Sodium glucose co-transporter 2 (SGLT2) inhibitors: Good or Bad?

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Outlines

- History of development of SGLT2 inhibitors.
- Available SGLT2 inhibitors.
- FDA warnings regarding SGLT2 inhibitors.
- Benefits associated with SGLT2 inhibitors.
- Risks associated with SGLT2 inhibitors.
- Target patients for SGLT2 inhibitors.

History

- Renal glucose reabsorption kinetics were demonstrated in the late 1930s.
- In the kidney, the filtered glucose is reabsorbed again in the proximal tubules via SGLT1 (10%) and SGLT2 (90%).
- Hyperglycemia stimulates proximal tubular growth and SGLT2 expression.
- Inhibition of SGLT2 induces glucosuria and lowers blood glucose levels.

- Phlorizin (isolated from the bark of apple trees) is the first natural substance with SGLT inhibitory activity.
- It inhibits both human SGLT1 and SGLT2.
- However, it is inappropriate for development as an anti-hyperglycemic due to:

1. Inhibits both SGLT1 & SGLT2 with low therapeutic selectivity.
2. The inhibition of SGLT1 can cause several GIT side effects.
3. Its metabolites inhibits (GLUT1), obstructing tissue glucose uptake.

- In 2008, dapagliflozin (1200-fold higher on SGLT2 Vs SGLT1) was developed. It was approved in Europe in 2012 then by FDA in 2013.

Available drugs

1. Canagliflozin (Invokana®)
2. Dapagliflozin (Farxiga®)
3. Empagliflozin (Jardiance®)

4. Others (mainly in Japan)

5. Four combination drugs: canagliflozin/metformin (Invokamet®), dapagliflozin/metformin (Xigduo XR®), empagliflozin/metformin (Synjardy®) and empagliflozin/linagliptin (Glyxambi®).

Annual sale

1. Canagliflozin:

- Jumped from $586 million in 2014 to $1.31 billion in 2015
- Added only $100 million in 2016 then 10% decline in 2017 due to lower prices.

2. Dapagliflozin:

- $1.4 billion in 2017 and expected to reach $2.7 billion by 2023.

3. Empagliflozin:

- Earned another FDA approval in 2016 for reducing cardiovascular death in adults with type 2 diabetes.
- $1.1 billion and expected to be reach $3.5 billion in 2024.

Information on SGLT2 Inhibitors

- FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes
  8/29/2018
- FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)
  5/16/2017
- FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)
  6/14/2016
- FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate
  5-18-2016
- FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections
  12-4-2015
- FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density
  9-10-2015

Benefits associated with SGLT2 inhibitors:

- Weight reduction (about 2 kg).

- Renal benefits:

1. Reducing albuminuria and the progressive decline in renal function (in comparison to SU, patients with established nephropathy, in combination with RAS blocker).

Reduction of albuminuria is due to hemodynamic, metabolic, BP lowering effects. In addition, reduction of cortical O2 consumption and getting benefits of the good arm of RAS.

2. It also reduce O2 consumption in the cortex.
3. Fibrosis, histopathology, inflammation, cr clearance & kidney injury markers: little effect of any, only with high doses of dapagliflozin.

- Cardiovascular benefits:

1. Mild reduction of blood pressure (5/2)
2. Mild improvement of lipid profile.
3. Reducing congestive heart failure and reduce hospitalization and mortality from congestive heart failure.

