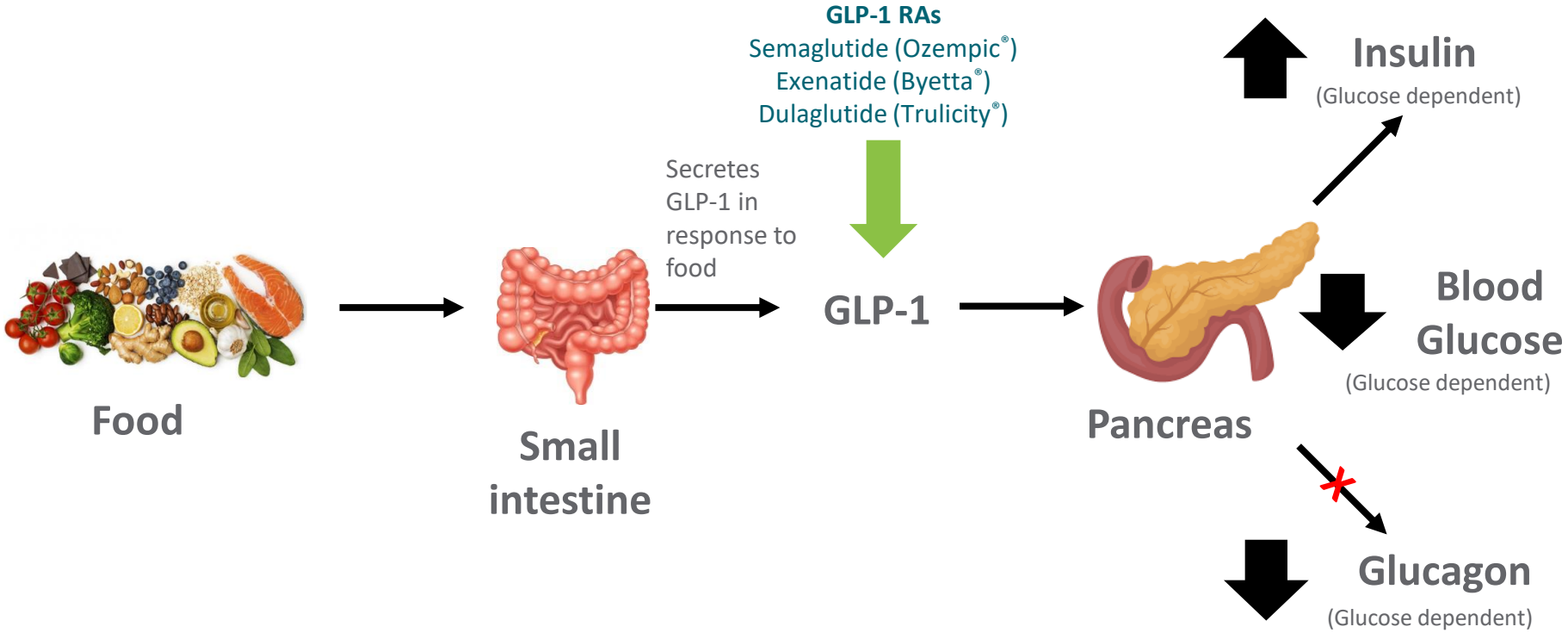
- Over the last few years there has been an increasing number of reports of patients with type 2 diabetes who are taking these medications developing severe acidosis requiring ICU/HDU admission during the peri-operative period.
- SGLT2i carry a small but definite risk of severe diabetic ketoacidosis (DKA). Sometimes this DKA is associated with near normal or only mildly elevated blood glucose levels (i.e. ***euglycaemic ketoacidosis*** [euDKA])
- The risk is increased if the patient has been fasting or has very restricted dietary intake, has undergone bowel preparation and/or a surgical procedure, is dehydrated or has an intercurrent illness such as active infection
- Blood ketone testing is strongly recommended to detect and monitor DKA as urine ketone testing may be unreliable

ALERT UPDATE January 2020
Periprocedural Diabetic Ketoacidosis (DKA)
with SGLT2 Inhibitor Use

- When commencing patients on SGLT2i, clinicians should inform patients about the risk of DKA associated with procedures, ideally with written information and management plans
- **For surgery and procedures** requiring one or more days in hospital, and/or requiring 'bowel preparation' including colonoscopy, cease SGLT2i at least **3 days pre-procedure** (2 days prior to surgery and the day of surgery/procedure)
  - This may require increasing other glucose-lowering drugs during that time. If the SGLT2i is part of a fixed dose combination, this will lead to withdrawal of two glucose lowering drugs unless the second drug is continued separately.
- For day-stay procedures (including gastroscopy), SGLT2i can be stopped just for the day of procedure.
  - However, fasting before and after the procedure should be minimised

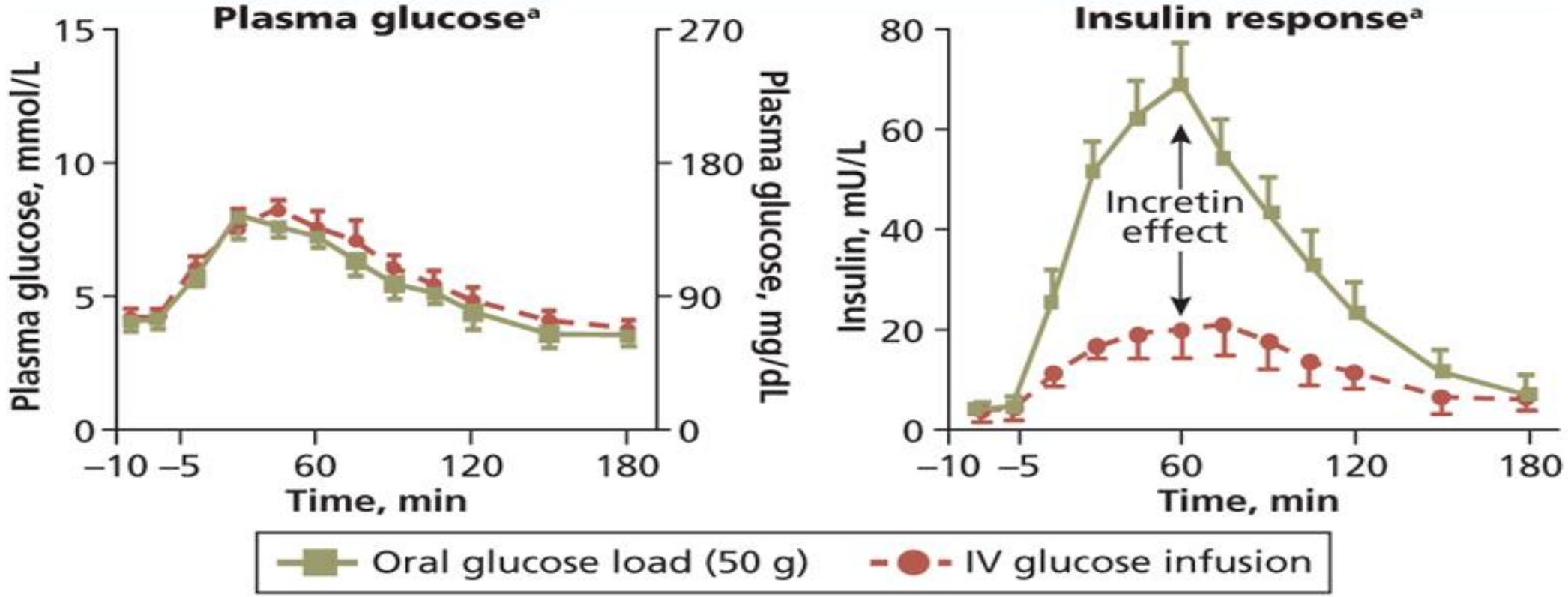
GLP-1 agonists

How does GLP-1 lower blood glucose?



GLP-1 has a physiological half-life of 2 minutes due to rapid deactivation by DPP-4 enzyme

