Overview T2DM medications

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BENDIGO HEALTH

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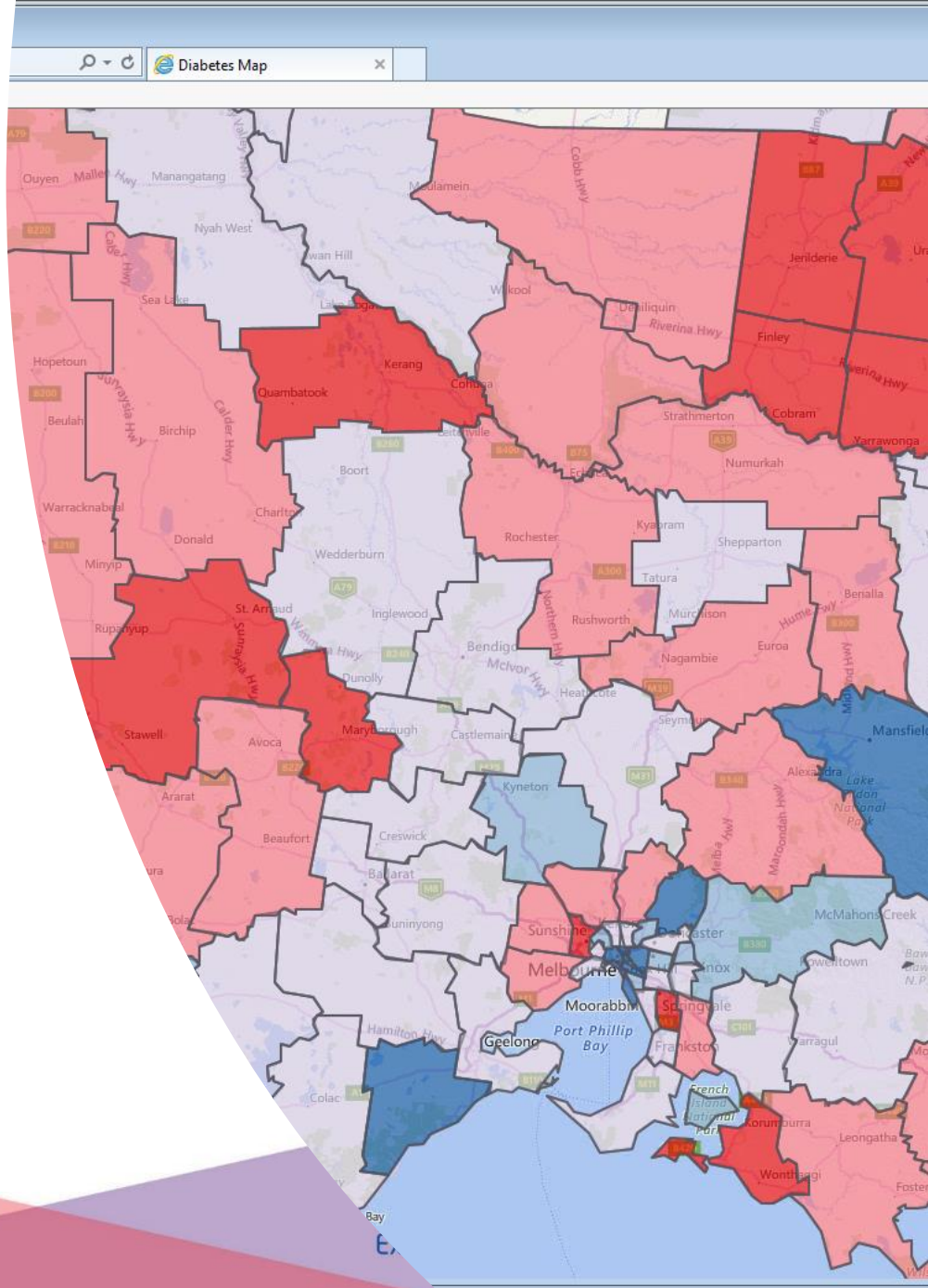
Diabetes in Australia

- 1.7 million Australians with diabetes, of these 85% have T2DM
- 2-fold excess risk CV death in patients with diabetes
- Risk factor for progression of heart failure, admission for heart failure and premature death
- Significant individual, societal, economic cost