The NEW ENGLAND JOURNAL of MEDICINE

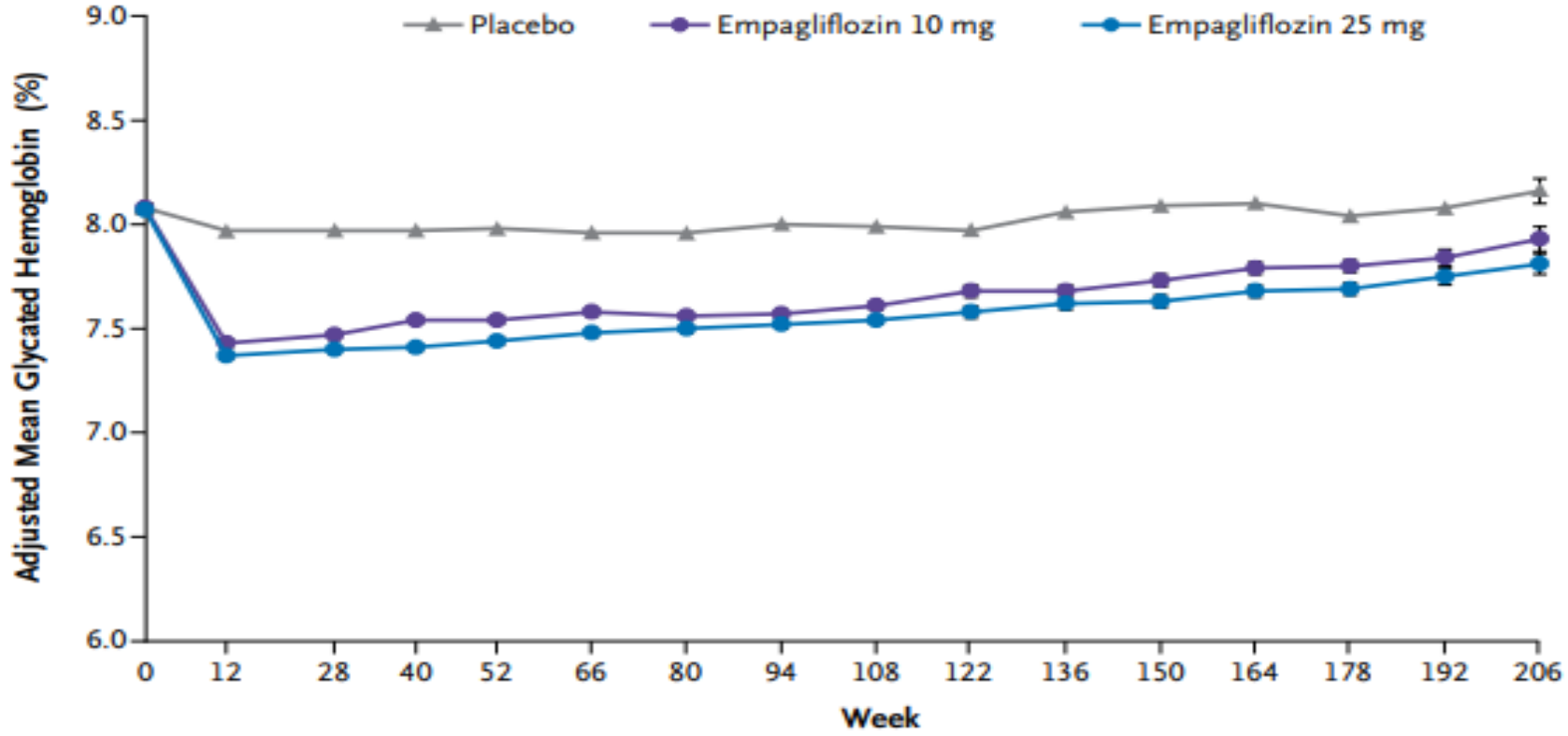
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001



No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Figure 3. Glycated Hemoglobin Levels.

Shown are mean (±SE) glycated hemoglobin levels in the three study groups, as calculated with the use of a repeated-measures analysis as a mixed model of all data for patients who received at least one dose of a study drug and had a baseline measurement. The model included baseline glycated hemoglobin as a linear covariate, with baseline estimated glomerular filtration rate, geographic region, body-mass index, the last week a patient could have had a glycated hemoglobin measurement, study group, visit, visit according to treatment interaction, and baseline glycated hemoglobin according to visit interaction as fixed effects.

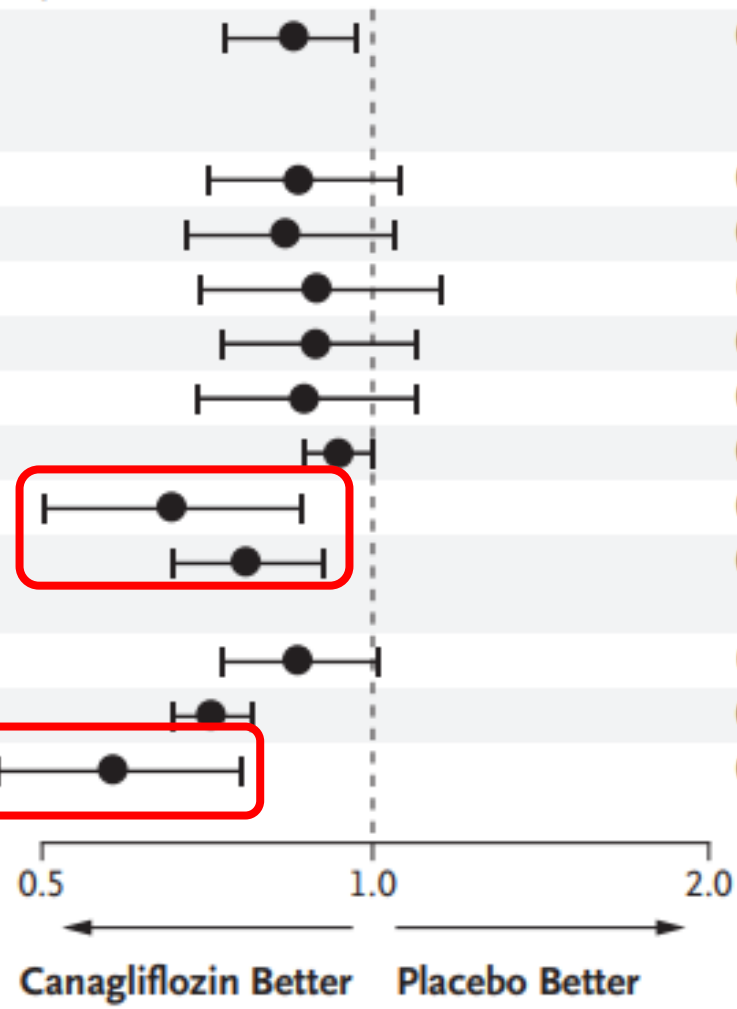
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