Incretin Hormones Play a Crucial Role in Healthy Insulin Response

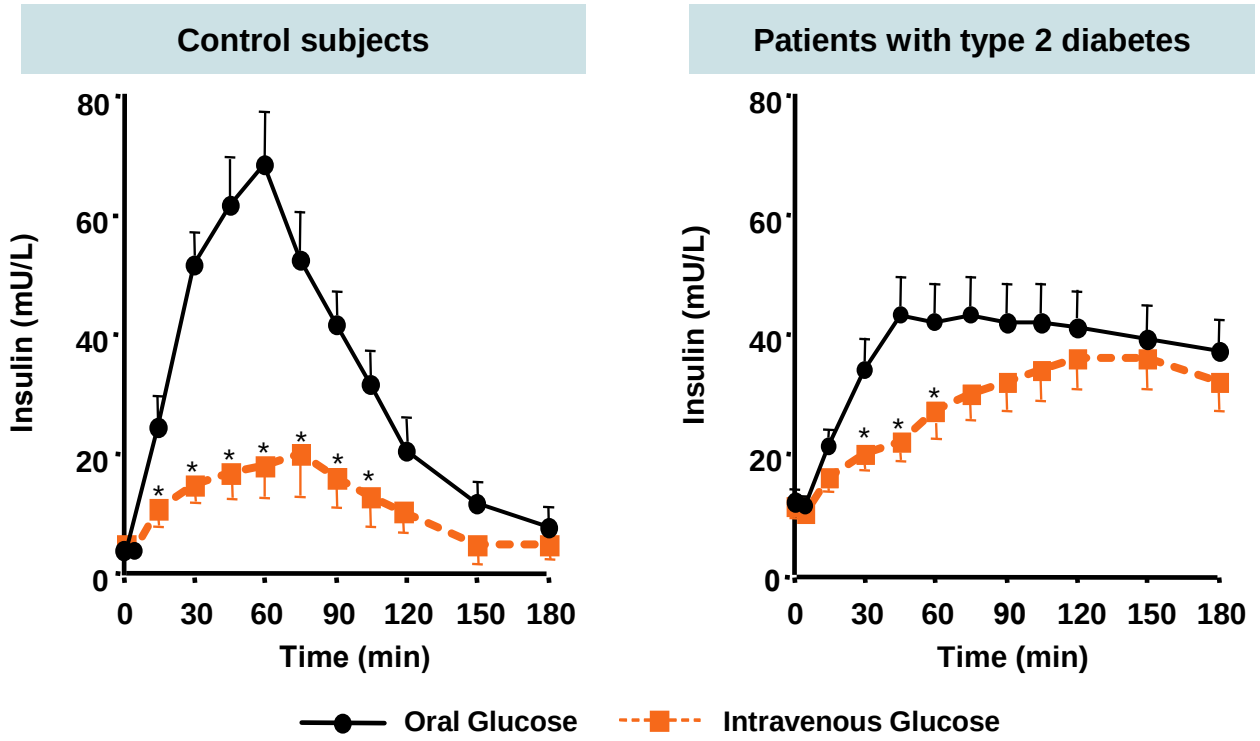


- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

[a] In healthy volunteers (n = 8).

N. McIntyre *et al.*: *Lancet* 2:20-21, 1964 (23) © The Lancet Ltd.].

The Incretin Effect is Reduced in Patients with Type 2 Diabetes



*$P \leq .05$ compared with respective value after oral load.
Nauck MA, et al. *Diabetologia* 1986;29:46–52.

Exenatide – When Science Mimics Nature

Gila monster

- Venomous lizard native to the United States and Mexico

- *Exendin-4* is derived from its venomous saliva protein
- *Exenatide* is a degradation resistant mimetic isolated in 1992
- Was approved for medical use by the FDA in 2005 sold as *Byetta* and *Bydureon*

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA)

Administered by subcutaneous injection only

Stimulate ß-cell insulin release and slows gastric emptying, inhibits release of glucagon

Superior effects on BGL to oral agents

Side effects:

High likelihood of gastrointestinal symptoms: nausea, vomiting, diarrhoea, constipation

Risk of gall bladder disorders, pancreatitis

Rapid weight loss

Trade names:

Exenatide (Bydureon – Extended-release, Byetta – Immediate release bd dose), Lixisenatide (Lyxumia), Dulaglutide (Trulicity), Liraglutide (Victoza & Saxenda), Semaglutide (Ozempic),

Gunton, J et al. A new blood glucose management algorithm for type 2 diabetes: a position statement of the Australian Diabetes Society. MJA 2014

Long term effects of GLP-1 agonists

Largely unknown – no long-term outcome trial data

Pancreatic cancer, medullary thyroid cancer

Sarcopaenia – reductions in muscle mass compared to fat mass

Overworked beta cells leading to impaired insulin secretion and islet function

Bone loss

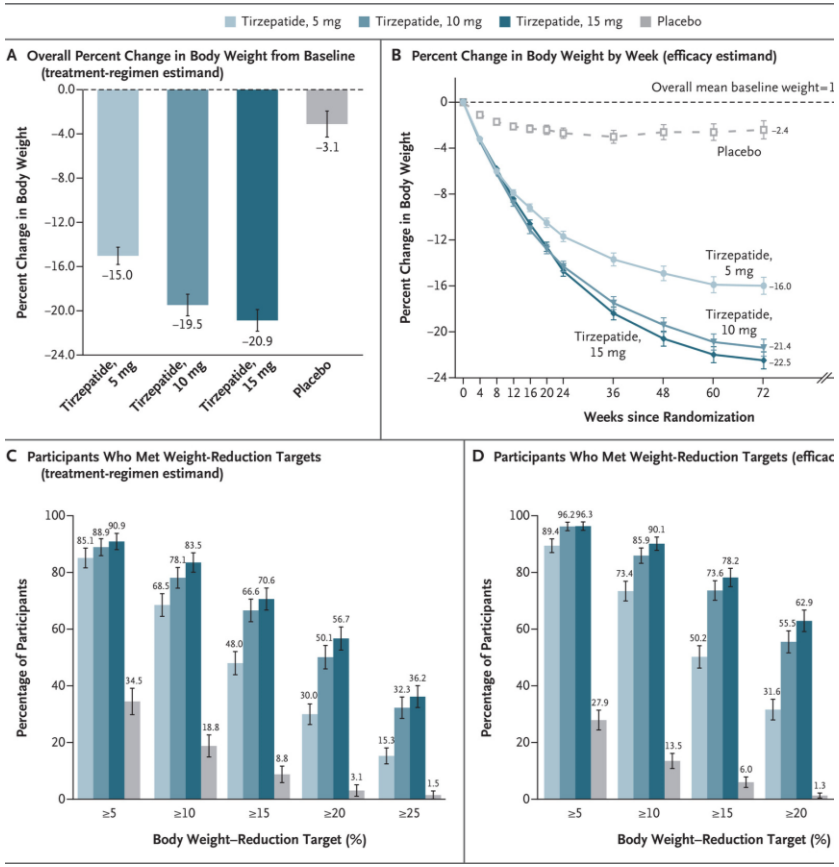
Reduction of weight loss – tolerance to effects

Massimo, E et al. Cells, 2021

Holmes, Natures Reviews Endocrinology, 2016

Tirzepatide – GLP-1 and GIP agonist

- Glucose-dependent insulinotropic polypeptide (GIP) is another nutrient-stimulated hormone, regulates energy balance through cell-surface receptor signaling in the brain and adipose tissue.
- A molecule that combines both GIP and GLP receptor agonism theoretically may lead to greater efficacy in weight reduction.
- GIP activation appeared to act synergistically with GLP-1 receptor activation to allow greater weight reduction in mice than that achieved with GLP-1 receptor monoagonism.



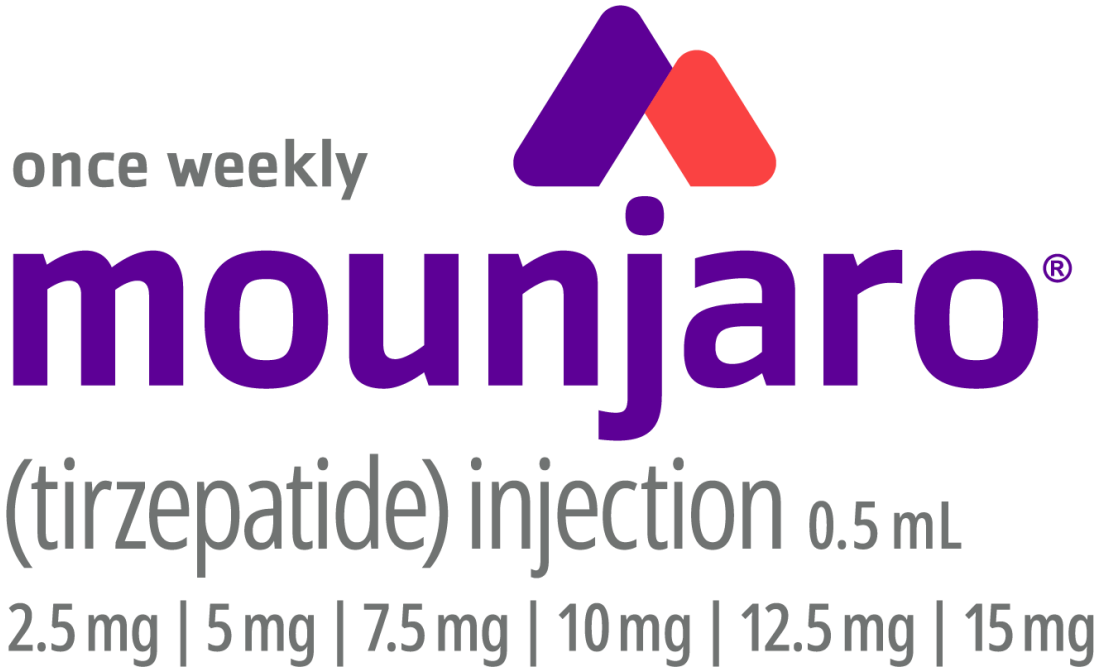
Tirzepatide (Mounjaro)

