Novel Therapy – SGLT-2 inhibitors Pros and Cons

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Outline

- Introduction to SGLT-2 inhibitors
  - History lesson
  - Pharmacology
  - Available forms
- Pros
  - Treatment effects
  - Secondary benefits
- Cons
  - Major side effects
  - Ketoacidosis

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2

SGLT inhibitors, a brief history

- 1835 – Phlorizin is isolated from the bark of fruit trees (apple and cherry trees)
- 1886 – Experiments performed by Von Mering demonstrated that ingesting 1g/kg body weight of phlorizin resulted in glucosuria
- 1930s – Action of phlorizin described
- 1950s to 1970s – specifics are learned that phlorizin competitively inhibits SGLT1 and SGLT2 (with greater affinity for SGLT2)
- 2003 – mutations in the SGLT2 gene described related to Familial Renal Glucosuria

Clin J Am Soc Nephrol 5: 133–141, 2010

Endocrine Reviews, August 2011, 32(4):515–531

Scheen, AJ; Drugs. Jan 2015, Volume 75, Issue 1, pp 33-59

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3

Sodium glucose co-transport

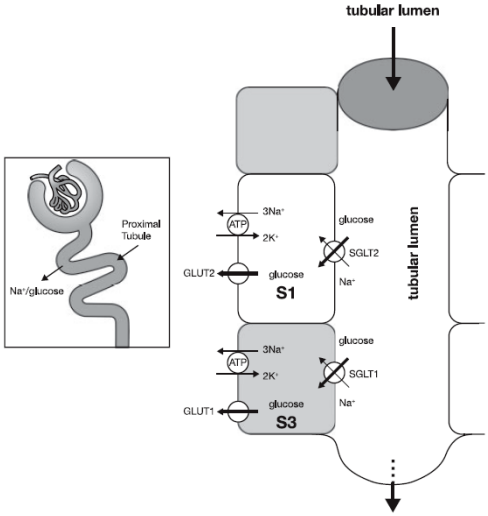

Figure 1. A model for Na^+/glucose transport in the kidney. SGLT2 is predominantly expressed in the S1 segment of the proximal tubule and is responsible for the vast majority of glucose reabsorption from urine.

- SGLT2
  - High throughput, low affinity
- SGLT1
  - High affinity, low throughput

Clin J Am Soc Nephrol 5: 133–141, 2010

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4

Sodium Glucose Co-transporters

Table 1. Substrates and distribution of human glucose transporters

Transporter (Gene)	Substrate	Size (Amino Acids)	Distribution
SGLT1 (*SLC5A1*)	Glucose Galactose	664	Intestine, trachea, kidney, heart, brain, testis, and prostate
SGLT2 (*SLC5A2*)	Glucose	672	Kidney, brain, liver, thyroid, muscle, and heart
SGLT4 (*SLC5A9*)	Glucose Mannose	699	Intestine, trachea, kidney, liver, brain, lung, uterus, and pancreas
SGLT5 (*SLC5A10*)	Glucose (predicted)	596	Kidney
SGLT6/SMIT2 (*SLC5A11*)	Myoinositol Glucose	675	Brain, kidney, and intestine
SMIT1 (*SLC5A3*)	Myoinositol Glucose	718	Brain, heart, kidney, and lung

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5

Pharmacology SGLT2 inhibitors

- Under normal conditions, the glomeruli filter 180 L of plasma per day, with an average of 90 mg/dL of glucose; ~162 g/day of glucose.
- 100% of the glucose is reabsorbed
  - 90% by SGLT2
  - 10% by SGLT1
- Under normal conditions, the threshold for these transporters is around 375 mg/min or a plasma glucose of about 180 mg/dL; above this level glucose is secreted in the urine.

