



## **Is SGLT2 induced ketosis in T2DM Predictable with a Risk stratification score?**

**ABCD Winter Meeting Presentation**

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# Case History

- DP, 59 year old Caucasian woman
- Known type 2 diabetes on metformin and Dapagliflozin
  - 2-day history of nausea, emesis (more than 5 episodes) and a 4-day history of urinary symptoms (frequency, urgency and nocturia).
- No family member affected or recent travel

## On Examination

- Afebrile, comfortable at rest,
- Dehydrated
- CVS : pulse 100 /min, BP 129/88
- Resp: Chest clear, RR 19, sats 98%
- Abdo: Soft, non tender, BS present
- Neuro – normal

# Investigations

- Na 136 mmol/l
- K 4.7 mmol/l
- **Urea 8.3 mmol/l**
- Creatinine 83umol/l
- Amylase 70 U/l
- **CRP 60.7**
- LFTs normal
- FBC
  - Hb 150 **WBC 8.5**
  - Neuts 6.5
  - Plts 352
- ECG – sinus tachycardia, rate 100bpm, normal axis
- CXR & AXR – NAD

# Investigations

- **VBG:**
- pH 7.19,
- pCO<sub>2</sub> 4.19 kPa
- pO<sub>2</sub> 4.12 kPa,
- HCO<sub>3</sub> 11.60 mmol/L
- glucose 14.80 mmol/L
- lactate 2.19 mmol/L
- base excess 15.30 mmol/L.
- **Blood ketones 4.6 mmol/L** (normal <0.5)
- Urine analysis
  - Ketones 3+
  - Glucose 3+

# Treatment

- Rehydration
- Fixed insulin infusion & 10% dextrose
- Basal insulin glargine
  - Metformin withheld
  - Dapagliflozin discontinued
- Resolution of acidosis by 48hrs
- Discharged on metformin

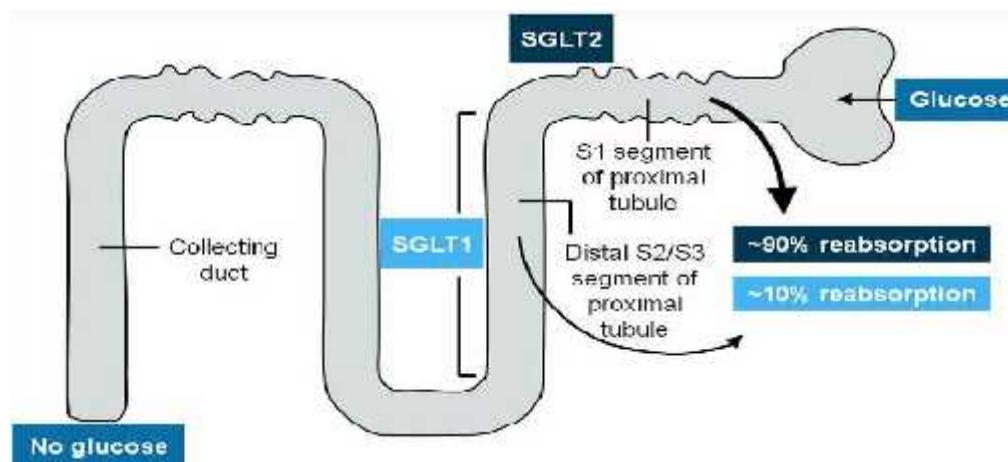
# Causes of ketoacidosis

- **In patients with diabetes**
  - DKA (Type 1)
  - Ketosis prone DKA (Type 2)
  - Euglycaemic DKA (Type 1 and 2)
    - Pregnancy
    - Insulin pump failure
    - Associated with SGLT-2 inhibitors
- **In patients without diabetes**
  - Alcoholic ketoacidosis
  - Starvation ketosis

# Euglycaemic DKA

Associated with SGLT-2 inhibitors

- Sodium Glucose Linked co-Transporter -2 inhibitor
  - SGLT-2 inhibitor
  - A new oral hypoglycaemic class



