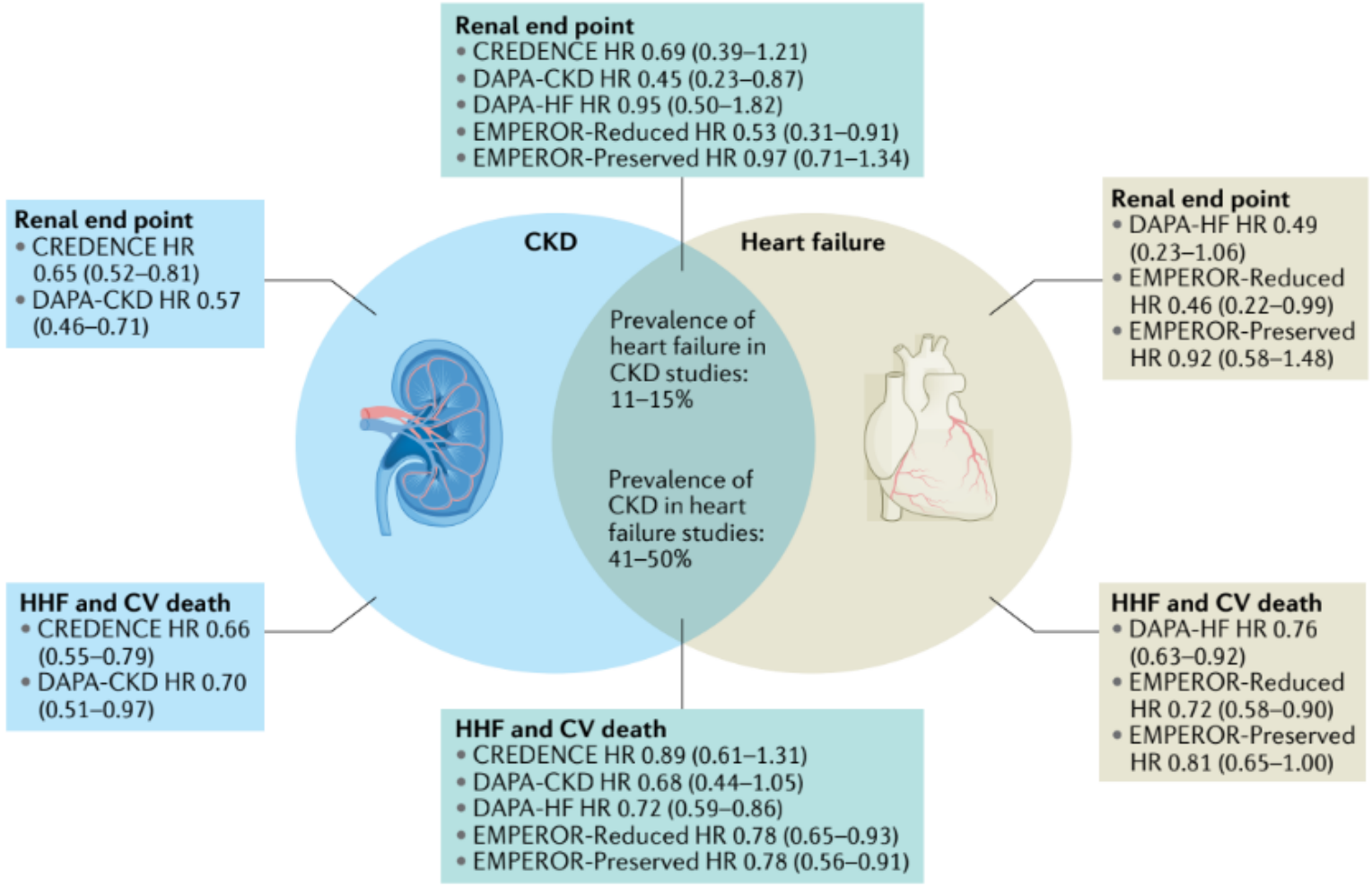
SGLT-2 inibitori: solo effetti positivi o potenziali rischi?