T2DM management
more than glucose lowering

Multidisciplinary care
Lifestyle intervention
Smoking cessation
BP lowering
Lipid lowering
Glucose lowering agents
Psychosocial care

Gunton J et al. Australian Diabetes Society , 2016
ADA Standards of Medical Care in Diabetes 2017

T2DM Current standards of medical care

- Lowering blood glucose levels in people with T2DM
  - clear benefits for preventing microvascular complications
  - potential benefits for reducing macrovascular complications and death
- Treatment should be individualised
- For patients with atherosclerotic heart disease, incorporate an agent with strong evidence for CV risk reduction

Gunton J et al. Australian Diabetes Society , 2016
ADA Standards of Medical Care in Diabetes 2017

Individualised Hba1c targets

Group	Target Hba1c (%)
Pregnancy planning	6.0
T2DM early disease no CVD	6.5
General	7.0
Reduced hypo awareness	8.0
Major co-morbidities	8.0
Short life expectancy	Symptom control

Gunton J et al A position statement of the Australian Diabetes Society , Nov 2016

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM
FOR TYPE 2 DIABETES

Australian Diabetes Society

Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).
If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm[1].

First line: Metformin is the usual first-line therapy unless contraindicated or not tolerated

Metformin	SU	DPP-4 inhibitor	SGLT2 inhibitor	Insulin	Acarbose	TZD

If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control

Second line: If metformin was not used first line, add it now, if not contraindicated

Sulfonylureas (SU) are the usual initial agent to add to metformin. If SU are contraindicated or not tolerated, another agent may be used.

SU	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1RA	Insulin*	Acarbose	TZD

How to select T2DM therapy?

Age/life expectancy	• QOL considerations
BMI	• Is weight a major concern?
Comorbidities	• Is there pre-existing atherosclerotic CVD, heart failure? • Is there CKD?
Complications	• Acute: risk of hypoglycaemia (unintentional & intentional), DKA • Chronic: microvascular vs macrovascular
Cost / PBS restrictions	
Patient preference	• Willing to inject? • Pregnancy planning?

Metformin

- Decreases hepatic glucose output, lowers fasting glucose
- Hba1c lowering: 1.5 %
- Dosage: 500mg tds to 3g 500mg (or max 2g for XR)
- Side effects: diarrhoea (start low go slow), vomiting, B12 deficiency
- Temporary cessation if acutely unwell/elevated lactate
- CKD:
  - CrCl 60-90ml/min: 2g daily
  - CrCl 30-69ml/min: 1g daily
  - CrCl 15-30ml/min: 500mg daily
- CV outcomes data
  - Reduction in MI and all cause- mortality in overweight patients (UKPDS)

Sulfonylureas

- Stimulates insulin release from beta-cells
- HbA1c reduction: 1.5- 2 %
- Side effects: hypoglycemia, weight gain
- CKD: dose reduction, short acting gliclizide/glipizide
- CV outcomes data
  - Overall CV safety (UKPDS, ADVANCE)
  - Increased mortality rate with target Hba1c of 6.4 % (ACCORD)
  - Neutral with target Hba1c < 7 %

TZDs

- PPAR -gamma agonists, lowers blood glucose levels through insulin sensitisation
- Hba1c reduction: 0.8%
- Side effects: weight gain, increased fracture risk, bone loss (rosiglitazone), increased risk of bladder cancer (pioglitazone)
- CKD: no dose reduction required
- CV outcomes data
  - No reduction in all-cause mortality (PROACTIVE, RECORD, TOSCA.IT)
  - Increased incidence/exacerbations of heart failure (RECORD)

Acarbose

- Alpha-glucosidase inhibitor, delays absorption of dietary CHO and reduces post-prandial blood glucose level excursions
- Hba1c reduction: 0.7%
- Weight: neutral
- Side effects: GI intolerance, discontinuation in up to 25%
- CV outcomes:
  - Neutral. No reduction in 5-point MACE (ACE)

