SGLT2 AGENTS
1ST OPTION FOR 2ND LINE THERAPY

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CONFLICTS OF INTEREST

- I receive honoraria/payment from the following companies
  - Astrazeneca, Abbot, Boehringher ingleheim, Inova, Lily, MSD, Novartis, Novo-nordisk, Roche acuchek, Sanofi, Takeda.
  - NPS (volunteer)
  - RACGP
  - ADS

OBJECTIVES

- What are the key clinical questions that help decide how, why and when to use the SGLT2 inhibitors versus alternate agents?

GOALS FOR THERAPY

Encourage all people with T2D to approach/reach these goals*	
Healthy diet	**Glycaemic control** (FBG 6–8 mmol/L, PPG 8–10 mmol/L, HbA_{1c} ≤7%)
BMI in healthy range	**Lipids** (TC <4.0 mmol/L, HDL-C ≥1.0 mmol/L, LDL-C <2.0 mmol/L, non-HDL-C <2.5 mmol/L, TGs <2.0 mmol/L)
Sufficient physical activity	**Blood Pressure** ≤140/90 mm Hg
Smoking cessation	**UACR ratio** <3.5 mg/mmol (women) and <2.5 mg/mmol (men); timed overnight collection <20 mcg/min; spot collection <20 mg/L
Reduced alcohol consumption	**Vaccination** (e.g. influenza, pneumococcal disease)

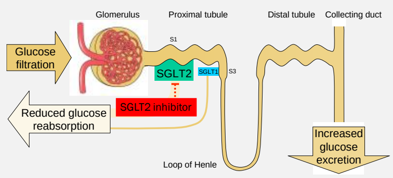
HOW DO THEY WORK?

- Agents available
- Mode of action

SGLT2 INHIBITORS ARE ALL PBS LISTED AS "ADD ON THERAPY" FOR T2D

- Dapagliflozin (Az FORXIGA) 50mgs only
- Empagliflozin (Boehringer JARDIANCE) 10mgs -> titrate to max 25mgs
- Ertugliflozin (MSD coming)
- Fixed dose combinations available
  - Metformin + SGLT2i
  - SGLT2I + DPP4 I
- Can be added to insulin but not GLP1 agonists(yet)

SGLT2 INHIBITORS BLOCK A REABSORPTION RECEPTOR IN THE KIDNEY



Renal threshold for blood glucose drops from 11mmol/L to @ 4mmol/L

SGLT2 INHIBITORS - WHAT WE KNOW

GLYCAEMIC EFFECTS ARE DEPENDENT ON ADEQUATE RENAL FUNCTION (eGFR>45/60) which results in

A. ↑ **Urinary glucose loss** **(50-80 gms)**

(+) ↓ *in plasma glucose*

Modest weight reduction(@2-3kgs) from loss of joules

(-) Urogenital infections

B. **β-cell (insulin) independent** + reactive increase of glucagon

(+) *low rates of hypoglycaemia* exc from Su's and Insulin

SGLT2 INHIBITORS - WHAT WE KNOW

C. ↑ **Urinary sodium loss + Diuresis**

(+) ↑ *haematocrit/decreased intravascular volume/reduced BP*

Possible renal protection

(-) Increased urination – one extra bladder volume/day

Volume depletion – careful of loop diuretics

SGLT2 INHIBITORS - WHAT WE KNOW

D. CVD Risk Reduction

(+) SECONDARY RISK MANAGEMENT (existing CVD disease)

JARDIANCE Empa-Reg CVOT in addition to best practice Mx of lipids/BP

38% Relative Risk Reduction of CVD death & 1.6% Absolute Risk reduction

(?) PRIMARY RISK MANAGEMENT

FORXIGA Declare –Timi CVOT (reports November) (Primary and Secondary)

TRANSLATING THE CARDIOVASCULAR OUTCOME STUDIES

Empa-reg Outcome (empagliflozin)[1] Specific cohort

- Patients with established CVD, 63 years, 70%–72% were men, mean HbA1c was approximately 8% and mean BMI was approximately 30.6 kg/m². Within the cohort, 80%–81% were using ACE inhibitors, and 76%–78% were using statins.
- **These study results apply to a small subset of the Australian population. AIHW data indicates 3%–5% of the Australian population aged ≥ 45 years have both conditions (based on 2011–12 data)(NPS)**

Declare-Timi 58 (dapagliflozin)[2] Broader more applicable cohort

- 40% with established CVD, 60% with risk factors for CVD 64 years, 62.6% males, diabetes duration 12 years, HbA1c 8.3%, statin use 80%(vs 64%)

1. https://www.nps.org.au/medical-info/clinical-topics/news/new-tga-indication-for-empagliflozin
2. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: Participants' baseline characteristics. Diabetes Obes Metab. 2018;20:1102–1110.