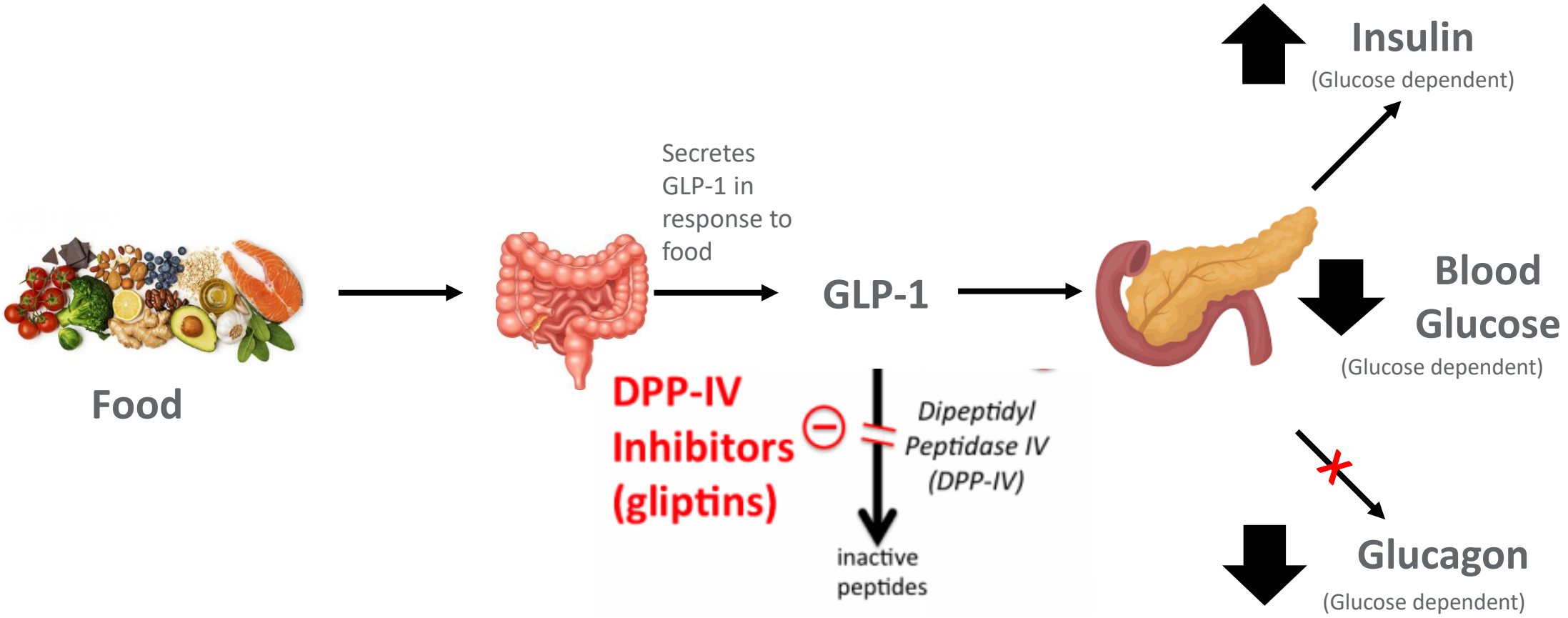
- TGA approved in Australia 22 December 2022 for Type 2 Diabetes Mellitus:
  - as monotherapy when metformin is not tolerated or contraindicated.
  - in addition to other medicinal products for the treatment of type 2 diabetes.
- PBS rejected August 2023
- The starting dose of tirzepatide is 2.5 mg once weekly.
  - After 4 weeks, increase the dose to 5 mg once weekly.
  - If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.
  - The recommended doses are 5 mg, 10 mg and 15 mg.
  - The 2.5 mg, 7.5 mg and 12.5 mg are not maintenance doses.
  - The maximum dose of tirzepatide is 15 mg once weekly.

Limited available of MOUNJARO

Eli Lilly Australia (Lilly) has recently notified the TGA of the limited availability of MOUNJARO® (tirzepatide) vial in Australia. The limited availability in supply is due to larger than expected demand, and is not related to any safety, efficacy, or quality issue for MOUNJARO®. Stock availability varies by dose of MOUNJARO®, currently:

- 2.5mg and 5mg are unavailable and expect limited availability from 15 December 2023.
- 7.5mg is unavailable and expect limited availability from 15 February 2024.
- 10mg is unavailable and expect limited availability from 15 January 2024.
- 12.5mg and 15mg MOUNJARO® doses have limited availability.





How does DPP-4 Inhibitor work to lower blood glucose?

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Decrease activation of GLP-1 thereby increasing its availability

Improves ß-cell function and insulin secretion

Slows gastric emptying

Decreases HbA1c by 0.6-0.7% (7-8 mmol/mol), except Vildagliptin (1% or 11mmol/mol)

Side effects:

Gastrointestinal disturbance

Nasopharyngitis

Rash

Trade names: Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina), Vildagliptin (Galvus)

Gunton, J et al. A new blood glucose management algorithm for type 2 diabetes: a position statement of the Australian Diabetes Society. MJA 2014

Joe's Treatment Options

a. Sulfonylurea
b. Sodium glucose co-transporter 2 inhibitor (SGLT-2 inhibitor)
c. GLP-1 agonist
d. DPP-IV inhibitor
e. Insulin e.g. glargine once daily

The Oldies

- Sulfonylureas: insulin secretagogue - enhance insulin secretion
  - lower HbA1C levels by ~1.5 percentage points
  - Major risk of hypoglycaemia, weight gain ~2kg
  - Second generation – gliclazide, glimiperide, glipizide are preferred
- Thiazolidinediones (TZDs or glitazones): peroxisome proliferator–activated receptor γ modulators
  - they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin (“insulin sensitizers”)
  - 0.5–1.4 percentage point decrease in HbA1C
  - Adverse effects of weight gain, mainly peripheral adiposity, fluid retention, peripheral oedema and 2x risk of congestive cardiac failure, increased risk of fractures in women
- Acarbose: α-Glucosidase inhibitors
  - reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia.
  - They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A1C levels by 0.5–0.8 percentage points
  - Cause bloating and gastrointestinal symptoms with high discontinuation rates (25-45%)

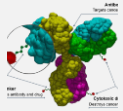
Watch This Space - New Incretin-Based Therapies

Cagrilinitide + semaglutide (CagriSema)

Insulin icodec + semaglutide (IcoSema)

Oral non-peptide GLP-1 RA (orforglipron, danuglipron)

Multiagonists incorporating glucagon receptor agonism (survodutide, retratrutide)



Bimagrumab + incretin-based therapies

Starting insulin

Case Study 2 - Lauren

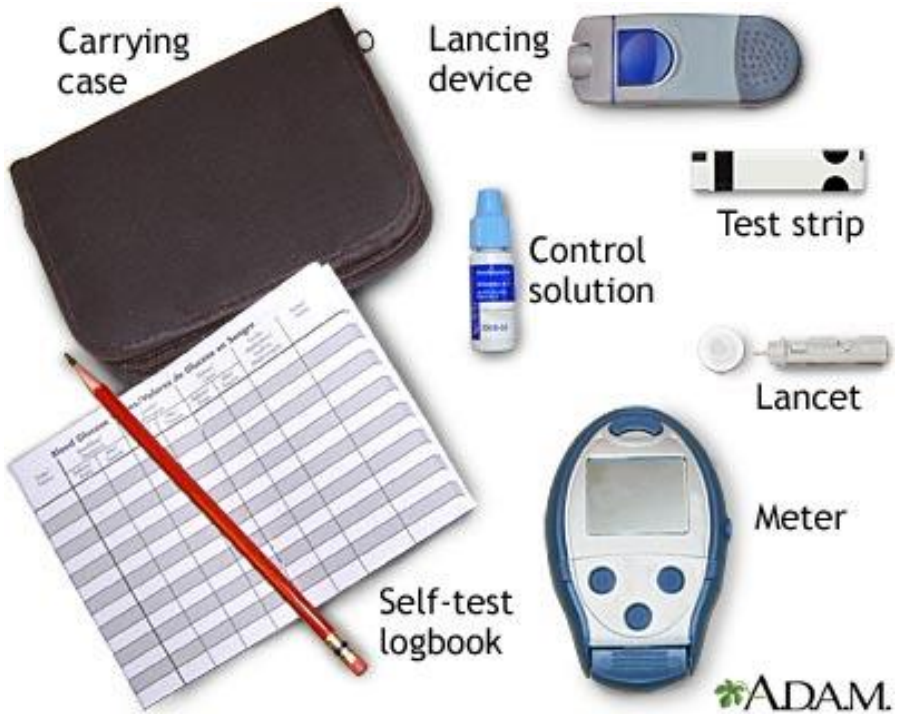
- Lauren is 53 years of age, works as an accountant
- Has had T2D for 20 years
- Complicated with microalbuminuria, retina microaneurysms
- She has seen an endocrinologist initially and tried on metformin which she doesn’t tolerate due to severe diarrhoea
- She now takes gliclazide 120mg mane, semaglutide 1mg weekly, and recently commenced on Lantus (insulin glargine) 52 units
- Her HbA1c has been 11% for at least 2 years, last HbA1c was 9%
- Lost 5kg weight

What Should You Do? 🤔 ❓

A. Retry metformin
B. Perform 1 week of self-monitoring blood glucose (SMBG)
C. Increase Lantus 60 units
D. Add in prandial insulin – Apidra/Humalog/Novorapid 10 units with meals
E. Start Ryzodeg 60 units with dinner

Self-Monitoring of Blood Glucose (SMBG)

- Aiding the achievement of HbA1c targets
- Minimizing glucose variability
- Helping to predict severe hypoglycaemia
- SMBG has also been reported to be associated with decreased diabetes-related morbidity and all-cause mortality in type 2 diabetes.
- SMBG can also heighten patients' awareness of the disease and the impact of lifestyle on blood glucose levels



Case 2 Cont.

- She has come back to you with a SMBG diary
- What would you now suggest for Lauren to do?

PATIENT NAME: Lauren

WEEK BEGINNING: _____ (DATE)

	Insulin Injections					Monitoring Blood Glucose								Remarks Activity, illness, diet changes, time of hypos (noting blood glucose and treatment).
	Type of Insulin	Units given				Breakfast		Lunch		Dinner		Before Supper or Bed	Over night	
		Breakfast	Lunch	Dinner	Before Bed	Before	After	Before	After	Before	After			
Mon						12.1	15.1	15.8	16.9	11.9	20.5			
	Lantus				50									
Tues						10.9	13.4	14.1	18.2	11.0	19.8			
	Lantus				50									
Wed						12.9	15.1	13.2	20.1	14.5	19.1		15.1	
	Lantus				50									
Thu						10.1	15.5		12.1	10.9	18.2			missed lunch
	Lantus				50									
Fri						14.1		12.1	19.1	15.1	18.9			
	Lantus				50									
Sat						13.4	14.2	10.6	13.5	14.9	16.5			
	Lantus				50									
Sun						12.5	13.2	11.9	14.0	15.9	17.0			
	Lantus				50									

What would you do for Lauren?