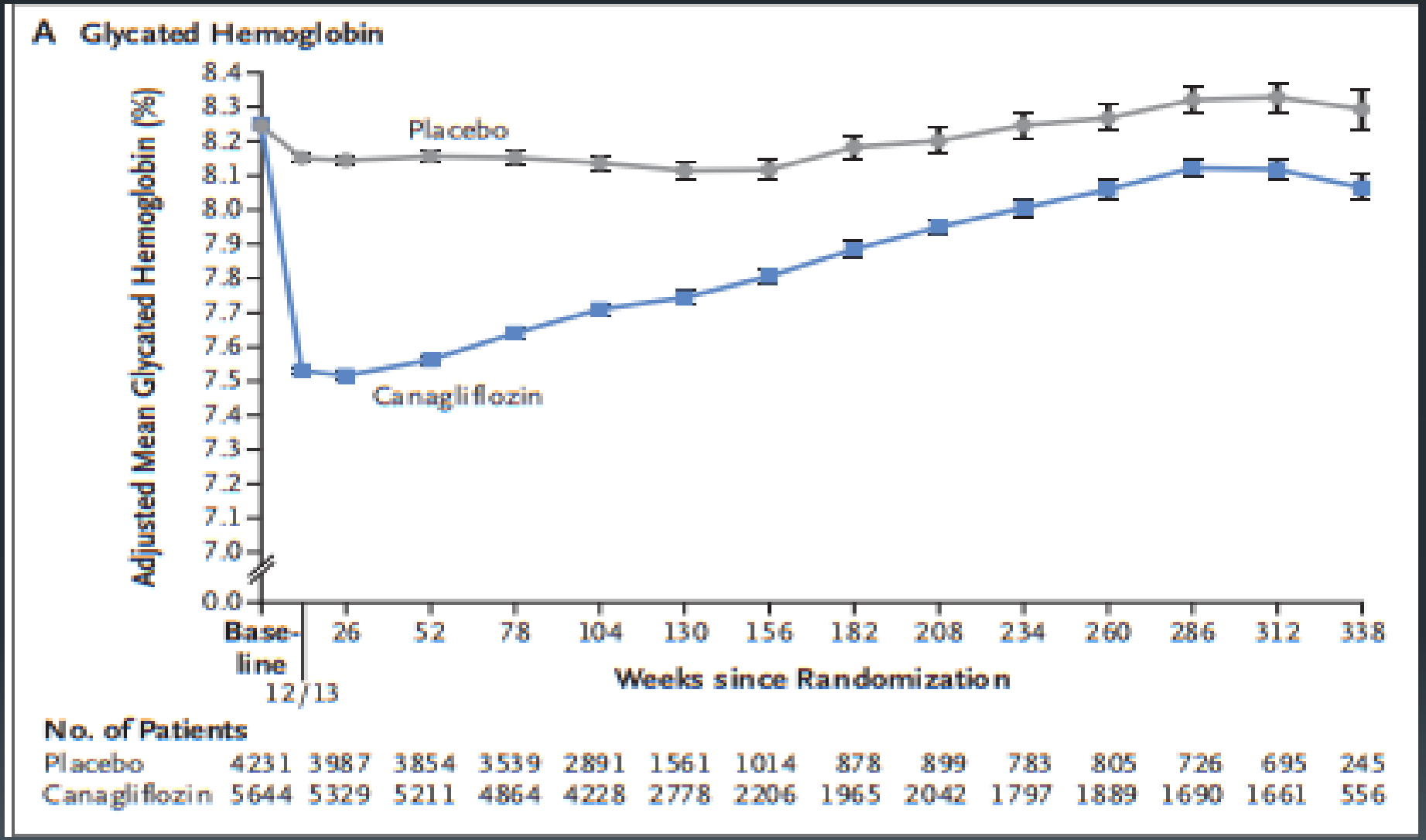
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