Riccardo Floreani

ASST dei Sette Laghi, Varese

Renal and cardiac positive outcomes associated with SGLT2-i use

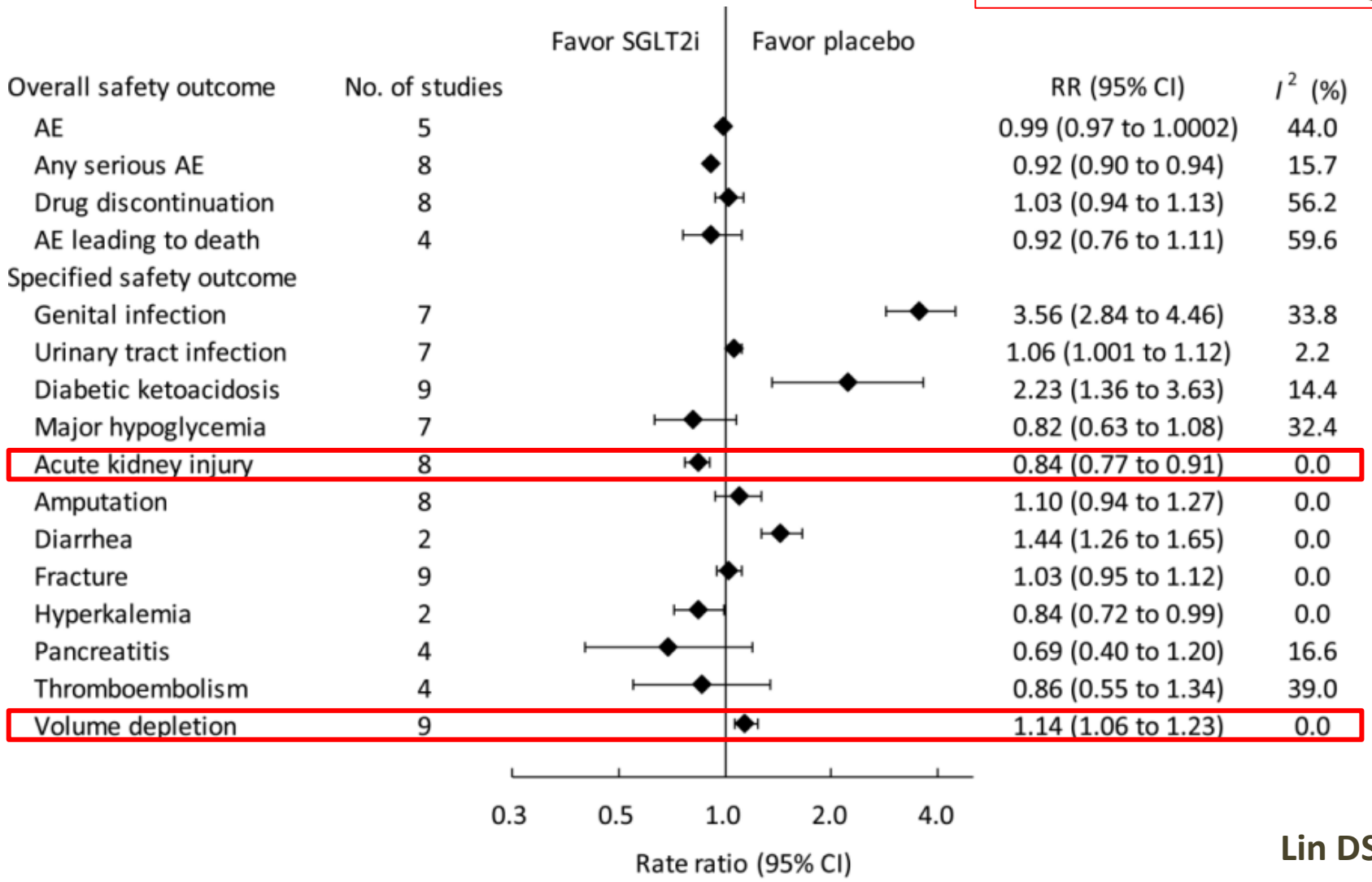


van der Aart-van der Beek A, Nat Rev Nephrol, 2022

- ACUTE KIDNEY INJURY
- VOLUME DEPLETION
- GENITAL INFECTIONS
- URINARY TRACT INFECTIONS
- DIABETIC KETOACIDOSIS
- LOWER LIMB AMPUTATIONS
- FRACTURES

ACUTE KIDNEY INJURY

Clinical Adverse Events Associated with Sodium–Glucose Cotransporter 2 Inhibitors: A Meta-Analysis Involving 10 Randomized Clinical Trials and 71 553 Individuals Get access >



Overall safety outcome	No. of studies	RR (95% CI)	I^2 (%)
AE	5	0.99 (0.97 to 1.0002)	44.0
Any serious AE	8	0.92 (0.90 to 0.94)	15.7
Drug discontinuation	8	1.03 (0.94 to 1.13)	56.2
AE leading to death	4	0.92 (0.76 to 1.11)	59.6
Specified safety outcome			
Genital infection	7	3.56 (2.84 to 4.46)	33.8
Urinary tract infection	7	1.06 (1.001 to 1.12)	2.2
Diabetic ketoacidosis	9	2.23 (1.36 to 3.63)	14.4
Major hypoglycemia	7	0.82 (0.63 to 1.08)	32.4
Acute kidney injury	8	0.84 (0.77 to 0.91)	0.0
Amputation	8	1.10 (0.94 to 1.27)	0.0
Diarrhea	2	1.44 (1.26 to 1.65)	0.0
Fracture	9	1.03 (0.95 to 1.12)	0.0
Hyperkalemia	2	0.84 (0.72 to 0.99)	0.0
Pancreatitis	4	0.69 (0.40 to 1.20)	16.6
Thromboembolism	4	0.86 (0.55 to 1.34)	39.0
Volume depletion	9	1.14 (1.06 to 1.23)	0.0

Lin DS, J Clin Endocrin Metabol, 2021

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

[06-14-2016]

On June 14, 2016, FDA strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (brand names Invokana, Invokamet) and dapagliflozin (brand names Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

Table 3 Absolute and relative reporting to FAERS of AKI events associated with SGLT2 inhibitors

SGLT2 inhibitor	Reporting period	Total reports	AKI reports[a]	Non-AKI reports	AKI reports (%)
Canagliflozin	Jan 2013–Sept 2016[b]	12,693	928	11,765	7.3
	Jan 2017–Jul 2019	9803	2063	7740	21.0
Dapagliflozin	Jan 2013–Sept 2016[b]	3651	177	3474	4.8
	Jan 2017–Jul 2019	2538	199	2339	7.8
Empagliflozin	Jan 2013–Sept 2016[b]	2652	124	2528	4.7
	Jan 2017–Jul 2019	6632	335	6297	5.1