A. Increase insulin glargine (*Optisulin/Semglee*) to 60 units
B. Add in ultra short acting insulin – glulisine (*Apidra*)/lispro (*Humalog*)/aspart (*Novorapid*) 10 units with meals
C. Try Mixed Insulin – (aspart 30%/protamine 70%) *Novomix 30/70* to 40 units twice a day
D. Try Mixed insulin – degludec 70%/aspart 30% (*Ryzodeg 70/30*) 35 units bd
E. Review again in 2 weeks

PATIENT NAME: Lauren

WEEK BEGINNING: _____ (DATE)

	Insulin Injections					Monitoring Blood Glucose								Remarks Activity, illness, diet changes, time of hypos (noting blood glucose and treatment).
	Type of Insulin	Units given				Breakfast		Lunch		Dinner		Before Supper or Bed	Over night	
		Breakfast	Lunch	Dinner	Before Bed	Before	After	Before	After	Before	After			
Mon						12.1	15.1	15.8	16.9	11.9	20.5			
	Lantus				50									
Tues						10.9	13.4	14.1	18.2	11.0	19.8			
	Lantus				50									
Wed						12.9	15.1	13.2	20.1	14.5	19.1		15.1	
	Lantus				50									
Thu						10.1	15.5		12.1	10.9	18.2			missed lunch
	Lantus				50									
Fri						14.1		12.1	19.1	15.1	18.9			
	Lantus				50									
Sat						13.4	14.2	10.6	13.5	14.9	16.5			
	Lantus				50									
Sun						12.5	13.2	11.9	14.0	15.9	17.0			
	Lantus				50									

What would you do for Lauren?

A. Increase insulin glargine (*Optisulin/Semglee*) to 60 units ✓
B. Add in ultra short acting insulin – glulisine (*Apidra*)/lispro (*Humalog*)/aspart (*Novorapid*) 10 units with meals ✓
C. Try Mixed Insulin – (aspart 30%/protamine 70%) *Novomix 30/70* to 40 units twice a day
D. Try Mixed insulin – degludec 70%/aspart 30% (*Ryzodeg 70/30*) 35 units bd ✓
E. Review again in 2 weeks ✓ ✓

Starting Insulin

Starting and adjusting basal insulin[1–3]

STEP 1. SELECT basal insulin and injecting device

STEP 2. START basal insulin: 0.1 units/kg or **10 units** at bedtime or morning

CONTINUE oral glucose-lowering medication

If fasting blood glucose (FBG) is high (pre-breakfast), consider evening or morning insulin dosing of a long-acting (>24 hours) basal insulin

If FBG is on target, but pre-dinner blood glucose level (BGL) is high, consider morning insulin dosing of intermediate-acting insulin

STEP 3. TITRATION

If using long-acting basal insulin doses (morning or evening doses), adjust doses to achieve FBG targets

If using intermediate-acting basal insulin, use pre-dinner glucose targets to adjust the morning doses and FBG targets to adjust any additional evening doses

Practitioner-led titration (below left) can achieve target in a shorter time period than **patient-led titration (below right)**

Practitioner-led titration OR Patient-led titration

Adjust insulin dose twice weekly as shown, until FBG target is achieved

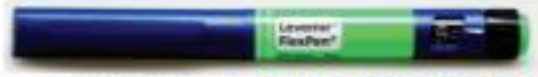
Mean FBG over previous two days (mmol/L)*	Insulin dose adjustment
≥10.0	↑ by 4 units
8.0–9.9	↑ by 2–4 units
7.0–7.9	No change or ↑ by 2 units
6.0–6.9	No change
4.0–5.9	No change or ↓ by 2 units
<4.0	↓ by 2–4 units

Adjust insulin dose every three days. Increase by 2 units until FBG target is achieved

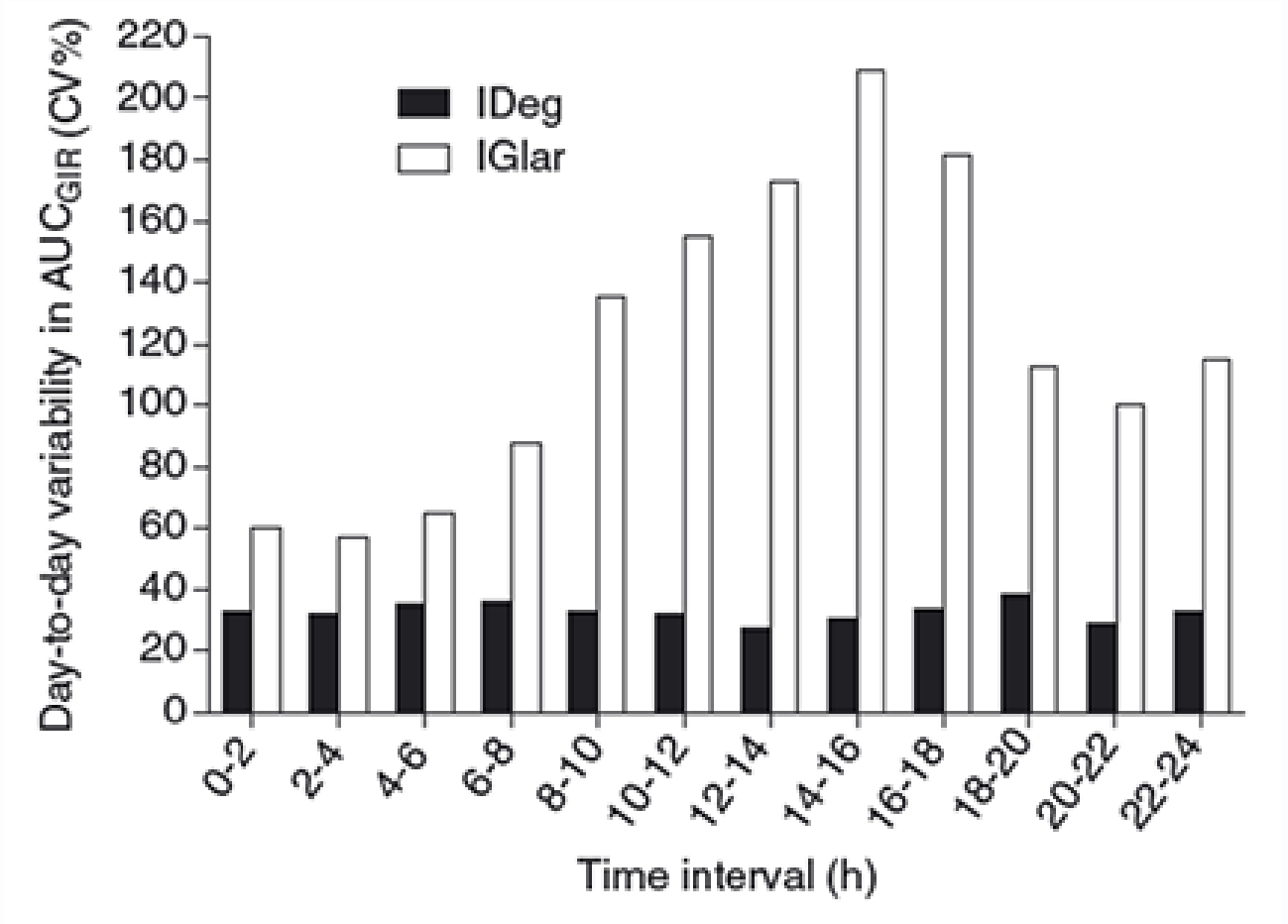
Mean FBG over previous three days (mmol/L)*	Insulin dose adjustment
≥6.0 mmol/L but ≤8.0 mmol/L	No change
4.0–6.0 mmol/L	↓ insulin dose by 2 units
<4.0 mmol/L	↓ insulin dose by 4 units

*Do not increase insulin dose if FBG <4.0 mmol/L at any time in the preceding week.

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

Mixed long acting with ultra short acting	 NovoMix 30® Flexpen (Insulin aspart/insulin aspart protamine) Other less commonly used formulations include Humalog Mix 50® (Insulin lispro/insulin lispro protamine)  Humalog Mix 25® KwikPen (Insulin lispro/insulin lispro protamine)	ONCE or TWICE daily IMMEDIATELY before meals
Mixed ultra long acting with ultra short acting	 Ryzodeg 70/30® FlexTouch (Insulin degludec/Insulin aspart)	ONCE or TWICE daily IMMEDIATELY before meals
Long acting	 Levemir® Flexpen (Insulin detemir)	ONCE or TWICE daily
	 Optisulin® Solostar (Insulin glargine)  Semglee® (Insulin glargine)	ONCE daily
Long acting high concentration	Different strengths of insulin glargine are not interchangeable It is recommended patients continue their same preparation whilst in hospital.  Toujeo® Solostar (Insulin glargine) 300units/1mL	ONCE daily

diabetes queensland



Case Study 3 - Garry

- 75 year old gentleman
- Type 2 diabetes for 10 years
- Multiple microvascular complications – peripheral neuropathy and recurrent foot ulcers, CKD stage II nephropathy and non-proliferative retinopathy
- Other background:
  - BMI ~28, hypertension
  - Schizophrenia (stable)
- Saw a hospital endocrinologist ~5 years ago, discharged from clinic due to good control at the time
- Insulin glargine 30 units; insulin aspart 15 units with meals (only eats twice a day)
- HbA1c has been slowly creeping up:

24/11/2022	26/3/2023	8/9/2023
8.6%	8.9%	8.5%

What Would You Do for Garry?