On the other side, there is increased amputation, fractures, and genital infections


A Glycated Hemoglobin
Adjusted Mean Glycated Hemoglobin (%)
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
0.0
Placebo
Canagliflozin
Base-line
12/13
26
52
78
104
130
156
182
208
234
260
286
312
338
Weeks since Randomization
No. of Patients
Placebo 4231 3987 3854 3539 2891 1561 1014 878 899 783 805 726 695 245
Canagliflozin 5644 5329 5211 4864 4228 2778 2206 1965 2042 1797 1889 1690 1661 556

Risks associated with SGLT2 inhibitors

1. Diabetic ketoacidosis (DKA)
2. Kidney adverse effects
3. Genital and urinary tract infection
4. Cancer risk
5. Foot and toe amputation
6. Bone fracture risk

Diabetic ketoacidosis (DKA)

- SGLT2inhibitors are associated with DKA, and this association is not limited to any particular demographic or comorbid sub population.
- Further increase in risk when the drug is combined with DPP4 inhibitors.
- SGLT2 inhibitors deprive cells from glucose.
- SGLT2 inhibitors decrease the ketone excretion in urine and hence, lead to ketoacidosis.
- Euglycemic DKA.

Kidney adverse effects (potential)

1. Medullary hypoxia.
2. Uricosuric: leading to crystal deposition and renal damage secondary to inflammation and oxidative stress.
3. Increase accumulation of fructose, sorbitol and increasing gluconeogenesis leading to tubular injury and inflammation (2018)
4. Hyperkalemia.
5. Activation of RAS under certain situation.

Genital and urinary tract infection

- SGLT2 inhibitors are accompanied with the increased risk of urinary tract infection (attributed to glucosuria).
- SGLT2 inhibitors also linked to the increased incidence of sever genital mycotic infections.
- Patients having previous occurrence of genital mycotic infection are at higher risk.
- Latest FDA warning (2018).

Cancer risk

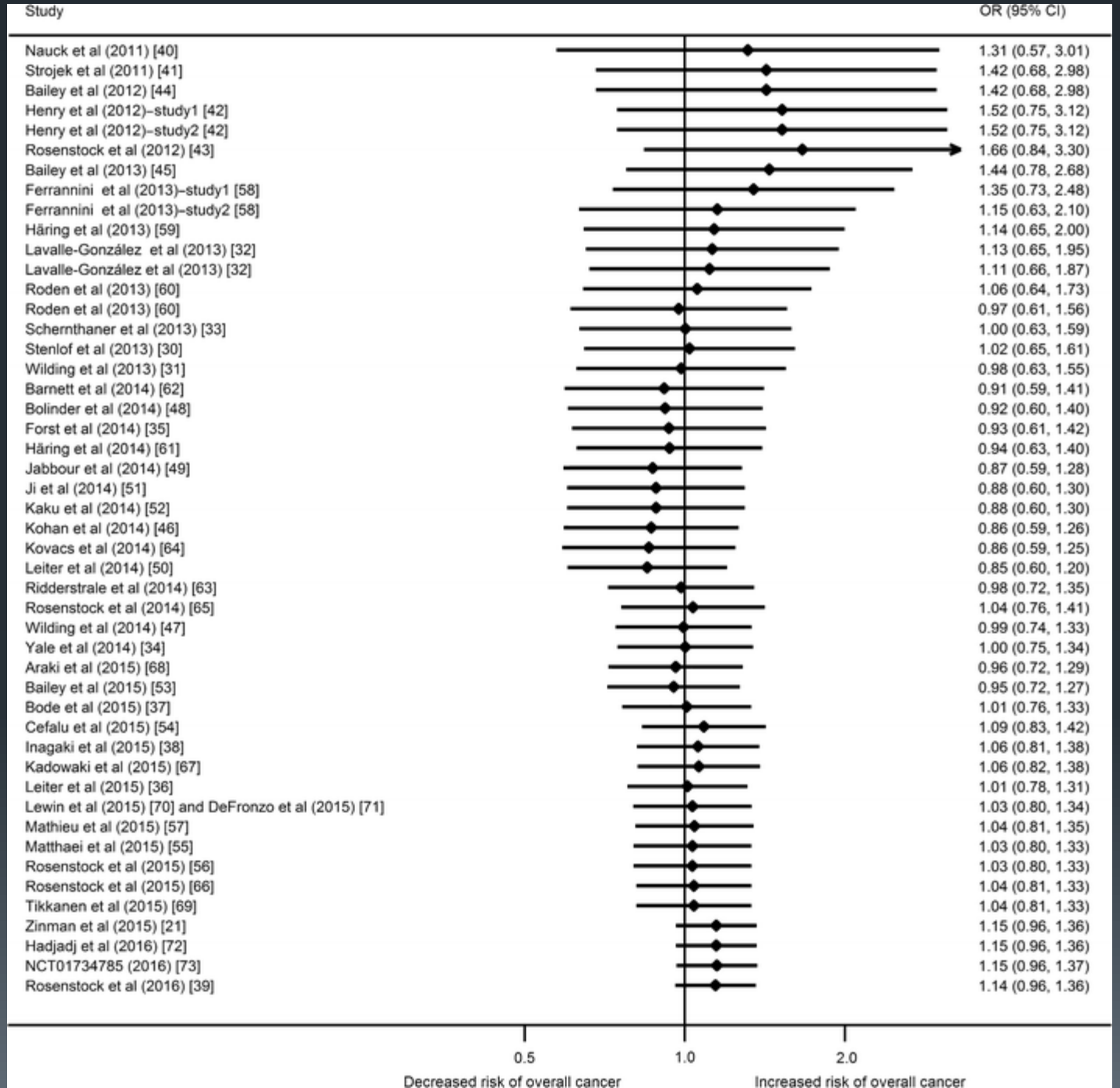
- Obesity and diabetes, by themselves, are risk factor for cancer.
- Experimentally:

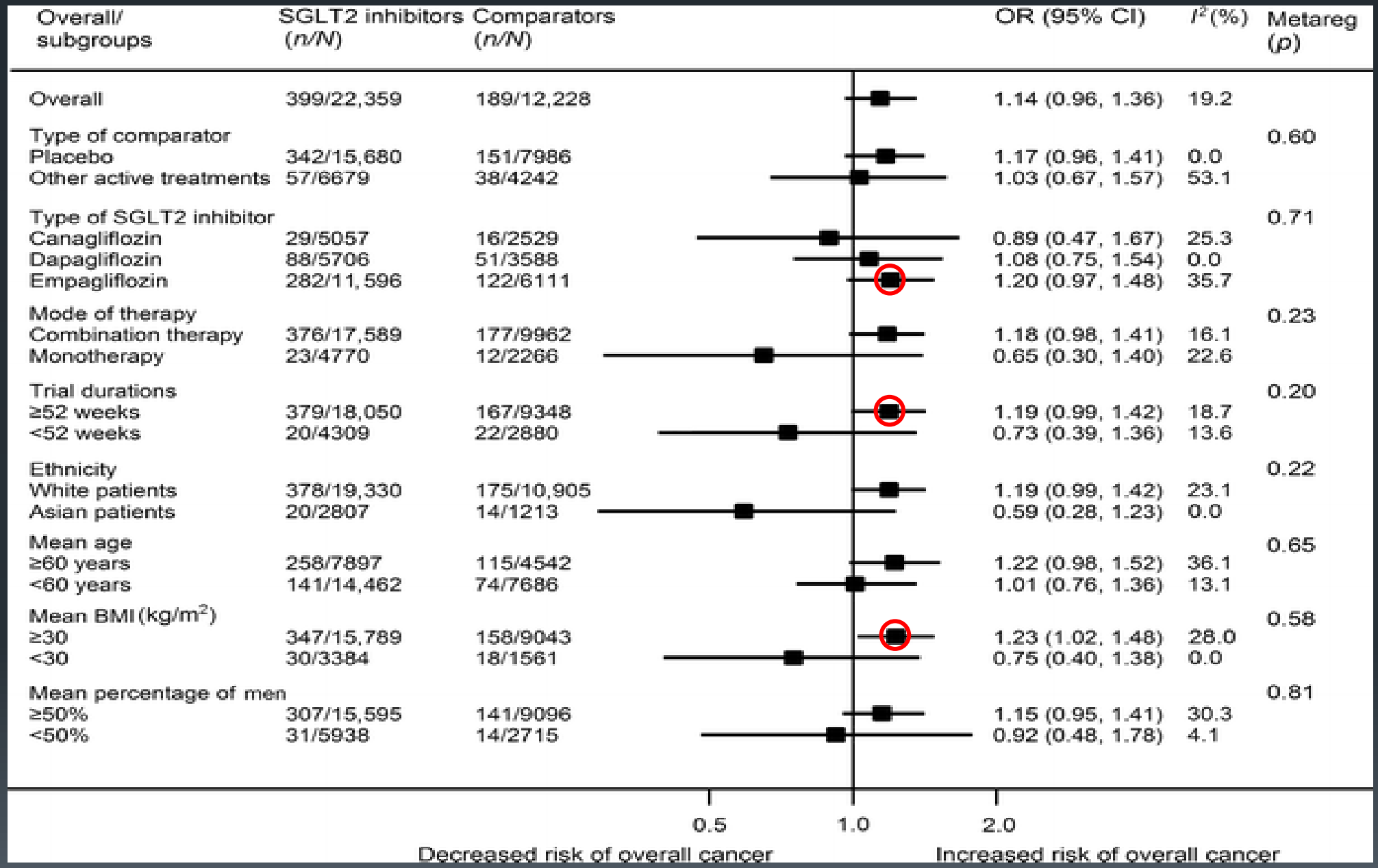
1. High doses of dapagliflozin for up to 2 years found no increase tumor incidence.
2. Canagliflozin gave variable results in experimental studies (carcinogenic mechanisms not applicable to human).
3. SGLT2 knockout mice did not show increased hyperplasia or neoplasia in the urinary bladder mucosa, urogenital tract or kidney.