DPP-4 inhibitors

- Inhibits the inactivation of GLP-1 (Stimulates beta-cell insulin release, slows gastric emptying, suppresses glucagon)
- Hba1c reduction: 0.7%
- Weight neutral
- Side effects: mild GI, nasopharyngitis
- Contraindicated: history of pancreatitis
- CV outcomes
  - Overall CV safety (SAVOR-TIMI, EXAMINE, TECOS)
  - Increased hospitalization for heart failure with saxagliptin (SAVOR-TIMI)

DPP4 inhibitors in CKD

- Saxagliptin
  - CrCl ≥ 50ml/min: 5mg daily
  - CrCl < 50ml/min: 2.5mg daily
- Sitagliptin
  - CrCl > 50ml/min: 100mg daily
  - CrCl 30-50ml/min: 50mg daily
  - CrCl < 30ml/min: 25mg daily
- Vildagliptin
  - CrCl > 60ml/min: 50mg BD
  - CrCl < 60ml/min: 50mg daily
- Linagliptin
  - 5mg daily, no dose adjustment required

DPP-4 inhibitors "Gliptins"

- **Sitagliptin** (Januvia®)
- **Sitaglitpin**/Metformin (Janumet®)
- **Linagliptin** (Trajenta®)
- Empagliflozin/**Linaglitpin** (Glyxambi®)
- **Vildagliptin** (Galvus®)
- **Saxagliptin** (Onglyza ®)
- **Saxagliptin**/Dapagliflozin (Qtern®)
- **Alogliptin** (Vipidia®)

SGLT2 inhibitors

- Reduces renal glucose reabsorption / promotes glycosuria
- Hba1c reduction: 0.58%
- Side effects:
  - Weight loss, genital infection, reduction in BP, dizziness, dehydration, fractures & distal lower limb amputations (canagliflozin)
- CV outcome data:
  - Reduction in all- cause mortality and CV mortality (EMPAREG, CANVAS)
  - NNT = 39 to prevent one CV death (EMPAREG)
- CKD:
  - Slow progression CKD (EMPAREG)
  - Empagliflozin: do not use if eGFR < 45ml/min
  - Dapagliflozin: do not use if eGFR <60ml/min

Empagliflozin new indication

----------INDICATIONS AND USAGE----------

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitations of Use: Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

Euglycaemic DKA with SGLT2i

- Increased risk euglycaemic DKA with all SGLT inhibitors (FDA warning)
- Uncommon, but risk may be increased in
  - Long-standing T2DM with marked B cell insufficiency
  - LADA with rapid evolution toward T1DM
  - Prolonged starvation / low carb diet
  - Intercurrent illness
  - Periop period (recent severe cases requiring ICU/HDU)
- Cease SGLT2 inhibitors 3 days preop

SGLT2 inhibitor ("flozins")

- **Dapagliflozin** (Forxiga®)
- **Dapagliflozin**/metformin (Xigduo®)
- Saxagliptin/**Dapagliflozin** (Qtern®)
- **Empagliflozin** (Jardiance®)
- **Empagliflozin**/Metformin (Jardiance Duo®, Synjardy ®)
- **Empagliflozin**/Linaglitpin (Glyxambi®)

GLP-1 receptor agonists

- Stimulates beta-cell insulin release, slows gastric emptying, suppresses glucagon (injection)
- Hba1c reduction: up to 0.85%
- Side effects: weight loss up to 4.3kg, nausea, gallstones (liraglutide), retinopathy (semaglutide)
- CKD:
  - Dose reduce or reconsider use if eGFR 30-50
  - Not recommended eGFR < 30 lack of data
- Summary of CV outcomes
  - Reduction in 3-point MACE with liraglutide (LEADER) and semaglutide (SUSTAIN-6)

Insulin

- Most potent glucose lowering agent:
  - consider if blood glucose levels are very high, signs of metabolic decompensation, preoperatively, high dose corticosteroids
- Side effects:
  - hypoglycaemia, weight gain
- CKD:
  - eGFR > 50: no change
  - eGFR 10 – 50: reduce by 25%
  - eGFR < 10: reduce by 50%
- CV outcomes
  - Neutral: insulin glargine (ORIGIN), insulin dugludec (DEVOTE)

