Type 2 Diabetes

Sodium Glucose Co-Transporter 2 Inhibitors
Empagliflozin (Jardiance)
Dapagliflozin (Forxiga)

SGLT-2i's "First Option For Second Line Therapy?"

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General Practice Education Day
Perth 3rd November 2018

Conflicts

- Presenter honoraria from Lilly, BI, AZ, Novo, MSD
- Travel sponsorship from Lilly, BI and AZ
- I performed none of the research I will discuss

since 2015

Summary

- **Goals of treatment for patients with T2DM are to**
  - Prevent or delay complications
  - Maintain quality of life
- **Many therapeutic choices now available for T2DM**
  - Medications that decrease CV events & promote weight loss are desirable
- **SGLT-2i are beneficial to many patients**
  - but do not need to be the "first option for second line therapy" in all patients

Outline

- 20 slides
- Introduction
- Why glycaemic control/treatment matters
- Glucose lowering medications
- SGLT-2i pros and cons

Unfit
Sad
Fat

Fit
Happy
Lighter

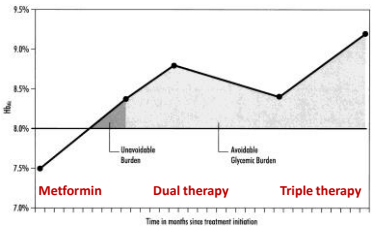
Setting the scene

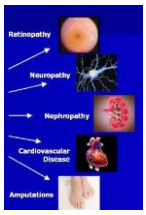
- Most oral hypoglycaemic agents reduce HbA1c by 0.5-1.0%
- Worldwide, guidelines recommend **metformin** as 1st medication
- **2nd line treatment needed in nearly all patients**
  - Little consensus on next agent should be/lack of good comparative data
  - Considerable variation across clinicians/countries
- **2nd line treatment often delayed***
  - Australian 1° care study, n=76,341 on non-insulin therapies (2005–2013)
  - Mean time spent with HbA1c >7% before intensification was 15 months

*Diabetes Res Clin Pract 2017

Glycaemic burden

Cumulative amount by which HbA_{1c} exceeds a specified treatment goal





Age at Dx:

Diabetes journey

Diabetes Care 2013

Summary glucose lowering T2DM RCT's pre-2008
"less intensive VS intensive glucose control"

RCT's 1998-2008	Microvascular	CV disease	Mortality
UKPDS 9% → 7.9% v 7%	↓	↓	↔
ACCORD 8.3% → 7.5% v 6.4%	↓ Albuminuria	↔	↑
ADVANCE 7.5 % → 7.3% v 6.5%	↓	↔	↔
VADT 9.4 % → 8.4% v 6.9%	↓	↔ ↓	↔

Initial trial
Extended

UKPDS at Dx
Others approx. 10yrs duration

Go hard early, less hard later

Summary of T2DM CVOT's since 2008
"individual new drug vs placebo" matched for glucose lowering

RCT's >2008	Agent	CV events	CV mortality	Heart Failure
EXAMINE	**DPP4i** Nesina	↔	↔	↔
SAVOUR	**DPP4i** Onglyza	↔	↔	↑ (HR1.27)
TECOS	**DPP4i** Januvia	↔	↔	↔
ELIXA	**GLP-RA**	↔	↔	↔
EXSCEL	**GLP-RA** Bydureon	↔	↔	↔
LEADER	**GLP-RA** Victoza	↓ HR 0.87	↔	↔
SUSTAIN-6	**GLP-RA**	↓ HR 0.74	↓ HR 0.78	↔
HARMONY	**GLP-RA**	↓ HR 0.78	↔	↔
EMPA-REG	**SGLT2i** Jardiance	↓ HR 0.86	↓ HR 0.62	↓ HR 0.65
CANVAS	**SGLT2i**	↓ HR 0.86	↔	↓ HR 0.67

CARMELINA – Linagliptin
DECLARE - Dapagliflozin

>70,000 patients. Most with CVD, overweight, HbA1c 8.5%

Metformin, then what?

Sulphonylureas
Gliclazide/Diamicron
Glimepiride/Amaryl

SGLT2i
Empagliflozin/Jardiance
Dapagliflozin/Forxiga

Alpha glucosidase inhibitors
Acarbose/Glucobay

DPP-4i
Sitagliptin/Januvia
Linagliptin/Trajenta
Saxagliptin/Onglyza
Vildagliptin/Galvus
Alogliptin/Nesina

TZD
Actos/Pioglitazone

Injectables
GLP-RA
Byetta, Bydureon, Trulicity, Victoza
Insulin's
xxxx

Combination therapies
MET/DPP4i: Janumet, trajentamet, kombiglyzide
MET/SGLT2i: Jardiamet, Xigduo
DPP4i/SGLT2i Glyxambi, Qtern

Too Many Choices
A Problem That Can Paralyse

Questions to consider

- Is there clinical CVD?
- Is there clinical HF?
- Is there mild/mod DKD?
- Is there a compelling need to avoid hypoglycaemia?
- Is there a compelling need to avoid weight gain or promote weight loss?
- Patient preferences?
- Is cost is a major issue?