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6

The SGLT2 inhibitors

	Dapagliflozin [12, 13, 24]	Canagliflozin [16, 25]	Empagliflozin [17, 26]
Trade name	Forxiga® (Europe); Farxiga™ (USA)	Invokana® (Europe and USA)	Jardiance® (Europe and USA)
Tablets (mg)	5, 10	100, 300	10, 25
Pharmacokinetic parameters			
Oral bioavailability (%)	78	≈65	>60
Food effect	Not clinically relevant	Not clinically relevant	Not clinically relevant
t_{max} (h)	1–2	1–2	1
Volume of distribution (L)	118	119	74
Plasma protein binding (%)	91	98	86
$t_{½}$ (h)	12.2	11–13	12.4
Metabolism	Extensive glucuronidation to inactive conjugates (primarily dapagliflozin 3-*O* glucuronide)	Extensively metabolised by *O*-glucuronidation to two major inactive metabolites (M5 and M7)	Extensively metabolised by glucuronidation and, to a lesser extent, oxidation to 6 inactive metabolites
Elimination	Primarily in urines as inactive metabolites: <2 % eliminated as unchanged drug in urine	Elimination in urines and faeces: <1 % eliminated as unchanged drug in urine	Eliminated in urine and faeces: 28.6 % excreted unchanged in urine
Drug interactions	Not clinically relevant	Not clinically relevant	Not clinically relevant

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7

Comparison of SGLT2 inhibitors (-gliflozins)

Name (# pts)	A1C (%) Reduction	Renal dose adjustment	Liver dose adjustment	Cost – retail*
Dapa (3,986)	-0.52 (-0.6 to -0.45)	Not recommended if GFR < 60	none	$370 30 days
Cana (6,700)	-1.08 (mono) (-1.25 to -0.9) -0.73 (add on) (-0.84 to -0.61)	Max dose 100mg GFR 45-60 Not recommdened GFR < 45	Class C: not recommended	$370 30 days
Empa (6,200)	-0.62 (10 mg) (-0.68 to -0.57) -0.66 (25 mg) (-0.76 to -0.57)	Max dose 10mg if GFR 45-60 Not recommended for GFR < 45	none	$370 30 days

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*GoodRx.com

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8

Pros

Case 1

- 49 year old morbidly obese male with GERD, OSA, HTN, NAFLD, and DM II for 6 months.
  - Weight: 338 lbs
  - BMI: 44.95 kg/m2
- Home glucose levels:
  - 170-200 fasting, 110-150 at HS
  - A1C: 9.4%
- Meds:
  - Metformin 1000 daily
  - Sitagliptin 100mg daily
  - Glimepiride 1mg daily
  - Amlodipine, losartan, HCTZ, atorvastatin, and fenofibrate
- Plan:
  - Diabetes education, weight loss goal of 3-5%, increase Metformin to twice daily.

Case 1

- Four months later:
  - Only med change Metformin 1000mg 2XD
  - Weight down to 330 lbs (-2.4%)
  - A1C now 7.2%
  - Added canagliflozin 100mg daily
- Five months later:
  - Remains on Metformin 1000mg twice a day, Glimperide 1mg, Canagliflozin 100mg, stopped Sitagliptin when the prescription ran out.
  - Glucose now 90-110 fasting (not testing otherwise)
  - Weight is 319 lbs (-5.6%)
  - A1C is 6.2%

SGLT-2 Glucose lowering effect

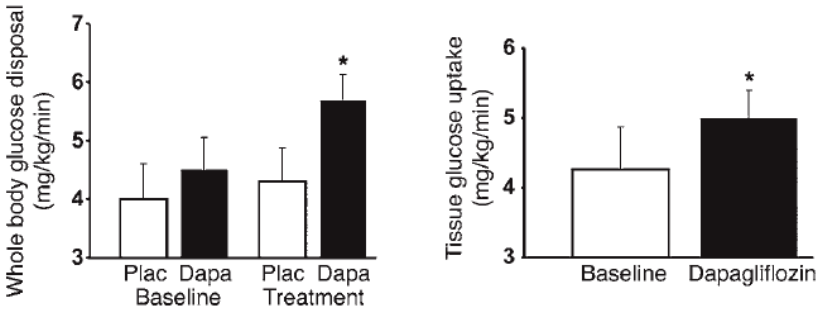

Figure 1
Whole body and tissue glucose disposal during the euglycemic insulin clamp studies performed in subjects with type 2 diabetes before (Baseline) and after 14 days of treatment with dapagliflozin (Dapa) or placebo (Plac). *$P < 0.05$.