# SGLT-2 inhibitors

## Currently licenced in UK

- Empagliflozin
- Dapagliflozin
- Ipragliflozin



# NICE guidelines [NG28] - Dec 2015

## on SGLT-2 inhibitors

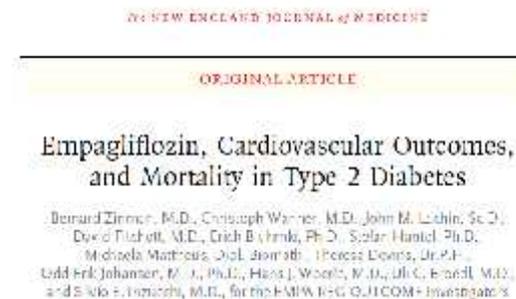
- Licenced for Type 2 diabetes;  
mono/combination Rx with-
  - Metformin
  - Sulphonylureas
  - DPP4 inhibitors
  - Thiazolidinediones
  - Insulin

  
*National Institute for  
Health and Clinical Excellence*

# EMPA-REG OUTCOME

RCT 7020 - T2DM subjects  
590 sites /42 countries, 2010-2013

- T2DM R<sub>x</sub> OHA +/- insulin
  - RCT- Placebo, 10mg or 25mg empagliflozin added to usual treatment
- After 12 week run in - no changes to Rx, optimisation of glycaemia, lipids & BP in all groups

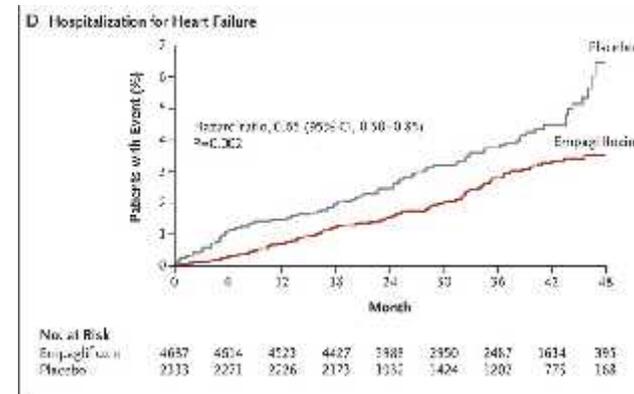


(Zinman et al, NEJM 2015; 373:2217-2128)

# EMPA-REG OUTCOME

Median observation 3.1 yrs

- Primary outcome – any cardiovascular death
- Empagliflozin vs. placebo
  - CVD death  
3.7% vs 5.9% (38% RR reduction)
  - Death from any cause  
5.7% vs 8.3% (32% RR reduction)
- Lower hospitalisation from heart failure  
2.7% vs 4.1% (35% RR reduction)



(Zinman et al, NEJM 2015; 373:2217-2128)

# EMPA-REG OUTCOME

## Empagliflozin vs. placebo

- Mean HbA1c
  - 7.81% vs 8.16%
- Weight loss
  - mean 2kg
- Systolic BP
  - mean fall 4mmHg
- Genital infection
  - 6.4% vs 1.8%
- UTI (18%)
  - No differences
- Sepsis due to UTI
  - 1.7% vs 1.8%
- DKA 0.1% vs <0.05% (p=0.002)
- Hypoglycaemia (27%)
- AE leading to discontinuation
  - 17.3% vs 19.4%

# DKA due to SGLT-2 inhibitors

- Increasingly recognised
  - 1:1000 - 1:10000 patients
- UK – 118 yellow cards reports
- Generally euglycaemic or plasma glucose <14 mmol/L
- Many cases related to off label use in type 1 diabetes



(18<sup>th</sup> April 2016 - [www.gov.uk/drug-safety-update/sglt2-inhibitors](http://www.gov.uk/drug-safety-update/sglt2-inhibitors))