A. Intensify insulin – increase insulin aspart and insulin glargine doses by 10%
B. Add in Metformin
C. Add in DPP-IV (e.g. linagliptin, sitagliptin, saxagliptin)
D. Add in SGLT-2 inhibitor (e.g. dapagliflozin, empagliflozin)
E. Add in GLP-1 RA (e.g. exenatide short acting)
F. Change to a mixed insulin – e.g. Ryzodeg

What I Did 🤔🤔🤔

~~A. Intensify insulin – increase insulin aspart and glargine doses by 10%~~

B. Add in Metformin

C. Add in DPP-IV (e.g. **linagliptin**, sitagliptin, saxagliptin)

D. Add in SGLT-2 (e.g. dapagliflozin, **empagliflozin**)

~~E. Add in GLP-1 RA (e.g. exenatide short acting)~~

F. Change to a mixed insulin – **Ryzodeg 30 units with dinner**

G. Added in **Novorapid 10 units with breakfast**

Starting Mixed insulin

Starting and adjusting pre-mixed (biphasic) and co-formulated insulin

STEP 1. SELECT premixed or co-formulated insulin and injecting device

INSULIN-NAÏVE patients

STEP 2. START premixed or co-formulated insulin **10 units** immediately before or soon after the largest meal (usually evening meal)

CONTINUE metformin if indicated; consider tapering sulfonylureas as glycaemic control improves

STEP 3. TITRATION

Adjust the evening pre-mixed insulin dose once or twice a week according to the schedule below to FBG[2,3]

Co-formulated insulin should be titrated once a week

Lowest BGL reading (mmol/L) of the previous three days – fasting or preprandial	Insulin dosage adjustment
≥10	↑ by 6 units
8.0–9.9	↑ by 4 units
6.0–7.9	↑ by 2 units
4.0–5.9	No change
<4.0	↓ by 2 units

If a morning insulin dose is given, adjust the insulin dose according to evening preprandial BGL according to the same titration recommendations

Hypoglycaemia should prompt a review of other oral therapy. Which insulin is adjusted depends on regimen and target glucose

STEP 4. INTENSIFICATION: Once-daily insulin to twice-daily premixed insulin

When?

- With FBG at target, if evening preprandial BGL > FBG, or if evening preprandial BGL is high, or
- After three months if glycated haemoglobin (HbA1c) > target, despite FBG and evening preprandial BGL at target

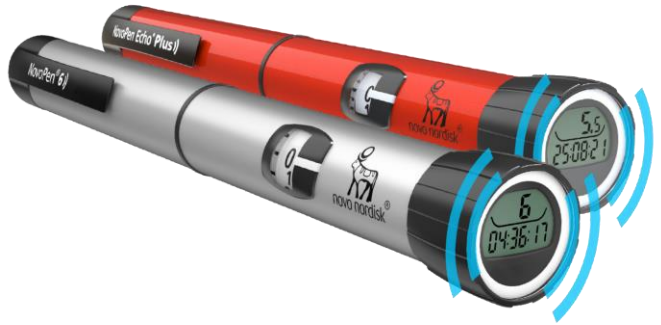
How?

- Calculate any increased total daily insulin dose and divide this into two doses, considering the continued need to maintain FBG and postprandial targets
- Give the increased dose adjustment as twice-daily injections (pre-breakfast and pre-dinner). This may not be a 50/50 split, as prandial targets may require a higher proportion to be given at the largest meal of the day (eg 60/40)
- Monitor pre-dinner BGL and FBG against targets
- Once a week, adjust both insulin doses independently (according to protocol above in step 3); pre-breakfast insulin is adjusted according to pre-dinner BGL, and pre-dinner insulin is adjusted according to FBG

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

Shortage of Ryzodeg 70/30 FlexTouch pens

- The Therapeutic Goods Administration (TGA) has advised of a current shortage of Ryzodeg 70/30 FlexTouch insulin prefilled pens. The shortage is expected to continue until mid-next year.
- To help manage the shortage, pharmacists can give people living with diabetes Ryzodeg 70/30 Penfill cartridges instead of Ryzodeg 70/30 FlexTouch prefilled pens under certain conditions. Both products contain the same medicine, at the same strength, have the same storage requirements, and are administered by injection under the skin (subcutaneous injection). However, the device used to administer the medicine is different.



https://www.diabetesaustralia.com.au/news/shortage-of-ryzodeg-70-30-flextouch-insulin-prefilled-pens/

Basal Plus Insulin

Guide to basal plus insulin intensification schedules

STEP 1. SELECT rapid-acting (prandial) insulin and injecting device to be added in addition to basal insulin

STEP 2. START rapid-acting insulin (4 units) to be given before the meal with the largest carbohydrate content

CONTINUE basal insulin at the current dose

CONTINUE metformin, consider tapering sulfonylureas as glycaemic control improves

MONITOR two-hour postprandial BGL. Continue to assess FBG and preprandial glucose levels – goal is 4.0–7.0 mmol/L

STEP 3. TITRATION

Increase rapid-acting (prandial) insulin dose by 2 units every three days to achieve target

Two-hour postprandial BGL (mmol/L)	Rapid-acting (prandial) insulin dosage adjustment
≥8 (for three consecutive days)	No change or ↑ by 2 units
6.0–7.9	No change
4.0–5.9	No change or ↓ by 2 units
<4.0 on any day	↓ by 2–4 units

STEP 4. Basal plus titration to basal bolus – intensification

When?

If HbA1c is not at target after three months, add a further prandial insulin dose to another meal (eg basal plus 2 to basal bolus)

How?

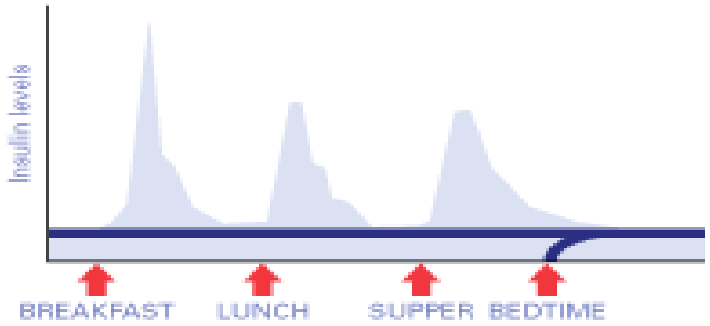
1. Keep the current prandial and basal insulin doses unchanged
2. Add a new rapid-acting (prandial) insulin to the next largest meal of the day (starting at 10% of the basal insulin dose or 4 units)
3. ↑ new prandial insulin dose by 2 units every three days until postprandial target is achieved as per Step 3 above

The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

Acting time	**100 units/1mL** unless otherwise stated	When to administer
Ultra short acting	 Fiasp® FlexTouch (Insulin aspart)  NovoRapid® Flexpen (Insulin aspart)  Humalog® KwikPen (Insulin lispro)  Apidra® Solostar (Insulin glulisine)  Humalog® U-200 KwikPen (Insulin lispro) 200 units/1mL	IMMEDIATELY before meals
Short acting	 Actrapid® (Neutral)  Humulin R® (Neutral) Insulin Infusat® (Neutral) is available via SAS	Within 30 minutes before meals
Intermediate acting	 Humulin NPH® (Isophane)  Protaphane® (Isophane)  Protaphane® Innolet (Isophane)	ONCE or TWICE daily

BASAL (Lantus®)

LONG-ACTING INSULIN

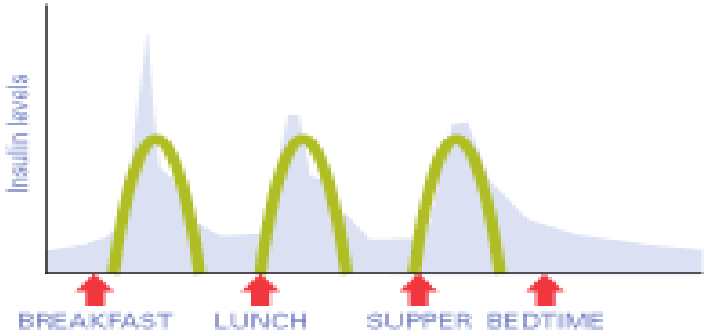


Onset
2-4 hours

Duration
24 hours

PRANDIAL

RAPID-ACTING INSULIN

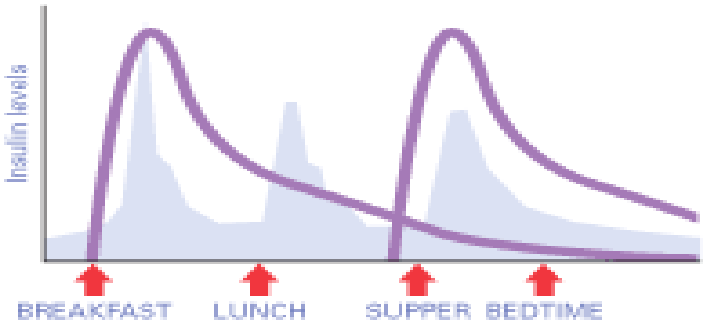


Onset
~5 minutes

Duration
4-5 hours

PREMIX

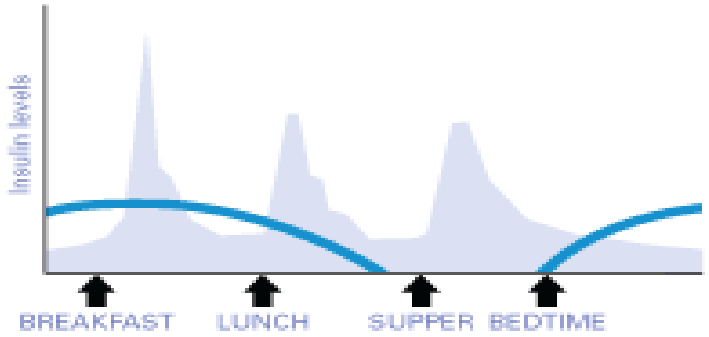
PREMIXED INSULIN (ANALOG)