- Clinically:

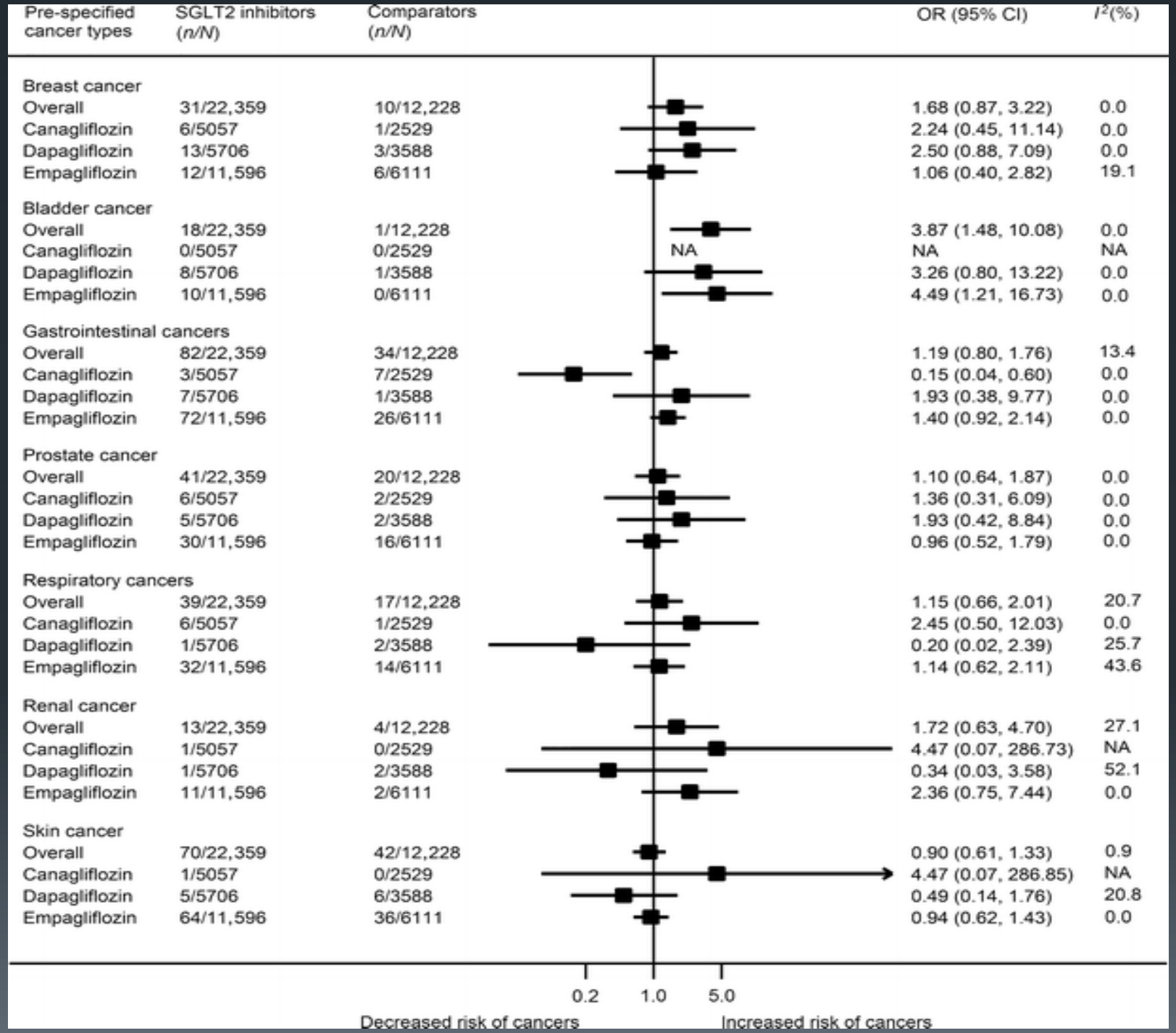
1. The first report of cancer risk was in 2011. Dapagliflozin was associated with higher incidents of male bladder cancer and female breast cancer.
2. Clinical trials on empagliflozin reported an increase in the risk of bladder cancer.
3. On the contrary, canagliflozin did not increase the overall incidence of bladder, breast and renal cancers in a pooled analysis of several clinical trials.