AKI acute kidney injury, *FAERS* FDA Adverse Events Reporting System

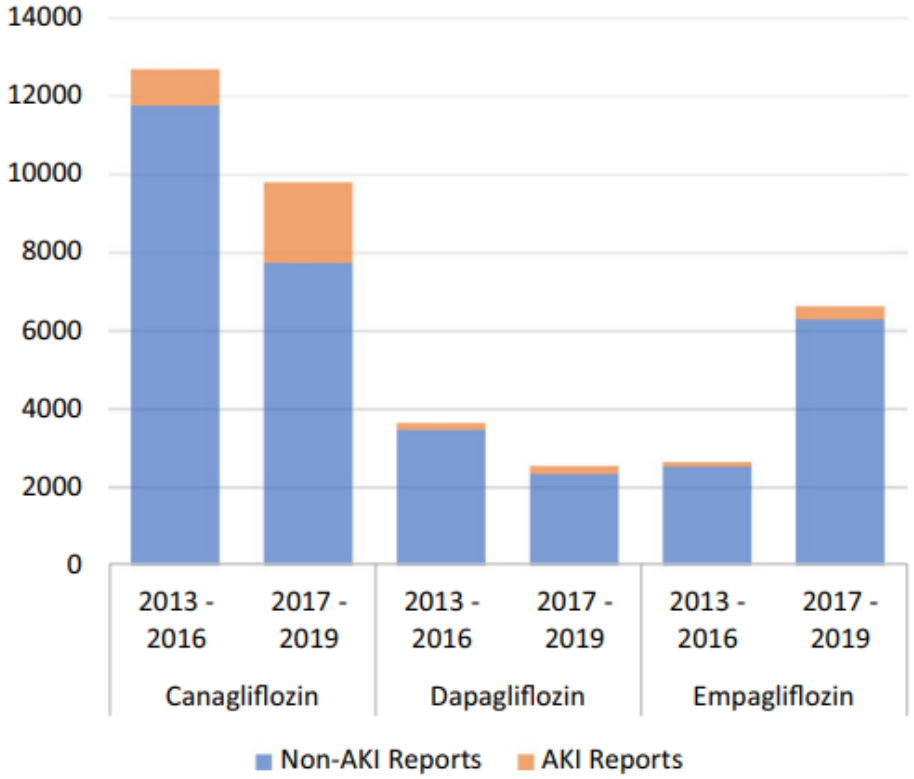


Fig. 2 Acute kidn in FAERS. Absolute of AKI with the SGL rt- ing System (FAER

Baker ML, J Neprology, 2020

SGLT2 inhibitor therapy in patients with type-2 diabetes mellitus: is acute kidney injury a concern?

Megan Leila Baker[1] · Mark Anthony Perazella[2,3]

Kidney protective factors

- Improved DM, BP control: Less diabetes- and BP- related injury
- Reduced TG gradient through TGF: reduced pressure-related injury
- Structural remodeling of glomerulus contributing to reduction in albuminuria

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- Reduced energy consumption by the proximal tubule's basolateral sodium potassium ATPase
- Induction of HIFs to promote resilience to hypoxemia, reduction of oxidative stress

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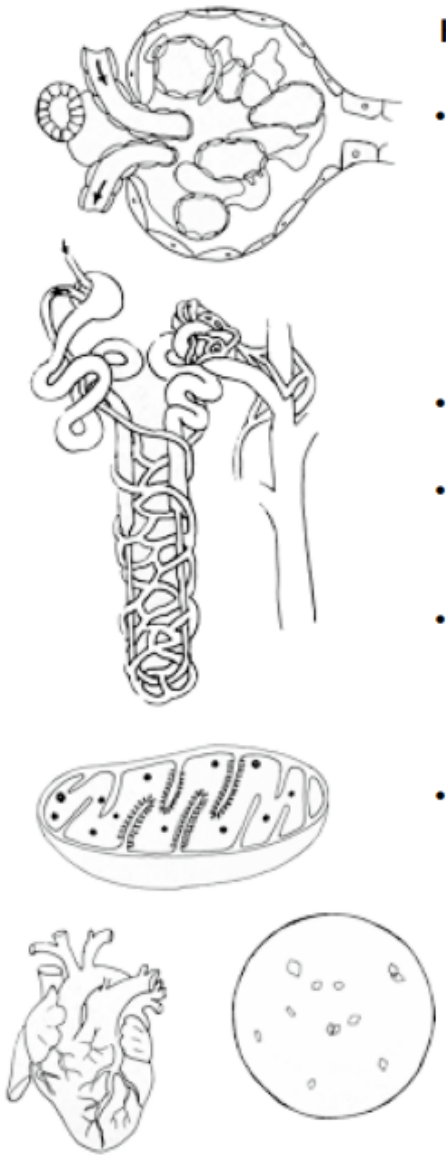
- Increased mitochondrial efficiency, ATP generation through shift toward ketogenesis
- Protective modification of tubular apoptotic signaling

- Improved regulation of neurohormonal systems impacting cardiorenal interactions



Kidney injury promoting factors

- Increased pre-renal physiology via:
  1) Reduced BP, kidney perfusion
  2) TGF-mediated reduction in afferent vasodilation
  3) Diuretic effect of volume depletion

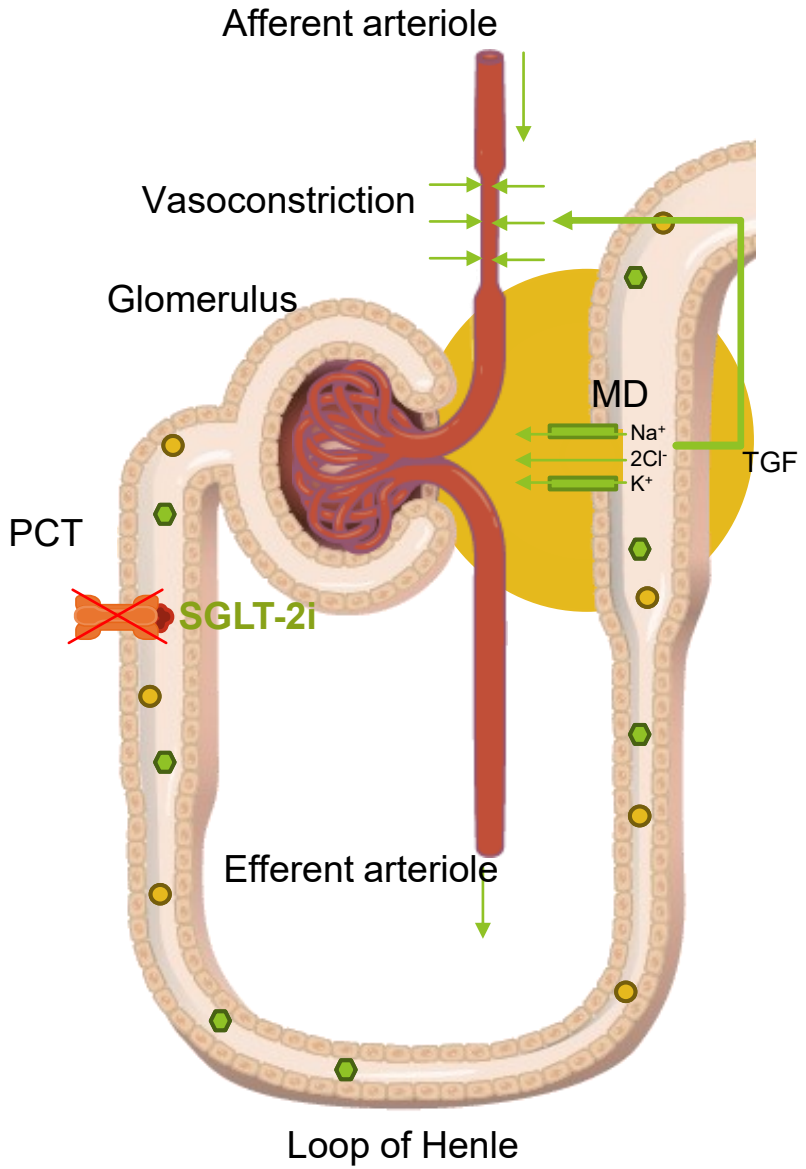
- Reduction in medullary perfusion from reduced afferent vasodilation
- Increase in compensatory energy expenditure in medulla by S3 segment of PCT and mTAL
- Possible structural remodeling in PCT from chronic hyperglycosuria, Armanni-Ebstein-like lesions