What diabetes medications am I familiar with?

ADA/EASD 2018

Sulfonylureas

- Increase insulin secretion
- Cheap, extensive experience, decrease microvascular risk

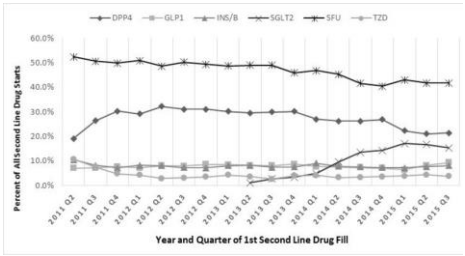
- Older SU's Glibenclamide: more hypoglycaemia/? CV risk
- Modern SU's **Gliclazide/Diamicron MR:** less harm

- Large meta-analysis of drug classes
  - SU's had higher risk of MI compared with DPP-4 inhibitors

- *Adverse*
  - ***Hypoglycaemia*** *and few kg* ***weight gain***
  - *No proven CV benefit and possible CV harm*
  - *Caution in certain groups i.e. elderly and certain occupations*

UKPDS Lancet 1998 ADVANCE NEJM 2008 JAMA 2018

2nd line diabetes medication in USA



SU's

DPP-4i

SGLT-2i
GLP/Insulin
TZD

Prescriptions. 77,744 adults enrolled in commercial or Medicare Advantage health plans from 2011 to 2015.

BMJ Open Diab Res Care 2017

Thiazolidinediones: TZD's "Glitazones"

- Increase insulin sensitivity of fat, muscle, liver
- Not often used anymore
  - low dose **Pioglitazone/Actos** may have a niche role
    - In very insulin resistant. Possible CV/NAFLD/CVA benefits
- *Patients should be made aware of:*
  - ***increased risk of oedema, heart failure, weight gain, bladder cancer and fractures***

Proactive study Lancet 2005, IRIS NEJM 2016

Dipeptidyl peptidase-4 inhibitors DPP-4i "Gliptins"

- Inhibits DPP-4 activity, increasing gut incretins: GLP-1, GIP
- Stimulate (glucose-dependent) insulin release from the pancreas and decrease glucagon secretion
- Very well tolerated with large safe evidence-base
  - **Sitagliptin/Januvia, Linagliptin/Trajenta**
- **Hypoglycaemia rare, weight neutral, CVD neutral.**
- Can be used with low GFR
- Adverse
  - Rare: angioedema/urticaria
  - Very rare: acute pancreatitis/IBD
  - ? heart failure hospitalisation HR 1.27 (saxagliptin/onglyza)
  - Don't use with GLP-RA's

Scirica NEJM 2013, Green NEJM 2015, EASD 2018

Glucagon-like peptide-1 receptor agonists: GLP-1RA "Incretins"

- Bind to the GLP-1 receptor:
  - Stimulates (glucose-dependent) insulin release and decreases glucagon secretion
  - Slows gastric emptying and increases satiety
- **Injected** subcutaneously OD, BD, OW - A1c reduction 0.7-1.7%
  - **Byetta** (+insulin), **Bydureon, Trulicity**
  - Victoza/Saxenda
- **Hypoglycaemia rare, weight loss 2-5kg**
- **CVD and mortality benefit in CVD patients** (Liraglutide/Semaglutide)
- Adverse
  - GI side effect: nausea, vomiting, diarrhoea.
  - Acute pancreatitis: ABDO PAIN/VOMITING =ED
  - Increases Heart rate
  - C-cell hyperplasia medullary thyroid tumours (animals)
  - Don't use with DPP-4i

Lancet Diab Endo 2018

Sodium-glucose cotransporter-2 inhibitors: SGLT-2i (blockers)"Flozins"

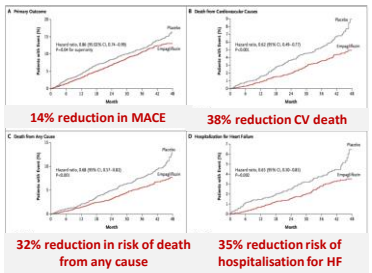
- Blocks glucose reabsorption in the proximal tubule of kidney = glycosuria/natriuresis
- Independent of insulin, SGLT2i do not need beta cell function to work
- Drug-induced glucose excretion requires some renal function hence SGLT-2i are CI with low GFR (<30)
- Strong evidence-base: **Empagliflozin/Jardiance,** Dapagliflozin/Forxiga
- **Hypoglycaemia rare, Weight loss: 1.5 to 3 kg, BP down 3–5 SBP, reduce progression of albuminuria/nephropathy**
- **CVD, mortality and CHF benefits in CVD patients**