Onset
5-15 minutes

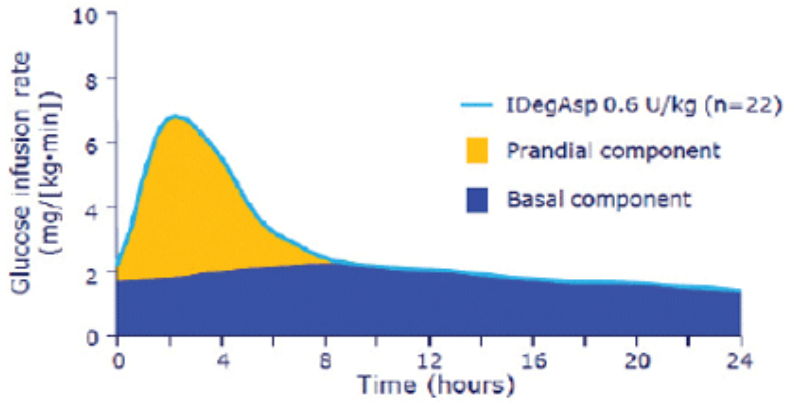
Duration
10-16 hours

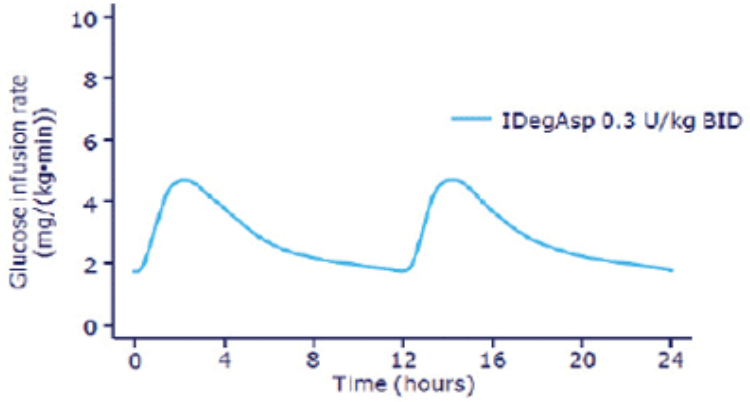
INTERMEDIATE-ACTING INSULIN (NPH)



Onset
0.5-1 hours

Duration
10-16 hours





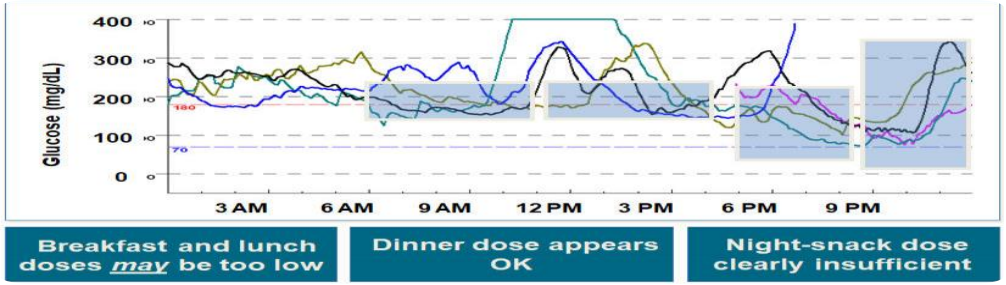
(a) (b)

Fig. 3: Pharmacodynamic profile of insulin degludec/insulin aspart. Mean glucose infusion rate profile of (a) once-daily and (b) simulated twice daily at steady state of insulin degludec/insulin aspart administered in subjects with type 1 diabetes mellitus. IDegAsp, Insulin degludec/insulin aspart; BID, twice daily. Source: Adapted from Ma et al. 2012, Heise et al. 2014

Unnikrishnan, J Association of Physicians in India, 2015

Bolus Dose Titration

- Use pre- and post- meal SMBG or CGM to determine whether the dose needs to be adjusted
- Gradually increment the bolus dose by approximately 10-20% per meal until range is 5-10 mmol/L post meal
- Up titration is limited by any hypoglycaemia experienced
- Encourage patient to vary dose according to carbohydrate serves (1 serve = 15g CHO)
  - E.g. 1 serve = 2 units extra
- Alternatively limit their carbohydrate variation if dose adjustment isn't possible
  - e.g. 3 serves of CHO each meal



STEP 3. TITRATION

If using long-acting basal insulin doses (morning or evening doses), adjust doses to achieve FBG targets

If using intermediate-acting basal insulin, use pre-dinner glucose targets to adjust the morning doses and FBG targets to adjust any additional evening doses

Practitioner-led titration (below left) can achieve target in a shorter time period than patient-led titration (below right)

Practitioner-led titration OR Patient-led titration

Adjust insulin dose twice weekly as shown, until FBG target is achieved

Mean FBG over previous two days (mmol/L)*	Insulin dose adjustment
≥10.0	↑ by 4 units
8.0–9.9	↑ by 2–4 units
7.0–7.9	No change or ↑ by 2 units
6.0–6.9	No change
4.0–5.9	No change or ↓ by 2 units
<4.0	↓ by 2–4 units

Adjust insulin dose every three days. Increase by 2 units until FBG target is achieved

Mean FBG over previous three days (mmol/L)*	Insulin dose adjustment
≥6.0 mmol/L but ≤8.0 mmol/L	No change
4.0–6.0 mmol/L	↓ insulin dose by 2 units
<4.0 mmol/L	↓ insulin dose by 4 units

*Do not increase insulin dose if FBG <4.0 mmol/L at any time in the preceding week.

Case 4 - Robert

- Robert is a 59 year old gentleman, has been diagnosed with Type 2 diabetes 5 years prior, just moved into the area
- Works for himself, repairs boats
- Muscular build, nil central adiposity, weight 71kg
- Initially started on Metformin, has been up titrated to sitagliptin and empagliflozin by previous GP over the last 1 year
- Fasting levels are always elevated: 10-18 mmol/L
- Doesn't have time to check again until pre-dinner where they are 10-20 mmol/L
- Last HbA1c 10.4% (90 mmol/mol)
- You commenced him on insulin glargine (*Optisulin*) 10 units a few months back
- Reports readings are not much improved, brings only scant self-monitoring of blood glucose (SMBG) records

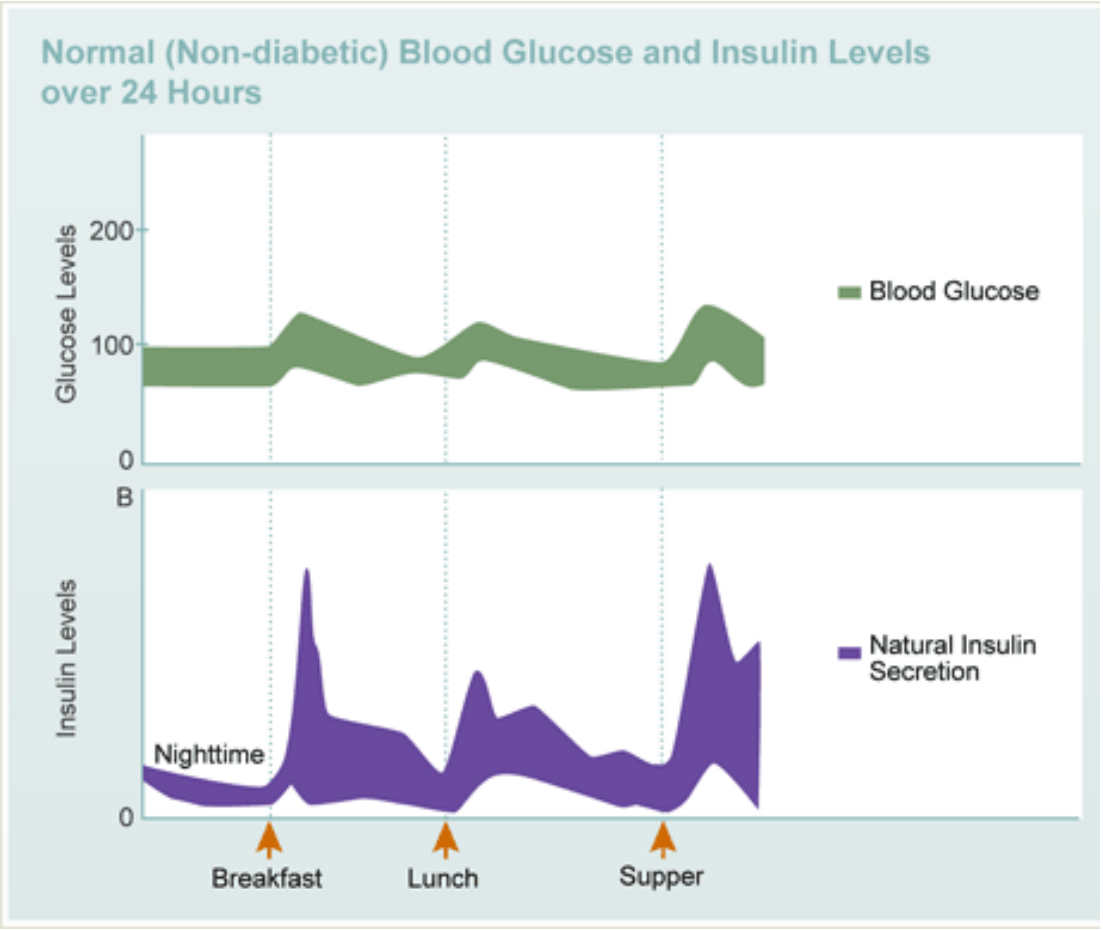
What Would You Recommend for Robert?