---

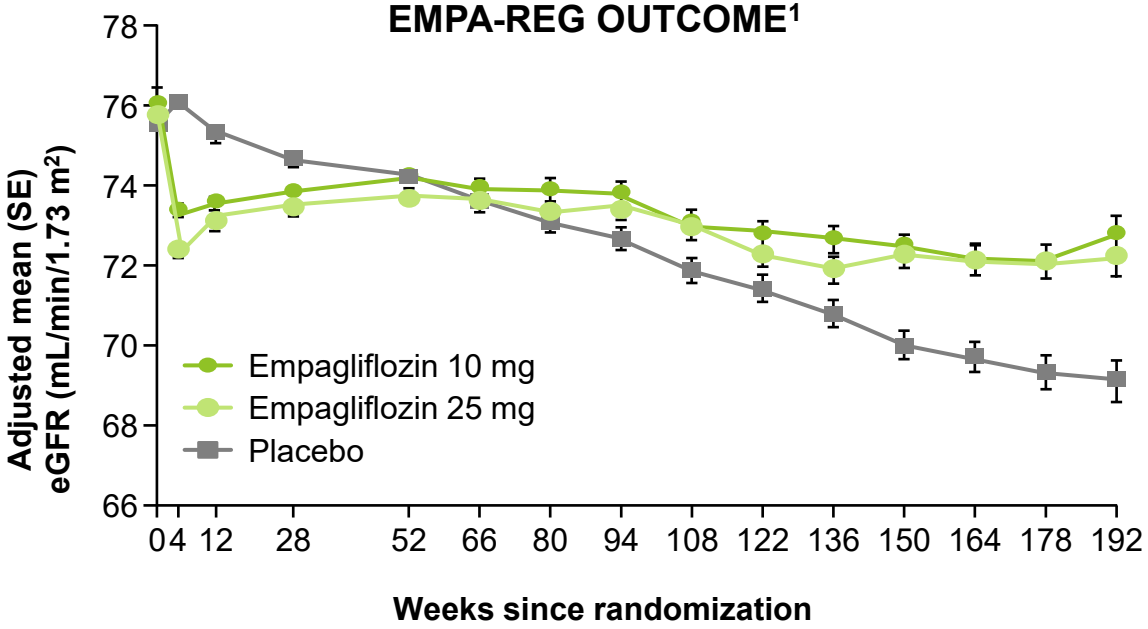
- Uricosuria from glucose delivery to GLUT-9b in PCT and osmolarity-induced sorbitol generation:
  1) Crystal formation: activation of TLRs, inflammation
  2) Epithelial to mesenchymal transition, MAPK activation, chemokine release, oxidative stress