Endocrine Reviews, August 2011, 32(4):515–531 *J Clin Invest.* 2013;124(2):499–508.
Scheen, AJ; Drugs. Jan 2015, Volume 75, Issue 1, pp 33-59

Favorable Metabolic Profile

- Weight loss (meta analysis data, variable timing)
  - Cana: 2.37 – 3.26 kg
  - Dapa: 2.2 – 3.1 kg
  - Empa: 1.38 – 2.3 kg
- Greater durability of A1C lowering effect
  - Not related to insulin secretion or beta cell function
- Cardiovascular benefit

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13

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EMPA-REG OUTCOME

- Study enrolled over 7000 participants (97% completed protocol), A1C 7-10%, established CVD*
  - Mean age 63, 70% male
  - LDL 84-86 in all groups
  - Similar proportion stopped study drug and placebo
- Primary outcomes:
  - Death from CVD cause, nonfatal MI, nonfatal CVA
- Secondary outcome:
  - Composite of primary outcomes plus hospitalization for unstable angina.

N Engl J Med 2015;373:2117-28.

14

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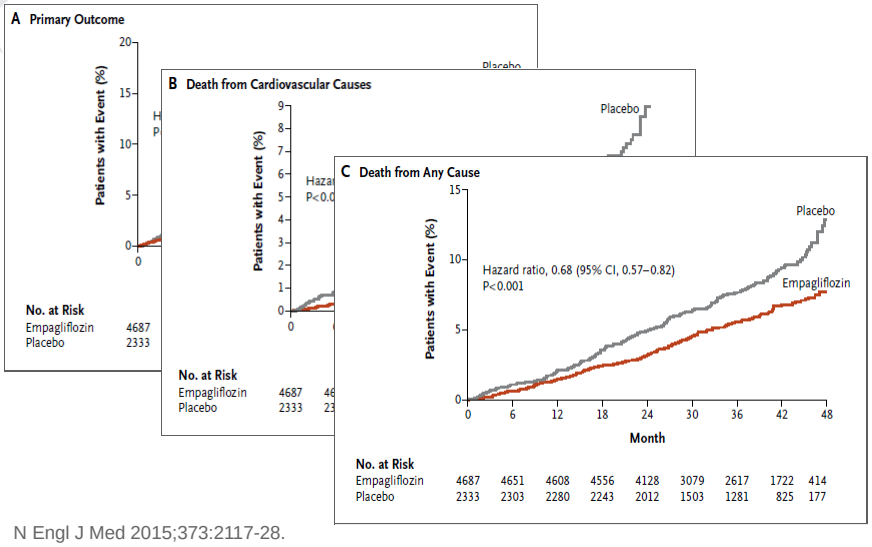
EMPA-REG OUTCOME



N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME

- Glucose Control (vs placebo):

Dose	12 weeks	94 weeks	206 weeks
10 mg	-0.54 %	-0.42 %	-0.24%
25 mg	-0.6%	-0.47%	-0.36%

- A1C: 12 weeks: 7.4%, 94 weeks: 7.5%, 206 weeks: 7.81% (8.16% at 206 weeks in placebo group)
- All were treated to usual standard for lipids and HTN
- Higher % of patients in the placebo group received SU and insulin, antihypertensive meds, and anticoagulants (aspirin) post-baseline.

N Engl J Med 2015;373:2117-28.

Cons

Case 2

- 44 y/o morbidly obese female with hypertriglyceridemia, pancreatitis, and DM II for 8 years
  - Pioglitazone 45mg
  - Glargine 68 units at HS
  - Lispro 15 units AC plus 1:25 over 150 scale
  - A1C: 8.6%
  - Triglyceride: 348
- Meds:
  - Lisinopril 10mg, rosuvastatin 40mg, fenofibrate 137 mg, omega-3 2000mg twice a day
- Home glucose:
  - 114-270s fasting, 90-400 during the day
- Plan:
  - Diabetes education, dietary counseling, adjust insulin dose timing and titrate.