A. Encourage diet and lifestyle changes
B. Increase SMBG
C. Add GLP-1 RA i.e. semaglutide
D. Add in a sulfonylurea
E. Uptitrate insulin glargine to 15 units
F. Add in basal insulin e.g. aspart (*Novorapid*), glulisine (*Apidra)* or lispro (*Humalog*)
G. Change to a mixed insulin e.g. Ryzodeg 70/30, NovoMix 30/70 or Humalog Mix 25
H. A + see him again in 3 months with repeat HbA1c

What Would I Recommend for Robert?

A. Encourage diet and lifestyle changes ✓
B. Increase SMBG ✓ ✓
C. Add GLP-1 RA i.e. semaglutide ✓
D. Add in a sulfonylurea
E. Uptitrate insulin glargine to 15 units ✓
F. Add in basal insulin e.g. aspart (*Novorapid*), glulisine (*Apidra)* or lispro (*Humalog*) ✓
G. Change to a mixed insulin e.g. Ryzodeg 70/30 ✓ , NovoMix 30/70 or Humalog Mix 25
H. A + see him again in 3 months with repeat HbA1c ✓

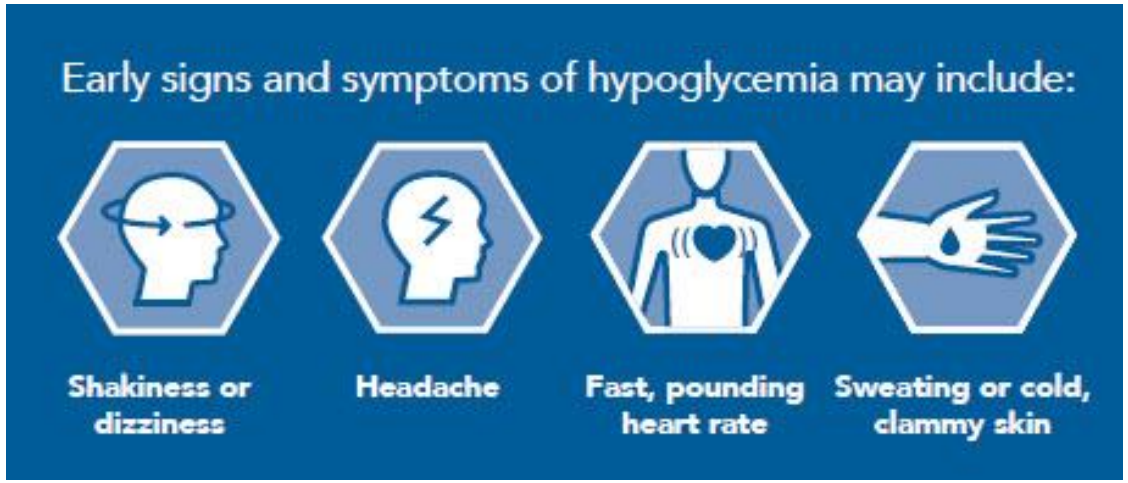
My Tips For Success on Insulin



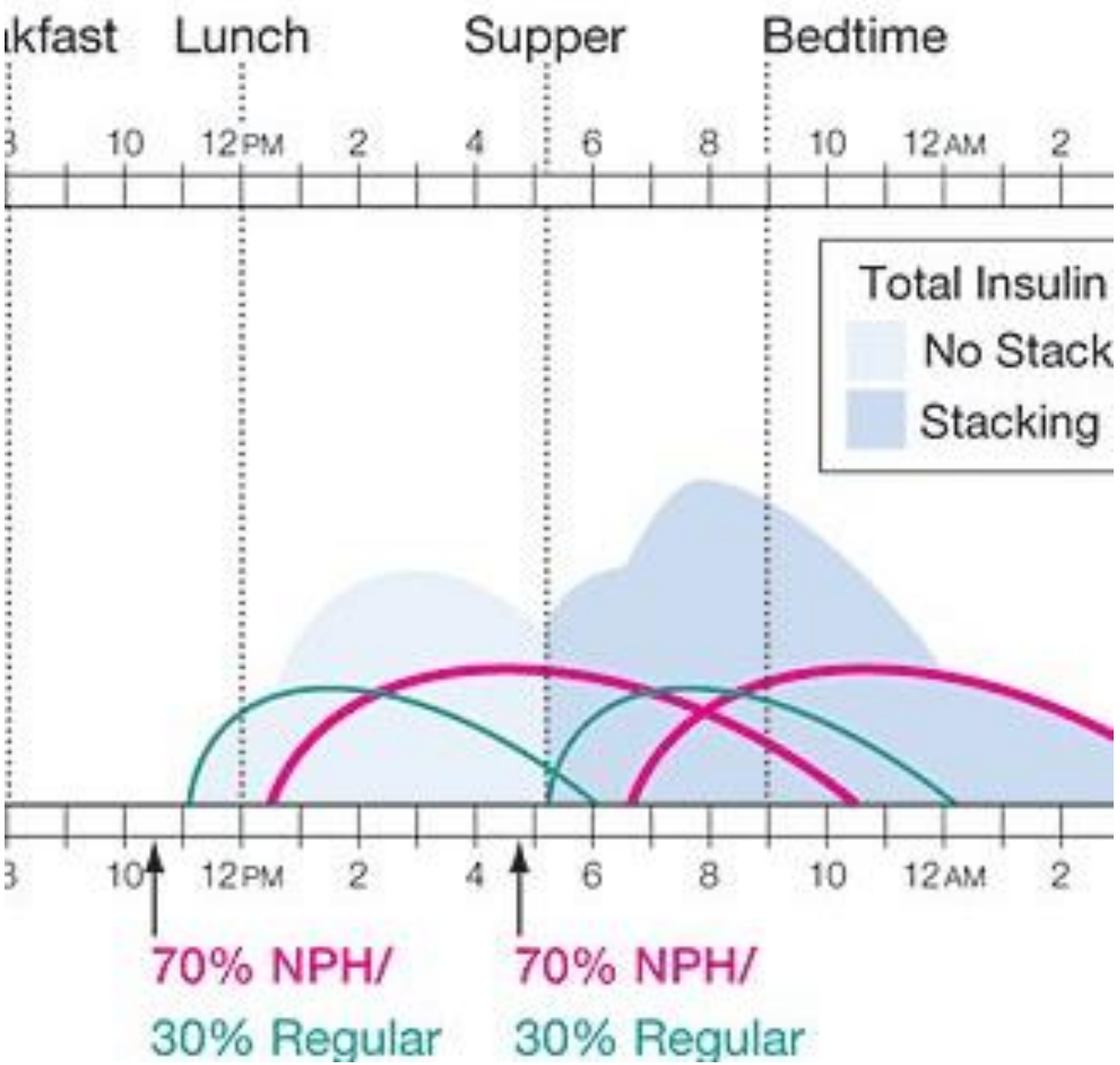
- Encourage daily self-monitoring of blood glucose (SMBG)
  - Ideally initially 6-8 times a day – this may be limited by strip access/costs
  - Can drop to 4 times a day when stable
  - Pre- and post-meal SMBG are best to assess bolus pattern
- Work out the patient's BGL pattern:
  - Fasting hyperglycaemia = increase basal insulin
  - Post-prandial hyperglycaemia = increase bolus insulin
  - Pre-prandial hyperglycaemia = increase basal insulin
- Experiencing hypoglycaemia:
  - Presence of fasting or pre-meal hypoglycaemia = reduce dose of basal
  - Hypoglycaemia after meals = over bolusing → reduce bolus doses
  - Overnight hypoglycaemia = change to morning basal insulin and reduce dose

Hypoglycaemia

- Although basal insulin is associated with less hypoglycaemia than prandial insulin, hypoglycaemia can occur when the dose of basal insulin is titrated to cover meals.
- If the patient subsequently eats less than usual, hypoglycaemia may occur.
- Alternatively, some patients develop daytime hypoglycaemia on a dose of basal insulin that controls fasting blood glucose (FBG).
- Both of these scenarios lead to obligate snacking, which may fuel insulin-associated weight gain.
  - This problem may be identified by asking about symptoms of hypoglycaemia when meals are skipped or snacking to prevent hypoglycaemia.
  - Other potential triggers (eg, changes in diet or activity) should be identified.
- Patients who make significant dietary changes (eg, starting a ketogenic diet) may require substantial reductions in insulin dosing (eg, ≥50% reduction).