Baker ML, J Neprology, 2020

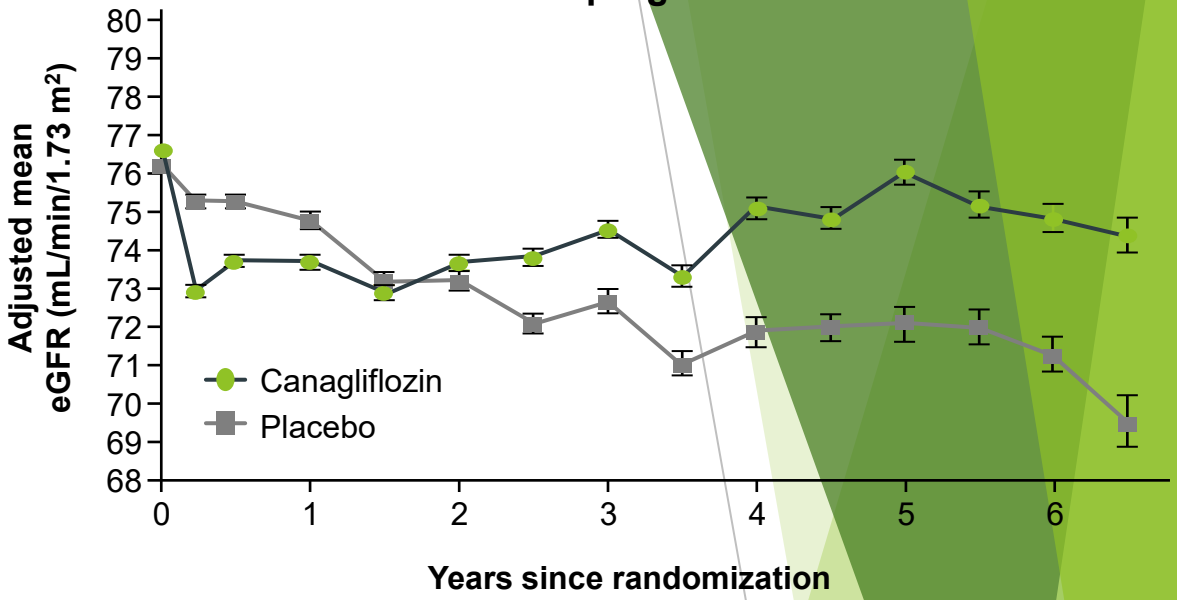
Tubulo-glomerular feedback restoration



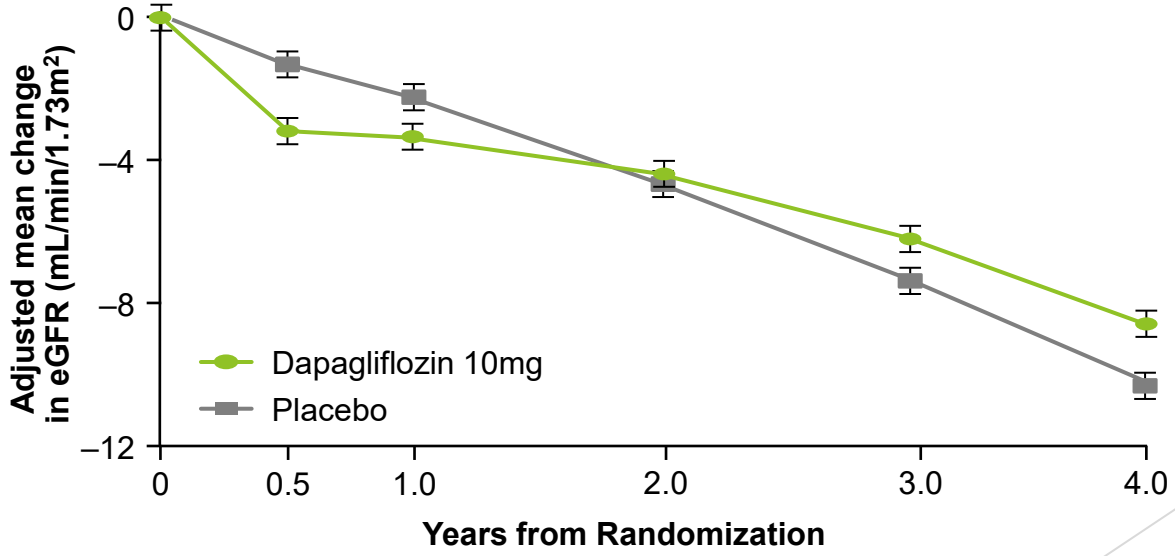
EMPA-REG OUTCOME[1]



CANVAS program[3]



DECLARE-TIMI 58 trial[2]

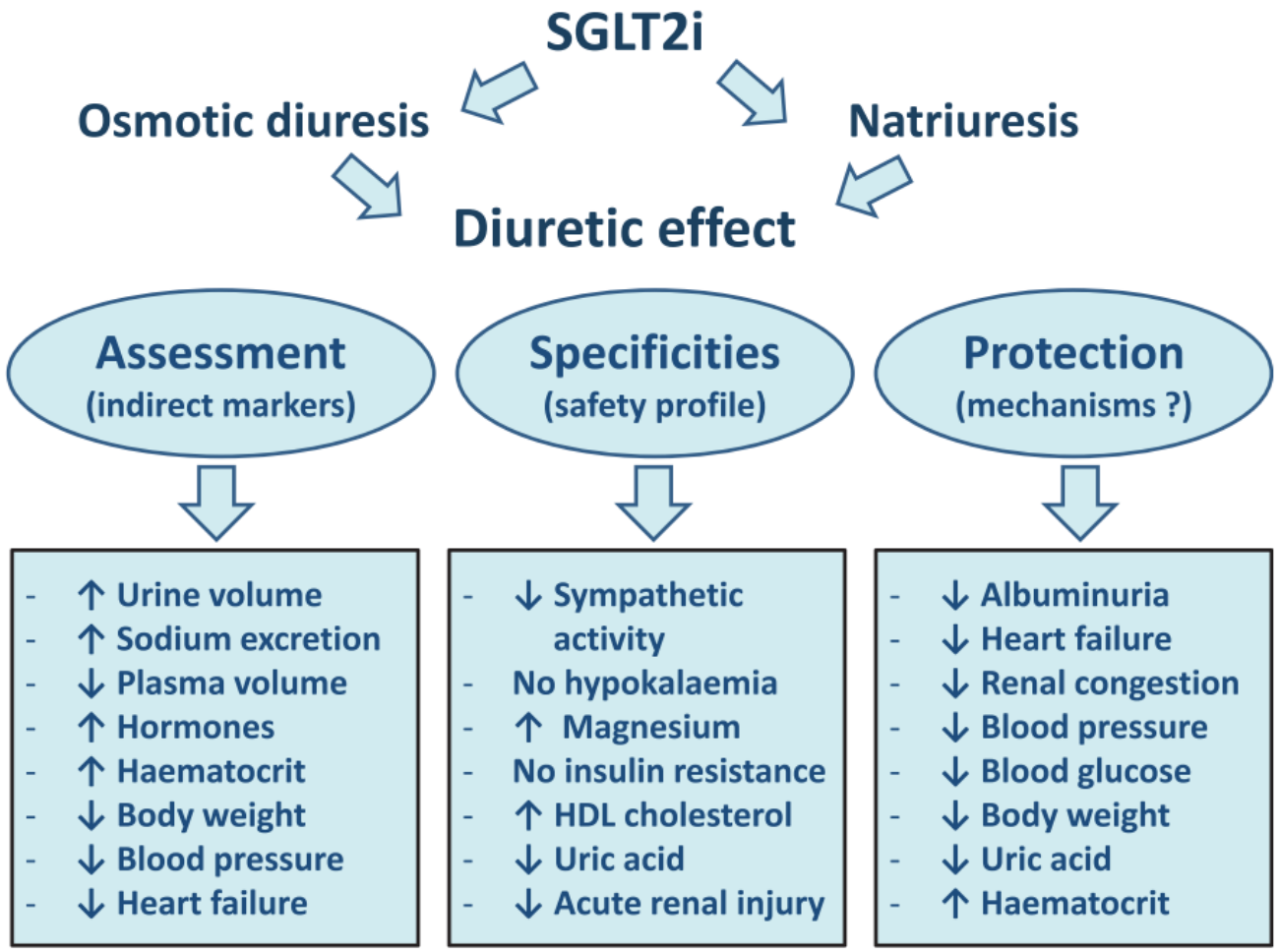


1. Wanner C, NEJM, 2016; 2. Mosenzon O, Lancet Diabetes Endocrinol 2019; 3. Perkovic V, Lancet Diabetes Endocrinol 2018

VOLUME DEPLETION

The diuretic effects of SGLT2 inhibitors: A comprehensive review of their specificities and their role in renal protection