NEJM 2015, NEJM 2017

EMPA-REG

RCT N=7020
Mean F/U 3.1 yrs.

difference in BG control between groups was small and not enough to explain CVD outcome

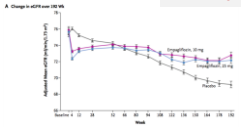


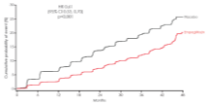
14% reduction in MACE

38% reduction CV death

32% reduction in risk of death from any cause

35% reduction risk of hospitalisation for HF

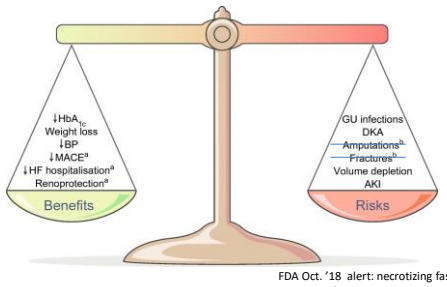




NEJM 2015, NEJM 2016

Slower progression of nephropathy

Major risks and benefits of SGLT2i



FDA Oct. '18 alert: necrotizing fasciitis of perineum, known as Fournier gangrene

[a/b] Agent specific data

Diabetologia 2018

SGLT-2i and DKA

- Rare between 1:1,000 and 1:10,000
  - March 2018: TGA received 219 reports of Empagliflozin/Dapagliflozin related DKA
- Consider DKA in patients taking SGLT2i who
  - Develop abdominal pain, nausea, vomiting, fatigue or unexplained ketonaemia/acidosis
  - NB: a normal glucose level does not exclude the diagnosis
- Risk groups
  - restricted dietary intake (e.g. fasted), surgery, dehydration, active infection, excess alcohol
- SGLT2i should be part of **'sick-day guidance'** and be stopped temporarily with other drugs such as metformin or ACE-i during acute dehydrating illness or major surgery
- **SGLT2i surgery advice**
  - **Cease 3 days pre-operatively**
  - **Restart post-operatively when the patient is eating and drinking (usually 3-5 days post-surgery)**
  - **Check blood glucose and blood ketone levels if patient is unwell in the week following surgery**

3 SLIDES TO GO

Who should you prescribe SGLT-2i to?

Most suitable	**Least** suitable
• Established CVD	• Insulin within 1year of Dx
• Clinical HF	• Previous DKA
• Hypertension	• Eating disorders/ XS alcohol
• Microalbuminuria	• Recent/upcoming major surgery
• eGR>45	• Diabetic foot/amputations
• Overweight/obese	• Poor self care behaviours
• Vulnerable to hypos	
• No leg amputations/DFU	

Education on risks of genital thrush/UTI and DKA. Check renal function esp if on diuretics

The treatment journey

Glycaemic Control Any/all agents

Statin
Anti-HT
RAAS blocker
Aspirin

Glycaemic Control Specific CV agent

Low CV risk ---- High CV risk ----- CV Disease

Multiple shared decisions along the way

Metformin, then what?

- Is there CVD, HF, CKD
- Is there a need to avoid hypo's and weight gain
- Is cost is a major issue

DPP-4i | **SGLT-2i**

Combination therapies
MET/DPP-4i
MET/SGLT-2i
DPP4i/SGLT-2i

GLP-RA injectables

Insulins

Sulphonylureas

TZD

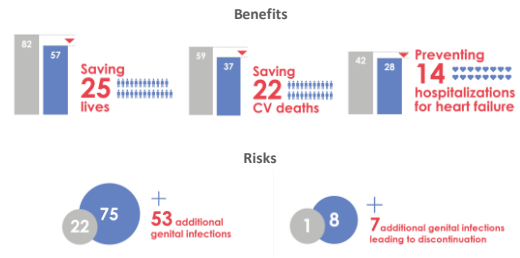
Alpha glucosidase inhibitors

Summary

- Goals of treatment for patients with T2DM are to:
  - Prevent or delay complications – *glycaemic burden*
  - Maintain quality of life
- Many therapeutic choices now available for T2DM
  - Medications that decrease CV events & promote weight loss are desirable
- SGLT-2i are beneficial to many patients
  - They could be "first option for second line therapy" in some patients but not necessarily all

THANK YOU FOR LISTENING

EMPA-REG OUTCOME
Treating 1000 T2DM patients at high CV risk with empagliflozin for 3 years



EMPA-REG N=7020, Mean F/U 3.1 yrs.

N Engl J Med 2015