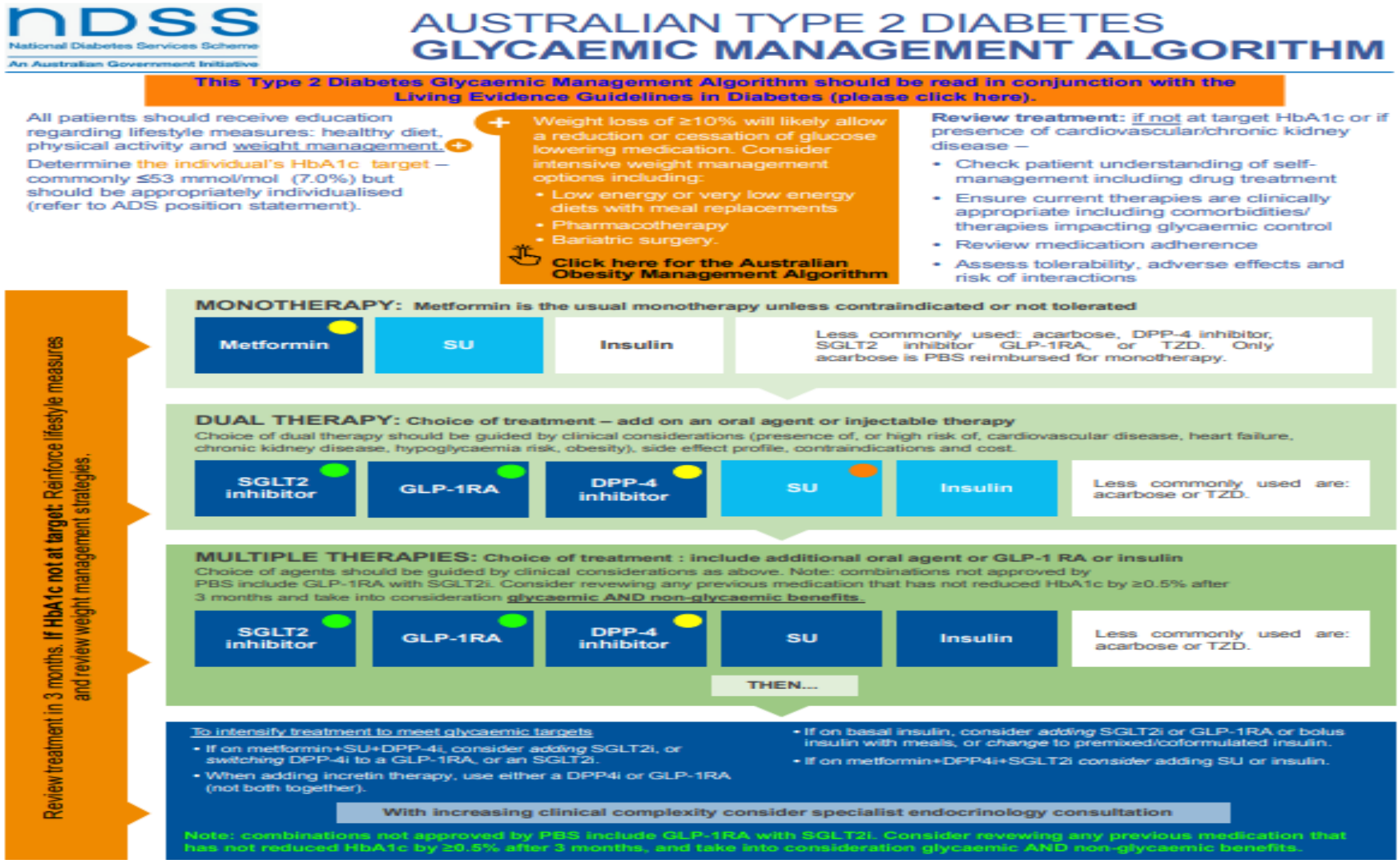


Insulin Stacking



What to do and when?

https://t2d.diabetessociety.com.au/plan/



Australian Blood Glucose Treatment Algorithm for type 2 diabetes

LIFESTYLE MEASURES

DIET, EXERCISE AND WEIGHT CONTROL SHOULD BE THE INITIAL APPROACH AND REINFORCED AT EACH STAGE.

ALL PATIENTS SHOULD RECEIVE EDUCATION REGARDING LIFESTYLE MEASURES: HEALTHY DIET, PHYSICAL ACTIVITY AND WEIGHT CONTROL.

IF NOT AT TARGET, OR IF A HbA1c REDUCTION OF ≥ 0.5% IS NOT ACHIEVED AFTER 3 MONTHS

MOVE DOWN THE ALGORITHM.

Press or click the lines to reveal the plan.

1ST LINE

METFORMIN IS THE USUAL 1ST LINE THERAPY UNLESS CONTRAINDICATED OR NOT TOLERATED.

(CLICK FOR MORE)

2ND LINE

IF METFORMIN WAS NOT USED IN THE FIRST LINE, ADD IT NOW IF NOT CONTRAINDICATED.

(CLICK FOR MORE)

3RD LINE

CONSIDER TRIPLE ORAL THERAPY OR GLP-1RA OR INSULIN.

(CLICK FOR MORE)

4TH LINE

NEXT STEPS

(CLICK FOR MORE)

Note:

PBS – Pharmaceutical Benefits Scheme
SU – sulfonylurea
TZD – thiazolidinedione
DPP-4 – dipeptidyl peptidase-4
GLP-1RA – glucagon like peptide 1 receptor agonist
SGLT2 – sodium glucose transporter.

Order of boxes is not meant to denote any specific preference

SEE THE CASE STUDIES

T2D Algorithm References

PBS Website

LIVING EVIDENCE FOR DIABETES CONSORTIUM

- The Living Evidence for Diabetes Consortium is a collaboration between the Australian Diabetes Society (ADS), Diabetes Australia (DA), the Australian Diabetes Educators Association (ADEA) and the Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED), with representation from the Royal Australian College of General Practitioners (RACGP) and Cochrane Australia.
- The Consortium has developed evidence based clinical guidelines for diabetes containing selected recommendations regarding:
  - Medical device technology for the management of Type 1 Diabetes; and
  - Medications for blood glucose management in adults with Type 2 Diabetes.

Current Recommendations

- The panel have considered evidence from an updated search conducted to October 2022.
- 57 studies were identified including over 50 000 participants looking at optimal add-on therapy
- There was no change in the strength and/or direction of the recommendations.

Optimal Initial Medication

- We suggest the use of **metformin** as first-line monotherapy in adults with type 2 diabetes.

Optimal add-on therapy

- We recommend the addition of an **SGLT-2 inhibitor** to other glucose lowering medication(s) in adults with type 2 diabetes who also **have cardiovascular disease**, multiple cardiovascular risk factors **and/or kidney disease**.
- We recommend the addition of a **GLP-1 receptor agonist** to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and have an intolerance or contra-indication to SGLT-2 inhibitors.
- We suggest the addition of a **DPP-4 inhibitor** to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.
- We suggest the addition of **either an SGLT-2 inhibitor, GLP-1 receptor agonist or a DPP-4 inhibitor** to metformin in adults with type 2 diabetes who **do not** have cardiovascular disease, multiple cardiovascular risk factors or kidney disease, and are unable to achieve optimal blood glucose levels.

Optional add-on therapy (cont.)

- We suggest that a sulphonylurea should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycaemia.

- We suggest that a thiazolidinedione should not be the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of hospitalisation for heart failure.

What does the PBS allow?

Dipeptidyl peptidase 4 inhibitors

- Alogliptin, Linagliptin, Saxagliptin, Sitagliptin
- The treatment must be in combination with metformin or sulfonylurea, AND
- Patient must have an HbA1c measurement greater than 7% despite treatment with dual oral combination therapy with metformin and an SGLT2 inhibitor; OR
- Patient must have, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation of triple oral therapy with a sodium-glucose co-transporter 2 (SGLT2) inhibitor, metformin and a gliptin.

SGLT2-inhibitors

- **Dapagliflozin, Empagliflozin and Ertugliflozin:**
- PBS subsidised for use with with metformin or sulfonylurea or both
- PBS subsidised for use with insulin
- Not PBS subsidised for use as monotherapy or in combination with thiazolidinedione (glitazone), or a glucagon-like peptide-1
- Must have HbA1c >7% despite treatment with metformin, sulfonylurea, or insulin
- PBS subsidised for symptomatic chronic heart failure – NYHA Class II-IV, LVEF ≤ 40% *(dapa/empa)*
- PBS subsidised for chronic kidney disease – eGFR 25 – 75 ml/min/1.73m2 and urine microalbuminuria (22.6 – 565 mg/mmol) (*dapa only*)

GLP-1 agonists

- **Dulaglutide (*Trulicity*) and semaglutide (*Ozempic*):**
- The treatment must be in combination with metformin, sulfonylurea or insulin
- Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR
- Patient must not have tolerated a combination of metformin and a sulfonylurea, AND
- Must have a HbA1c > 7% or BGLs > 10mmol/L in > 20% tests over 2 weeks despite metformin
- **Exenatide (*Byetta*), liraglutide (*Saxenda*), tirzepatide (*Mounjaro*)**
  - No PBS subsidisation

Case 5 - Gina

- 78 F
- Pensioner
- On metformin XR 1g bd
- Frequent falls at home
- HbA1c 8.5%
- Other meds – sifrol, irbesartan, aspirin, metoprolol

What would you recommend for Gina?

a. SGLT-2 inhibitor alone
b. GLP-1 agonist alone
c. Combined SGLT-2 inhibitor and GLP-1 agonist
d. Insulin
e. Sulphonylurea

What would you recommend for Gina?

a. SGLT-2 inhibitor alone
b. GLP-1 agonist alone
c. **Combined SGLT-2 inhibitor and GLP-1 agonist**
d. ~~Insulin~~
e. ~~Sulphonylurea~~

Any questions or comments?