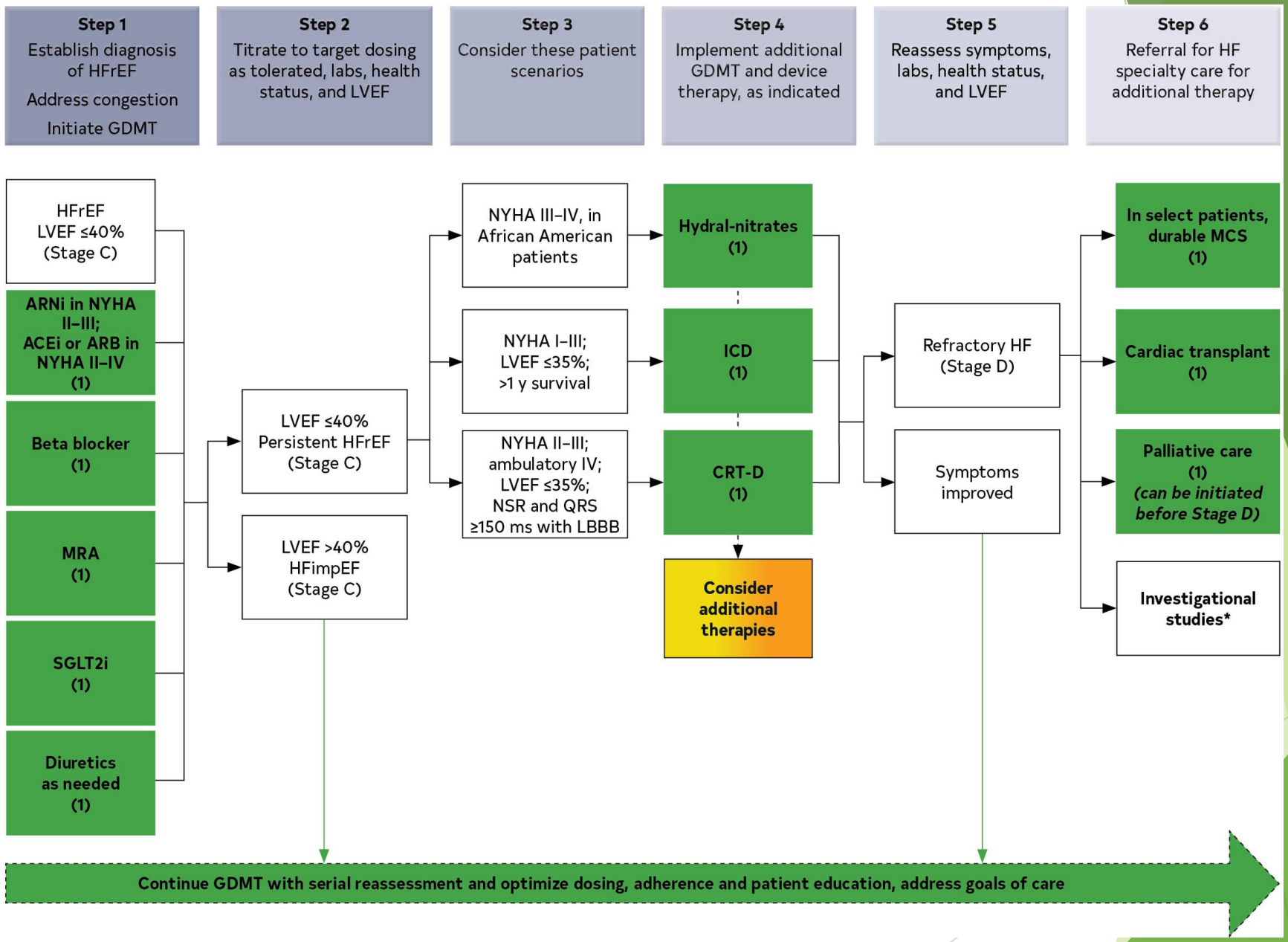
Pierre Delanaye[a,b,1], Andre J. Scheen[c,d,2,*]



Delanaye P., Diabetes and Metabolism, 2021

- The at least neutral (and apparently protective) effect of SGLT2is regarding AKI can be explained by several mechanisms which are not in contradiction with some diuretic effect. The diuretic effect of SGLT2is without an added risk of AKI could be explained by
  - the concomitant vasodilation effect of SGLT2is on the post-glomerular efferent arteriole
  - the diuretic effect predominantly focused on the extracellular volume
  - a major effect of SGLT2is on de novo heart failure, which is known to be associated with AKI episodes (cardio-renal syndrome)