T2DM drugs and CV outcomes

Drug	ASCVD	HF
Metformin	benefit	neutral
Sulfonylurea	neutral	neutral
Acarbose	neutral	neutral
TZDs	potential benefit (pioglitazone)	increased risk
DPP4i	neutral	? increased risk (saxagliptin, alogliptin)
GLP-1 RA	neutral (lixisenatide, exenatide ER)	neutral
	benefit (liraglutide, semaglutide)	neutral
SGLT2i	benefit (empagliflozin, canagliflozin)	Benefit (empagliflozin, canagliflozin)
Insulin	neutral	neutral

T2DM with comorbidities

- Atherosclerotic CVD predominates
  - SGLT2i or GLP-1 RA with proven CV benefit
- Heart failure or CKD predominates
  - SGLT2i if eGFR adequate
  - GLP-1 RA with proven CV benefit if SGLT2i not tolerated
- Compelling need to minimise weight
  - GLP-1 RA with good efficacy for weight loss or SGLT2i
  - DPP4i triple therapy or if GLP-1 RA or SGLT2i not tolerated
- Compelling need to minimise hypoglycaemia
  - DPP4i, GLP-1 RA, SGLT2i

Davies M et al. ADA/EASD consensus guidelines. Diabetologia Oct 2018

Take home message

- Individualise treatment targets in everyone
- Lifestyle interventions and CV risk factor modification in most
- Medical therapy
  - Metformin first-line where possible
  - SGLT2i when pre-existing ASCVD, HF, mild-mod CKD, weight control but assess risk of side effects before prescribing
  - GLP-1 RA when with pre-existing ASCVD, weight control
  - DPP4i otherwise, option in severe CKD (weight neutral)
  - SU in symptomatic, leaner patient (weight gain)
  - Insulin when rapid glycaemic control required (weight gain)

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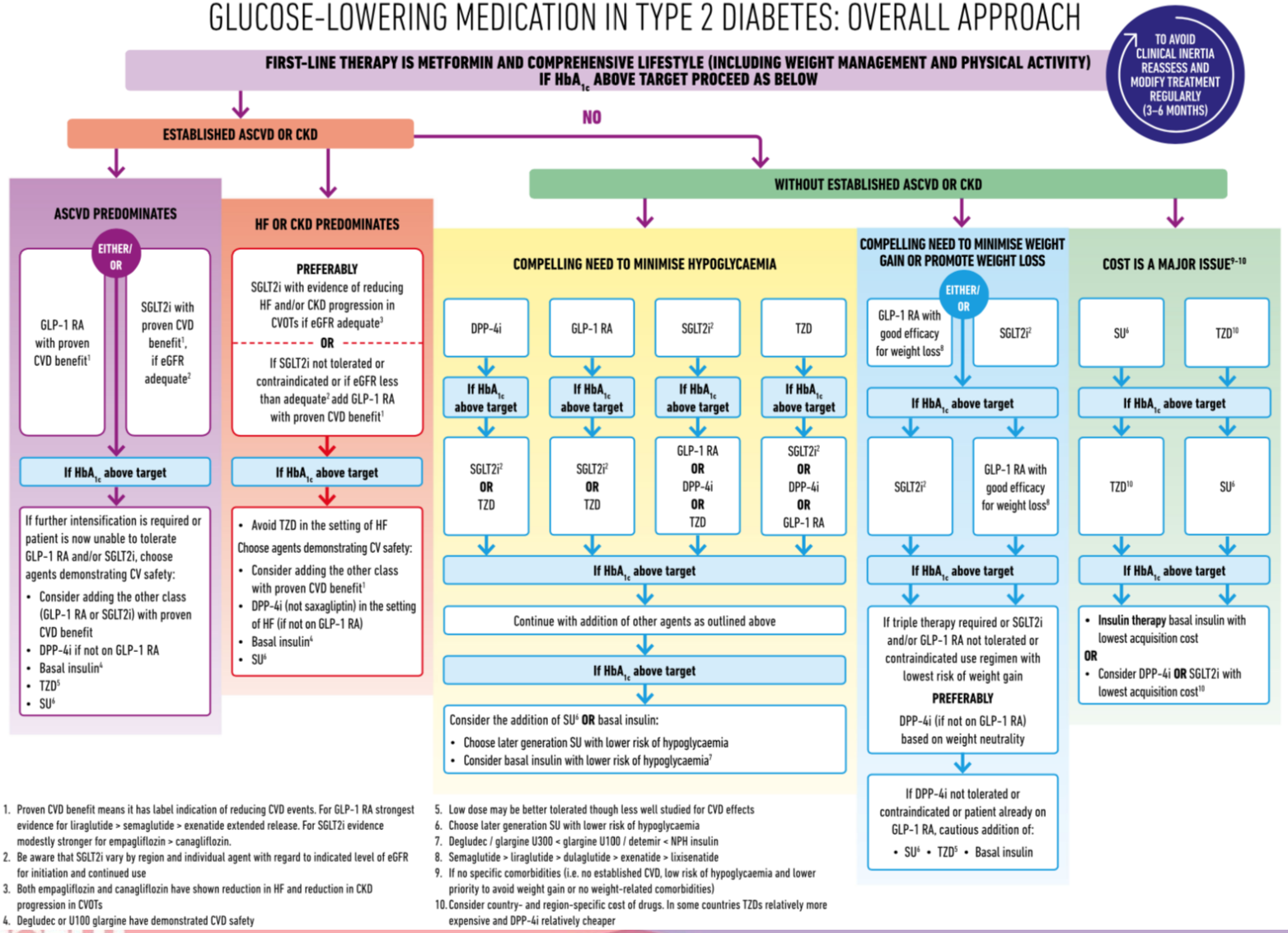
Extra slides

