SUGAR-DM-HF
Overview

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Excess calories (increased intake or reduced energy expenditure)

Subcutaneous stores overwhelmed (genes, ethnicity, ageing)

FAT ‘Spill over’

Liver fat accumulation

Insulin resistance
High sugar levels
High blood fat
High blood pressure

Obesity

Perivascular fat ⇒ Endothelial dysfunction

T2DM
Diabetes and the heart – lots of good news

- **Heart risks double but coming down**
  - Esp. heart attacks / stroke
  - Diabetes drugs? Or something else

- **Some risks now more common therefore?**
  - Heart failure – when heart pump action impeded
  - A new diabetes drug may tackle this and reduce death, substantially
Diabetes-related CV complications have declined with improved care, but substantial burden remains.

200 diabetes pts treated 5 years: BP & LLT trump glucose lowering for CVD events

Per
4mmHg lower SBP

Per
1mmol/L lower LDL-C

Per
0.9% lower HbA1c

Ray et al Lancet 2009 Meta-analysis of intensive glucose-lowering trials
Evolution of T2D agents

1950
1960
1970
1980
1990
2000
2010
2012
2013

Lente class of insulins produced
Recombinant human insulin produced
2nd generation SUs available
Insulin degludec

Older T2D agents

Newer T2D agents

DPP4 inhibitors
SGLT2 inhibitors
GLP1 receptor agonists

Metformin introduced in the UK
SUs first used

Three new classes introduced:
- α-glucosidase inhibitors
- meglitinides
- TZDs

New approaches to reducing blood glucose

- Incretins
  - GIP
  - GLP-1

- Help insulin release + Weight loss

- Reduce blood sugar

- GLP-1 agonists/analogues e.g. exenatide

- DPP-4 inhibitors ("gliptins")

- DPP-4 breakdown products

- Inhibit Kidney re-absorption (SGLT2 inhibitors)
SGLT2 inhibitors

Get rid of excess Sugar in urine

BUT opposite to what we preached
Adults with type 2 diabetes
HbA1c 7–10%*

ALL (99%) with Established heart disease

- Prior MI, CAD, stroke, UA or occlusive PAD

Baseline characteristics - EMPAREG

- Average age ~63
- BMI 30.7
- HbA1c ~8.07%
- SBP 135 mmHg
- ~26% kidney disease / ~10% heart failure
- 3.1 years mean duration follow-up trial
CV death

HR 0.62
(95% CI 0.49, 0.77)
p < 0.0001

Cumulative incidence function. HR, hazard ratio
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017

Cumulative incidence function. HR, hazard ratio

No. of patients
Empagliflozin  4687  4614  4523  4427  3988  2950  2487  1634  395
Placebo  2333  2271  2226  2173  1932  1424  1202  775  168

Cumulative incidence function. HR, hazard ratio
Empagliflozin
Reduced incident or worsening nephropathy

Kaplan-Meier estimate. Patients treated with at least one dose of study drug. Hazard ratios are based on Cox regression analyses. HR, hazard ratio; CI, confidence interval.

HR 0.61
(95% CI 0.53, 0.70)
p < 0.001

Wow wee.....cannae believe it
Many theories on how empagliflozin works

**Metabolism**
- Negative caloric balance
- ↓ Total body fat mass
- ↓ Total body fat mass
- ↓ Epicardial fat
- ↓ Inflammation
  - ↓ Glucose toxicity
- ↓ HbA1c
- ↑ Uricosuria
- ↓ Plasma uric acid
- ↓ Inflammation
- ↓ Glucose toxicity
- ↓ HbA1c
- ↓ Total body fat mass

**Volume**
- ↓ Plasma volume
- ↓ Blood pressure
- ↓ Arterial stiffness
- ↓ Ventricular arrhythmias

**Sodium**
- ↑ Tubulo-glomerular feedback
- Afferent arterial constriction
- ↓ Intraglomerular hypertension
- ↓ Hyperfiltration

**Cardiac & renal protection**
- Cardiac & renal protection
- Activation of ACE2 – Ang1/7
- No sympathetic nervous system activation

The kidney-heart axis:

- **SGLT2 inhibition**
  - Sugar and salt reabsorption in kidney
  - Kidney stress

- **Urinary glucose & sodium**
  - Generalized decongestion

- **Heart stress**
  - Heart failure hospitalization
  - Fatal arrhythmias

Slow renal dysfunction

*Sattar et al (2016) Diabetologia*
Get rid of excess Sugar
Salt
And water
In body system
Many people with type 2 Fluid overloaded?
Putting it all together

Atherogenesis

Volume overload heart stress

Reduced stroke and MI risk

Reduced CV death and HF risk

lowered by GLP-1 RA

lowered by SGLT2 Inhibitors

?↓ atherothrombosis+/-avoidance of hypoglycemia

Benefits in Heart failure? Kidney disease?
SUGAR-HF trial
SUGAR-HF trial

- 100 people with heart failure
  - West of Scotland – clinics
  - Half placebo / half active drug

- 9 months – repeat MRIs and other measures
  - Safety and benefits to heart and kidney function and measures of congestion

- Glasgow leading role in major heart failure trials