Delanaye P., Diabetes and Metabolism, 2021



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

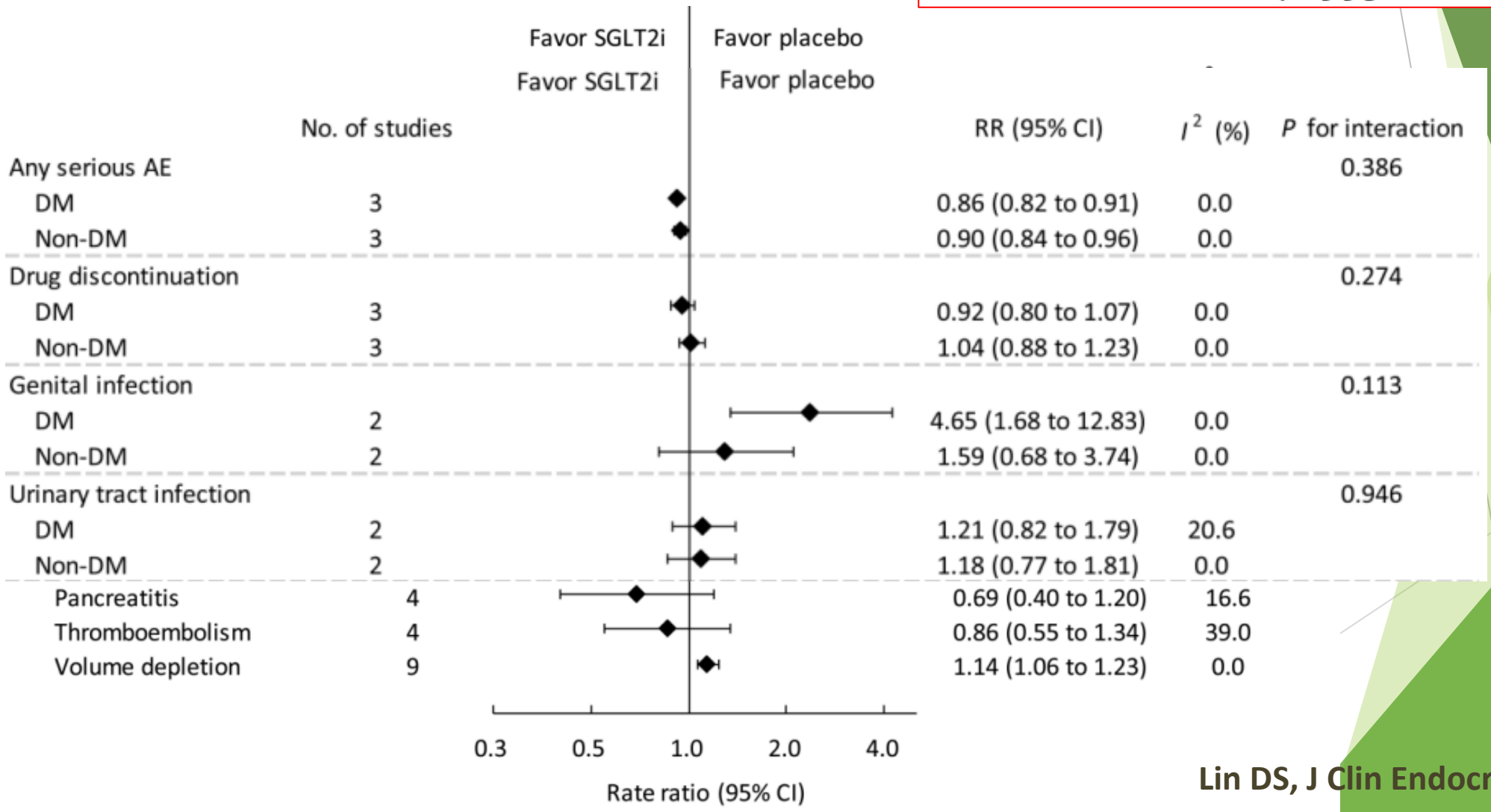
Recommendations for initiation and monitoring of SGLT2 inhibitor therapy (1)

- Optimize volume status and avoid hypotension prior to SGLT2 inhibitor initiation
- Concurrent RAAS inhibitor and/or diuretic use are not contraindications to SGLT2 inhibitor initiation, however, caution should be taken to minimize other risk factors for AKI prior to SGLT2 inhibitor initiation
- Cautious initiation of SGLT2 inhibitors in patients exposed to NSAIDs or other nephrotoxic agents
- Close monitoring should be undertaken in patients with stage 3b CKD and other risk factors for AKI (nephrotoxic drugs, contrast exposure, N/V, diarrhea, etc.) started on a SGLT2 inhibitor
- Employ a “sick day strategy” of holding SGLT2 inhibitors with acute illness, trauma, or major surgery when adequate fuid intake may be compromised or patients are otherwise prone to AKI

Baker ML, J Neprology, 2020

INFECTION

Clinical Adverse Events Associated with Sodium–Glucose Cotransporter 2 Inhibitors: A Meta-Analysis Involving 10 Randomized Clinical Trials and 71 553 Individuals Get access >



	No. of studies	RR (95% CI)	I^2 (%)	*P* for interaction
Any serious AE				0.386
DM	3	0.86 (0.82 to 0.91)	0.0	
Non-DM	3	0.90 (0.84 to 0.96)	0.0	
Drug discontinuation				0.274
DM	3	0.92 (0.80 to 1.07)	0.0	
Non-DM	3	1.04 (0.88 to 1.23)	0.0	
Genital infection				0.113
DM	2	4.65 (1.68 to 12.83)	0.0	
Non-DM	2	1.59 (0.68 to 3.74)	0.0	
Urinary tract infection				0.946
DM	2	1.21 (0.82 to 1.79)	20.6	
Non-DM	2	1.18 (0.77 to 1.81)	0.0	
Pancreatitis	4	0.69 (0.40 to 1.20)	16.6	
Thromboembolism	4	0.86 (0.55 to 1.34)	39.0	
Volume depletion	9	1.14 (1.06 to 1.23)	0.0	

Lin DS, J Clin Endocrin Metabol, 2021

Five comparative cohorts to assess the risk of genital tract -glucose cotransporter-2 etes mellitus