It seems that cancer risk is not “class effect” of SGLT2 inhibitors.


Study
OR (95% CI)
Nauck et al (2011) [40] 1.31 (0.57, 3.01)
Strojek et al (2011) [41] 1.42 (0.68, 2.98)
Bailey et al (2012) [44] 1.42 (0.68, 2.98)
Henry et al (2012)–study1 [42] 1.52 (0.75, 3.12)
Henry et al (2012)–study2 [42] 1.52 (0.75, 3.12)
Rosenstock et al (2012) [43] 1.66 (0.84, 3.30)
Bailey et al (2013) [45] 1.44 (0.78, 2.68)
Ferrannini et al (2013)–study1 [58] 1.35 (0.73, 2.48)
Ferrannini et al (2013)–study2 [58] 1.15 (0.63, 2.10)
Häring et al (2013) [59] 1.14 (0.65, 2.00)
Lavalle-González et al (2013) [32] 1.13 (0.65, 1.95)
Lavalle-González et al (2013) [32] 1.11 (0.66, 1.87)
Roden et al (2013) [60] 1.06 (0.64, 1.73)
Roden et al (2013) [60] 0.97 (0.61, 1.56)
Schernthaner et al (2013) [33] 1.00 (0.63, 1.59)
Stenlof et al (2013) [30] 1.02 (0.65, 1.61)
Wilding et al (2013) [31] 0.98 (0.63, 1.55)
Barnett et al (2014) [62] 0.91 (0.59, 1.41)
Bolinder et al (2014) [48] 0.92 (0.60, 1.40)
Forst et al (2014) [35] 0.93 (0.61, 1.42)
Häring et al (2014) [61] 0.94 (0.63, 1.40)
Jabbour et al (2014) [49] 0.87 (0.59, 1.28)
Ji et al (2014) [51] 0.88 (0.60, 1.30)
Kaku et al (2014) [52] 0.88 (0.60, 1.30)
Kohan et al (2014) [46] 0.86 (0.59, 1.26)
Kovacs et al (2014) [64] 0.86 (0.59, 1.25)
Leiter et al (2014) [50] 0.85 (0.60, 1.20)
Ridderstrale et al (2014) [63] 0.98 (0.72, 1.35)
Rosenstock et al (2014) [65] 1.04 (0.76, 1.41)
Wilding et al (2014) [47] 0.99 (0.74, 1.33)
Yale et al (2014) [34] 1.00 (0.75, 1.34)
Araki et al (2015) [68] 0.96 (0.72, 1.29)
Bailey et al (2015) [53] 0.95 (0.72, 1.27)
Bode et al (2015) [37] 1.01 (0.76, 1.33)
Cefalu et al (2015) [54] 1.09 (0.83, 1.42)
Inagaki et al (2015) [38] 1.06 (0.81, 1.38)
Kadowaki et al (2015) [67] 1.06 (0.82, 1.38)
Leiter et al (2015) [36] 1.01 (0.78, 1.31)
Lewin et al (2015) [70] and DeFronzo et al (2015) [71] 1.03 (0.80, 1.34)
Mathieu et al (2015) [57] 1.04 (0.81, 1.35)
Matthaei et al (2015) [55] 1.03 (0.80, 1.33)
Rosenstock et al (2015) [56] 1.03 (0.80, 1.33)
Rosenstock et al (2015) [66] 1.04 (0.81, 1.33)
Tikkanen et al (2015) [69] 1.04 (0.81, 1.33)
Zinman et al (2015) [21] 1.15 (0.96, 1.36)
Hadjadj et al (2016) [72] 1.15 (0.96, 1.36)
NCT01734785 (2016) [73] 1.15 (0.96, 1.37)
Rosenstock et al (2016) [39] 1.14 (0.96, 1.36)
0.5
1.0
2.0
Decreased risk of overall cancer
Increased risk of overall cancer



Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia. 2017;60(10): 1862-72.