Case 2

- 5 months later (January):
  - Glargine 80 units at HS (unable to remember twice daily dosing)
  - Lispro 15 units AC + correction scale
  - Pioglitazone 45mg
  - A1C: 8.4%, Triglyceride: 2003
  - Plan:
    - Increase lispro to 17 units AC, increase correction scale, add canagliflozin 100mg

Case 2

- 3 months later (late April):
  - Admitted with nausea, vomiting, abdominal pain, and dizziness. She admits she stopped testing glucose, stopped giving insulin, but denies any precipitating illnesses or stressors.
  - Admitting labs:
    - Glucose: 257
    - Anion Gap: 29
    - CO2: 9
    - Venous pH: 7.17
    - Cr: 1.58 (baseline 0.84), Lactate: 1.5
- At follow-up in June:
  - No prior history of DKA
  - A1C now 7.2% off of canagliflozin

Side Effects (minor)

- Dehydration and orthostasis
  - Related to ostmotic diuresis effect
  - Can be worrisome in elderly patients
- Weight loss
  - Observed to occur in both adipose and lean tissue
  - Could exacerbate sarcopenia
- Pharmacodynamics are dependent on intact GFR
  - With reduced GFR (< 45), the effect of the medication is less than 20% compared with normal GFR

Scheen, AJ; Drugs. Jan 2015, Volume 75, Issue 1, pp 33-59

Side Effects (major, FDA warnings)

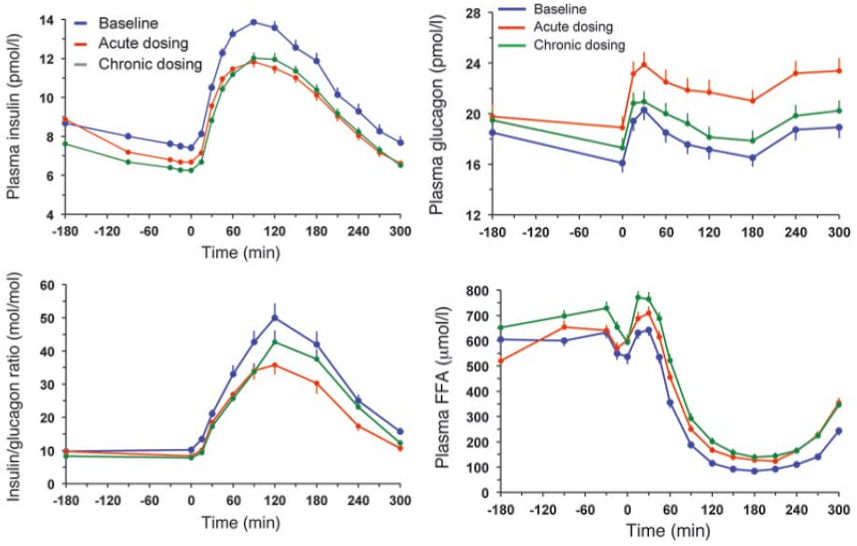
- DKA
  - May 2015
- Fracture Risk
  - September 2015
- Acidosis, UTI, and genital mycotic infection
  - December 2015

http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm446852.htm

DKA - classic

- Clinical Definition:
  - Hyperglycemia (usually > 300)
  - Presence of ketones (beta-hydroxybutyrate)
  - Acidemia
- Pathophysiology:
  - Lack of insulin, or relative lack
  - Hyperglycemia with fatty acid oxidation (for fuel) leading to build up of ketones/acid
  - Osmotic diuresis and dehydration

SGLT2 metabolic effects



J Clin Invest. 2013;124(2):499–508.