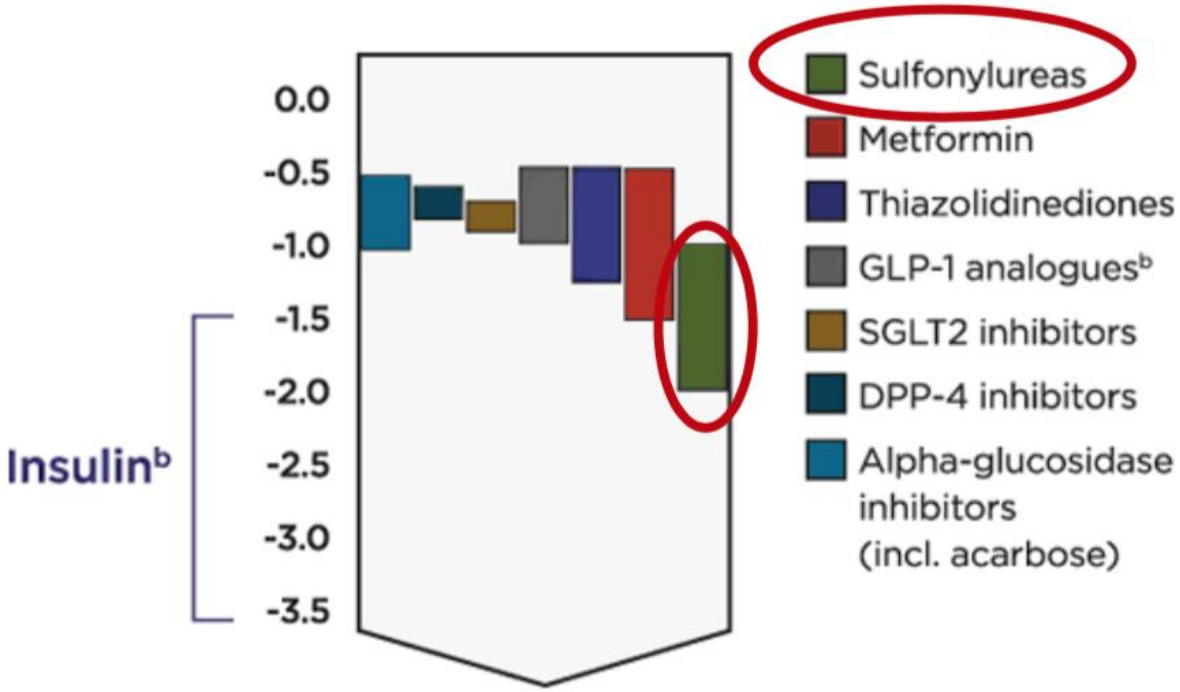
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