Pre-specified cancer types
SGLT2 inhibitors (n/N)
Comparators (n/N)
OR (95% CI)
I²(%)
Breast cancer
Overall 31/22,359 10/12,228 1.68 (0.87, 3.22) 0.0
Canagliflozin 6/5057 1/2529 2.24 (0.45, 11.14) 0.0
Dapagliflozin 13/5706 3/3588 2.50 (0.88, 7.09) 0.0
Empagliflozin 12/11,596 6/6111 1.06 (0.40, 2.82) 19.1
Bladder cancer
Overall 18/22,359 1/12,228 3.87 (1.48, 10.08) 0.0
Canagliflozin 0/5057 0/2529 NA NA NA
Dapagliflozin 8/5706 1/3588 3.26 (0.80, 13.22) 0.0
Empagliflozin 10/11,596 0/6111 4.49 (1.21, 16.73) 0.0
Gastrointestinal cancers
Overall 82/22,359 34/12,228 1.19 (0.80, 1.76) 13.4
Canagliflozin 3/5057 7/2529 0.15 (0.04, 0.60) 0.0
Dapagliflozin 7/5706 1/3588 1.93 (0.38, 9.77) 0.0
Empagliflozin 72/11,596 26/6111 1.40 (0.92, 2.14) 0.0
Prostate cancer
Overall 41/22,359 20/12,228 1.10 (0.64, 1.87) 0.0
Canagliflozin 6/5057 2/2529 1.36 (0.31, 6.09) 0.0
Dapagliflozin 5/5706 2/3588 1.93 (0.42, 8.84) 0.0
Empagliflozin 30/11,596 16/6111 0.96 (0.52, 1.79) 0.0
Respiratory cancers
Overall 39/22,359 17/12,228 1.15 (0.66, 2.01) 20.7
Canagliflozin 6/5057 1/2529 2.45 (0.50, 12.03) 0.0
Dapagliflozin 1/5706 2/3588 0.20 (0.02, 2.39) 25.7
Empagliflozin 32/11,596 14/6111 1.14 (0.62, 2.11) 43.6
Renal cancer
Overall 13/22,359 4/12,228 1.72 (0.63, 4.70) 27.1
Canagliflozin 1/5057 0/2529 4.47 (0.07, 286.73) NA
Dapagliflozin 1/5706 2/3588 0.34 (0.03, 3.58) 52.1
Empagliflozin 11/11,596 2/6111 2.36 (0.75, 7.44) 0.0
Skin cancer
Overall 70/22,359 42/12,228 0.90 (0.61, 1.33) 0.9
Canagliflozin 1/5057 0/2529 4.47 (0.07, 286.85) NA
Dapagliflozin 5/5706 6/3588 0.49 (0.14, 1.76) 20.8
Empagliflozin 64/11,596 36/6111 0.94 (0.62, 1.43) 0.0
0.2
1.0
5.0
Decreased risk of cancers
Increased risk of cancers

It was possible to support 6-year studies to come up with cardiovascular benefits of SGLT2 inhibitors but the same companies supported one-year follow up to evaluate cancer risk…..

Foot and toe amputation

- On 2017, FDA in its drug safety communication indicates the increased risk of leg and foot amputation with the use of canagliflozin in type 2 DM patients on the basis of two large clinical trials.

- These trials showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo.

Bone fracture risk

- SGLT2 inhibitor may elevates the risk of bone fracture and decreases the total hip bone mineral density.
- May be secondary to increase phosphate absorption.

- One meta-analysis analyzed various randomized controlled trials from various sources to analyze bone fracture risk of SGLT2 inhibitors and concluded that data did not support the bone fracture risk but future monitoring for the same should be done.

SGLT2 inhibitors are not just another medication for DM……

- Patient must have:
- Type 2 DM AND ALL of the following:

1. Inadequate treatment response, intolerance, or contraindication to metformin AND ONE of the following (alpha-glucosidase inhibitor, DPP-4, TZD, GLP-1 R agonist)
2. Patient must have a HgbA1C greater than 7.0%
3. Patient has an eGFR ≥ 60 mL/min/1.73m² OR ≥ 45 mL/min/1.73m² (according to selected drug and dose)
4. NO dual therapy with other SGLT2 inhibitors.

Take-home message

- We are midway in discovering the reality of SGLT2 inhibitors regarding their risk/benefits and full safety profile.
- Until that, the use of SGLT2 inhibitors should be limited to their specific indication.
- After initiation of metformin, consider GLP-1RAs in patients with CVD of atherosclerotic origin and SGLT2 inhibitors in patients with diabetes-related HF and/or CKD.

Thank you