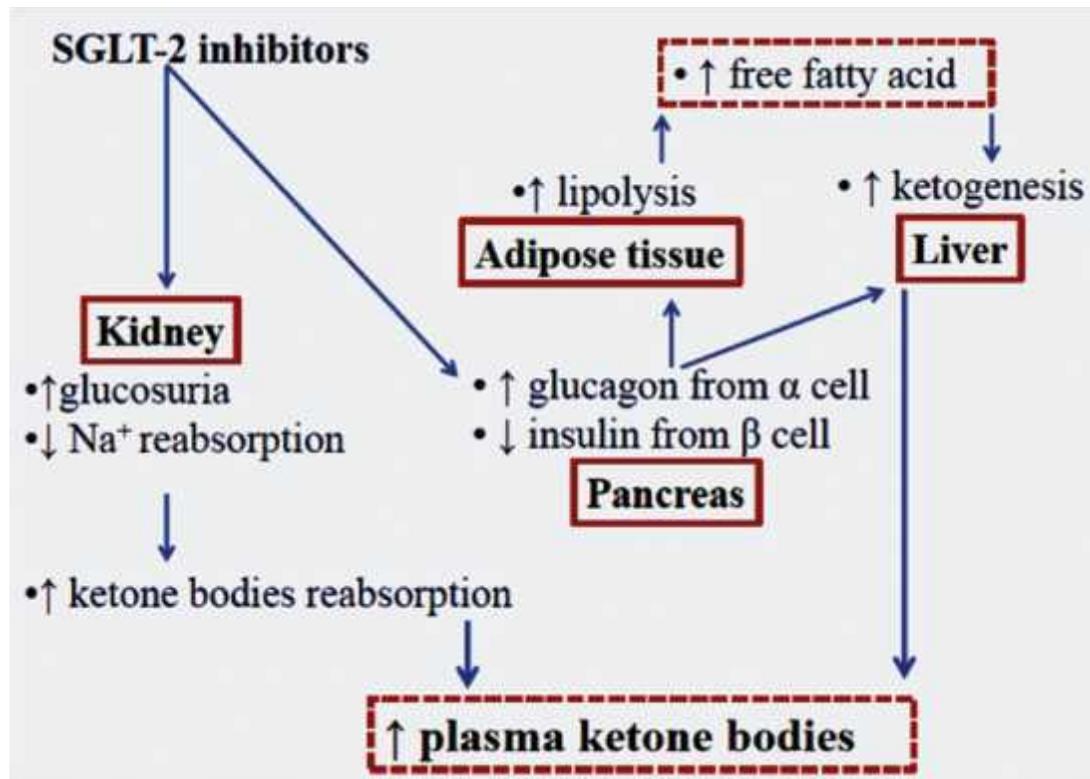
# DKA due to SGLT-2 inhibitors

- Often in the first 2 months of use
- Associated with:
  - Dehydration
  - Starvation and weight loss
  - Infections
  - Surgery
  - Vomiting



(18<sup>th</sup> April 2016 - [www.gov.uk/drug-safety-update/sglt2-inhibitors](http://www.gov.uk/drug-safety-update/sglt2-inhibitors))

# Mechanism of euglycaemic DKA



# Delayed Diagnosis of DKA

- SGLT2 inhibition can delay the diagnosis of DKA in T2DM patients by lowering the hyperglycemia typically associated with absolute insulin deficiency, and consequently delay timely treatment.
- The risk varies for different SGLT 2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) but there is a need for a risk stratification score (see table) to identify patients at high risk of DKA in T2DM on above therapy.

## Risk stratification score for T2DM patients on SGLT2 treatment

Signs or Symptoms of DKA e.g. rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat)	1 for each sign or symptom
<p>Risk factors for DKA i.e.</p> <ul style="list-style-type: none"> <li>• a low beta cell function reserve (eg, patients with type 2 diabetes who have low C-peptide levels, latent autoimmune diabetes in adults [LADA], or a history of pancreatitis)</li> <li>• conditions leading to restricted food intake or severe dehydration</li> <li>• sudden reduction in insulin</li> <li>• increased insulin requirements due to acute illness</li> <li>• surgery</li> <li>• alcohol abuse</li> </ul>	1 for each risk factor
No alternative diagnosis	1
Duration of treatment less than 2 months	1
Blood sugar moderately elevated i.e. less than 14 m mol	1

# To minimise risk of DKA

- **Risk Stratify: Risk assessment >1 more likely**
- Inform patients of symptoms and signs of DKA
- Stop drug 24hrs before elective surgery, planned invasive procedures or intense physical activity
- Stop during intercurrent illnesses or metabolic stresses
- Suspect DKA even in those with normal glycaemia

# Summary

- Increasing prescribing of SGLT-2 inhibitors
- NICE approved
- Improved cardiovascular outcomes
- Associated with DKA
- Suspect DKA even with a normal glucose
- Stop medication on admission

# References

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