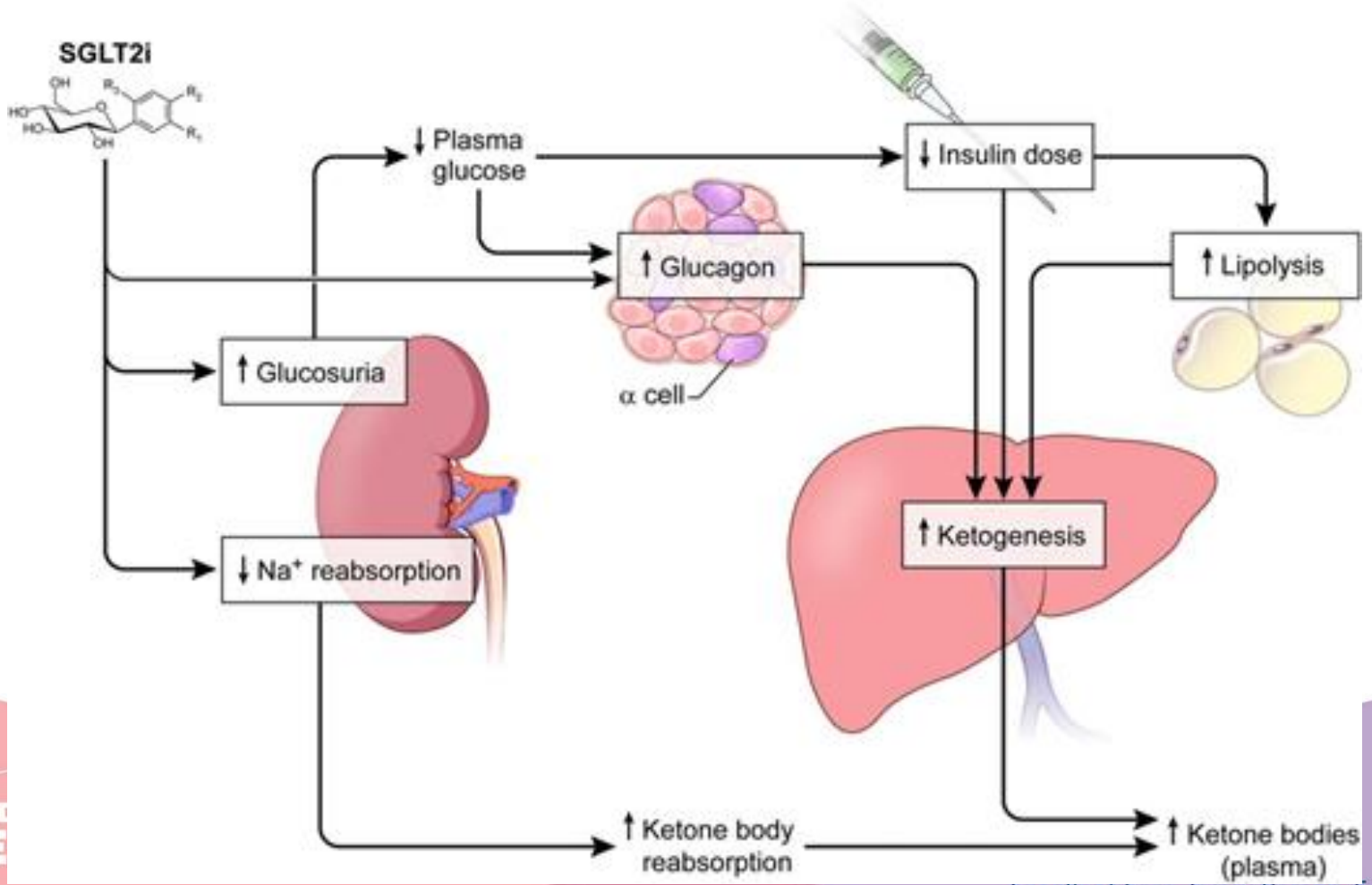
Davies M et al. ADA/EASD consensus guidelines. Diabetologia Oct 2018

T2DM drugs and Hba1c reduction



Source: www.npswise.com.au Slide courtesy Shane Hamblin

SGLT2i-induced ketoacidosis



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