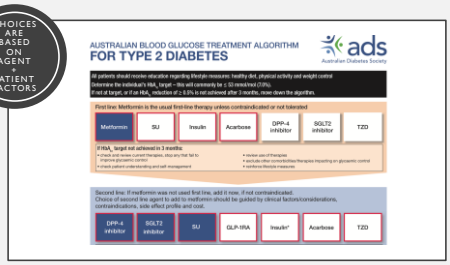
SGLT2 INHIBITORS – WHAT WE DON'T KNOW

- Limited long term safety data - still emerging
  - Euglycaemic DKA (rare)
  - Amputations (uncertain risk and v rare)
- Data limited in the >75yrs old

SGLT2 INHIBITORS – HOW DO YOU USE THEM?

- 2nd Line agent
  - ADDED TO METFORMIN &/OR SULPHONYLUREA
- 3rd Line agent
  - ADDED TO METFORMIN & DPP4I
- ADD ON TO INSULIN

CHOICES ARE BASED ON AGENT + PATIENT FACTORS



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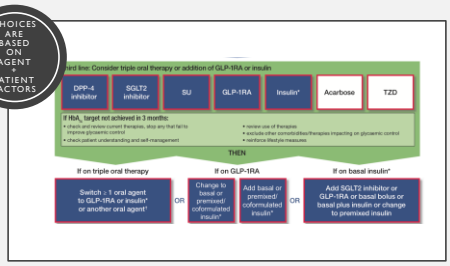

CASE STUDY

- Harry is 65 y o. T2D for 11 years.
- HbA_{1c} uncontrolled (7.7%) on metformin
- BMI 33 kg/m^2
- eGFR 75 ml/min/1.73^2
- History of hypertension, STEMI 2014 and hyperlipidaemia

WHAT GLYCAEMIC AGENT WOULD YOU CHOOSE?

CASE STUDY

- JANE IS 48 YEARS OLD. T2D FOR 6 YEARS
- PAST GESTATIONAL DIABETES
- BMI 30 kg/m^2
- eGFR 55 ml/min/1.73^2
- HbA_{1c} uncontrolled (7.6%) on metformin AND Sitagliptin

WHAT GLYCAEMIC AGENT WOULD YOU CHOOSE?

HBA1C LOWERING ADDED TO MET

Diet	Average weight loss in pounds over 6 mths	Average reduction in HbA1c (%) over 6 months	Diet's effect on heart disease risk factors
Low carb diet	25	1.4%	Lower LDL, higher HDL cholesterol
Low glycemic index	0.7	0.5%	Unknown
Low fat diet	11.6	none	Lower LDL and triglycerides, higher HDL cholesterol
Mediterranean	8.1	0.6%	Lower blood pressure, higher HDL cholesterol
Vegetarian/ vegan	6.3	none	Minimal impact
Very low calorie diet	33	0.9%	Little effect
High protein	23	0.28%	Lower LDL cholesterol

Sendook Z, et al. Diabetes with obesity: Is there an ideal diet? Cleveland Clinic Journal of Medicine. 2017;84(1):54-14

SELECTING AN ORAL AGENT FOR PATIENTS UNCONTROLLED ON METFORMIN

PBS listed	Demonstrated reduction in CV death	Key adverse events	Risk of hypoglycaemia	Effect on weight	Renal Impairment eGFR (ml/min/1.73m^2
SUs DIAMICRON® AMARYL®	X	Hypoglycaemia, weight gain[1,2]	Yes (common)[1,3]	Gain[2,4]	Stop when < 30[5]
SGLT2 inhibitors: JARDIANCE® FORXIGA®	✔ JARDIANCE® demonstrated CV death prevention[*6,7]	Genital infections, UTI, postural hypotension[1,8]	Low with metformin *Increased risk when combined with insulin/SU*[3,8]	Loss[3,8]	JARDIANCE® Stop when < 45[6] FORXIGA® Stop when < 60[9]
DPP4 inhibitors: TRAJENTA®, NESINA®, GALVUS®, ONGLYZA®, JANUVIA®	X	Potential risk of pancreatitis[2,3]	Low with metformin *Increased risk when combined with insulin/SU*[2,10]	Neutral[3,4]	Dose adjustments (except TRAJENTA® linagliptin)[5]

HEART FAILURE GUIDELINES

Prevention – pharmacological

Recommendation	GRADE strength of recommendation	GRADE quality of evidence
Blood pressure (BP) lowering and lipid lowering according to published guidelines are recommended, to decrease the risk of cardiovascular events and the risk of developing HF	Strong	High

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of HF hospitalisation

SUMMARY

- SLGT2 inhibitors have unique non-insulin dependent but renal dependent glucose lowering properties
- **Efficacy** – Oral agents have similar HbA1c drops (DPP4i, SU)
- **Cardiovascular Benefit** – Be careful in choosing clinical trial patient characteristics – though emerging trials may help solve class effect, and T2D patients at a lower risk classification than those already studied (narrow band established CVD disease)
  - Declare-Timi 58 versus Empa-reg Outome
- **CVD safety appears to be non-glycaemically driven** in these trials but much evidence supports multimodal CVD risk reduction
- **Safety** – common side-effects match real-world usage, However rare side-effects are seen in post-marketing surveillance but not in clinical trials