DKA – euglycemic, SGLT2 related

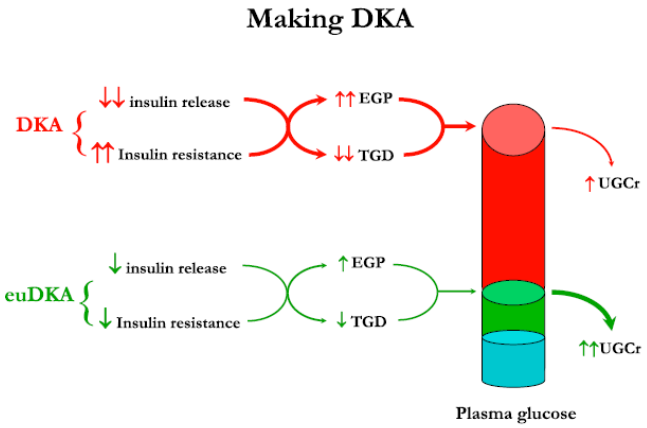


Figure 1—Essential pathophysiology of DKA and euDKA consequent of the use of SGLT2 inhibitors. TGD, tissue glucose disposal; UGCr, urinary glucose clearance rate.

Diabetes Care 2015;38:1638–1642

J Clin Invest. 2013;124(2):499–508.

Side Effects (potential)

- Initial bone/fracture related data (canagliflozin)
  - 716 women age 55 to 80 with osteopenia, at least three years post-menopause, assigned 1:1:1 placebo, cana 100mg, cana 300mg.
  - At 26 and 52 weeks, significant increase in serum CTx (breakdown marker) at both doses; Osteocalcin (bone formation) unchaged at 26 weeks then increased at 52 weeks (at both doses)
  - DXA showed statistical decrease in hip BMD at 52 and 104 weeks on both 100 and 300 mg doses of canagliflozin
  - Subjects with Fractures: 2.4%(cana) 1.7% (placebo)
    - 0.6% [0.0, 1.2] 95% CI

J Clin Endocrinol Metab. 2016;157: 44–51.

Kwohn H. Canagliflozin: clinical efficacy and safety. Endocrinology and Metabolic Drugs Advisory Committee Meeting; 2013 www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/

Side effects (potential)

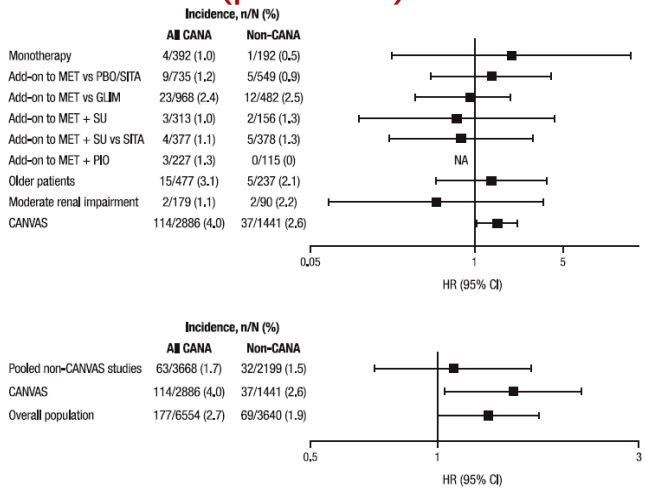


Figure 1. HRs (95% CIs) for pooled canagliflozin 100 and 300 mg vs noncanagliflozin in the incidence of fracture AEs in the 9 individual studies, the pooled non-CANVAS studies, CANVAS, and the overall population. CANA, canagliflozin; MET, metformin; PBO, placebo; SITA, sitagliptin; GLIM, glimepiride; SU, sulfonylurea; PIO, pioglitazone; NA, not assessed.

- In CANVAS, fractures occurred earlier < 12 weeks
- Difficult to interpret fall data (not actively collected)

J Clin Endocrinol Metab, January 2016, 101(1):157–166

UTI/Mycotic infections

- In a systematic review and meta-analysis of 45 placebo controlled studies (11,232) and 13 active comparator studies (5,175) they reported the following odds ratios:
  - UTI (29 studies)
    - 1.34 (1.03 to 1.74) vs placebo
    - 1.42 (1.06 to 1.90) active comparator
  - Mycotic infection (28 studies)
    - 3.50 (2.46 to 4.99) vs placebo
    - 5.06 (3.44 to 7.45) active comparator

Ann Intern Med. 2013;159:262-274.