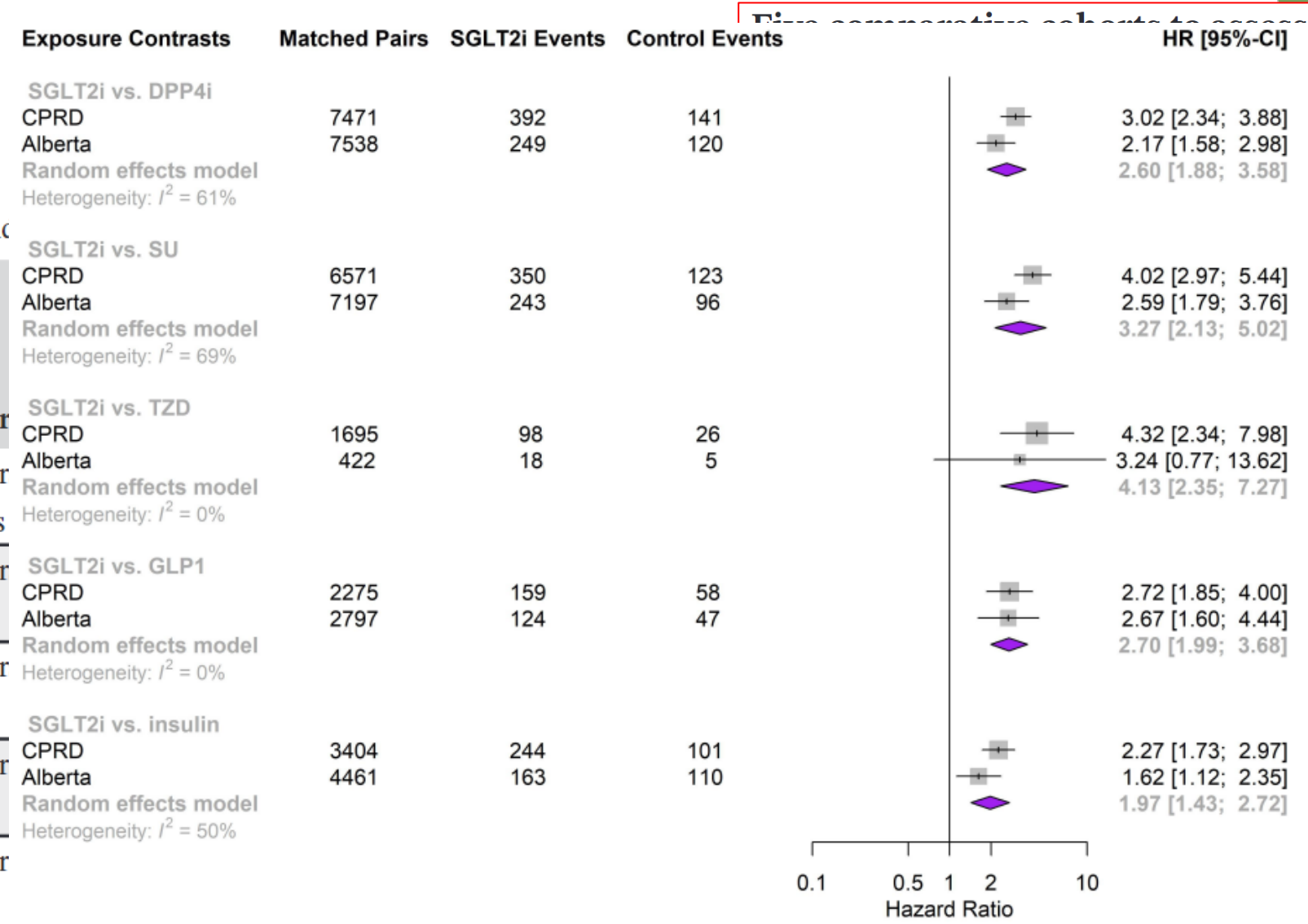


TABLE 2 Cruc

act infection

Exposure cohor	rt / imates / 5% CI
SGLT-2 inhibitor	2.27 – 39.37
DPP-4 inhibitors	1.21 – 15.70
SGLT-2 inhibitor	0.23 – 37.39
SU	.75 – 13.99
SGLT-2 inhibitor	3.95 – 35.96
TZD	.17 – 13.85
SGLT-2 inhibitor	1.90 – 43.80
GLP1-RA	2.02 – 20.47
SGLT-2 inhibitor	3.86 – 30.79
Insulin	4.13 – 18.09

FIGURE 3 Pooled hazard ratio for genital tract infections across databases, using matched Cox model with further adjustment for age, sex and previous use of other diabetes medications. Abbreviations: DPP4-i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones; GLP1, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; CI, confidence interval

Alkabbani W, Diabetic Medicine, 2022

Sodium glucose-linked transport protein 2 inhibitors: An overview of genitourinary and perioperative implications

Mohit Chandrashekar,[1] Stuart Philip,[2] Alexander Nesbitt,[2,3] Andre Joshi[2] and Marlon Perera[1,2,4,5]

- Genital (mycotic) infections associated with SGLT2-i use tend to be **mild to moderate** in nature and can be treated with standard antifungals. They include balanitis, vulvovaginal candidiasis, genital candidiasis, vulvovaginitis, vaginal thrush, bacterial vaginitis, vulvitis, and vulval abscess, balanitis, balanoposthitis, phimosis, paraphimosis and Fournier's gangrene
- **Glycosuria** resulting from diabetes likely provides a favorable substrate for growth of organisms, and this effect is further enhanced by the pharmacologic glycosuria induced by SGLT2 inhibitors
- **Risk factors** include poor genital hygiene, age, topical corticosteroid use, pregnancy, estrogen therapy, oral contraceptives, history of genital mycotic infections and (for men) to be uncircumcised.

Chandrashekar M, Int. J Urol, 2021

Recommendations for initiation and monitoring of SGLT2 inhibitor therapy (2)

- When choosing to commence a patient on SGLT2 inhibitors, a **careful history** of relevant risk factors should be obtained which includes a history of infections; however, the risk of potential mycotic infections should not necessarily exclude a patient from trialing therapy.
- Each patient should be given advice regarding **personal hygiene**, as studies have demonstrated that this leads to increased drug adherence and reduced risk of genital mycotic infections.
- **Fluid intake** should also be encouraged, as the production of dilute urine can help reduce the risk of infections, unless the patient has volume overload-related comorbidities.
- If the patient develops **recurrent genital infections**, then a decision to cease treatment is one that should be made together with the patient. Cessation of the drug is warranted in the event of **serious infections**.

Chandrashekar M, Int. J Urol, 2021

Fournier’s gangrene (FG)

- FG is a rare rapidly progressive necrotizing fasciitis of the perineum that typically requires surgical debridement and antibiotic treatment.
- In 2018, the Food and Drug Administration (FDA) issued a warning about the risk of FG with SGLT2 inhibitor treatment
- **Risk factors** for developing FG include medical factors such as diabetes and immune suppression, renal failure and liver failure, as well as lifestyle factors including smoking and alcohol consumption.
- **Large RCTs** have not demonstrated an increased risk of Fournier’s gangrene with SGLT2 inhibitor treatment. However, RCTs are not designed or powered to demonstrate or refute an increased risk of extremely rare events such as Fournier’s gangrene.

Chandrashekar M, Int. J Urol, 2021

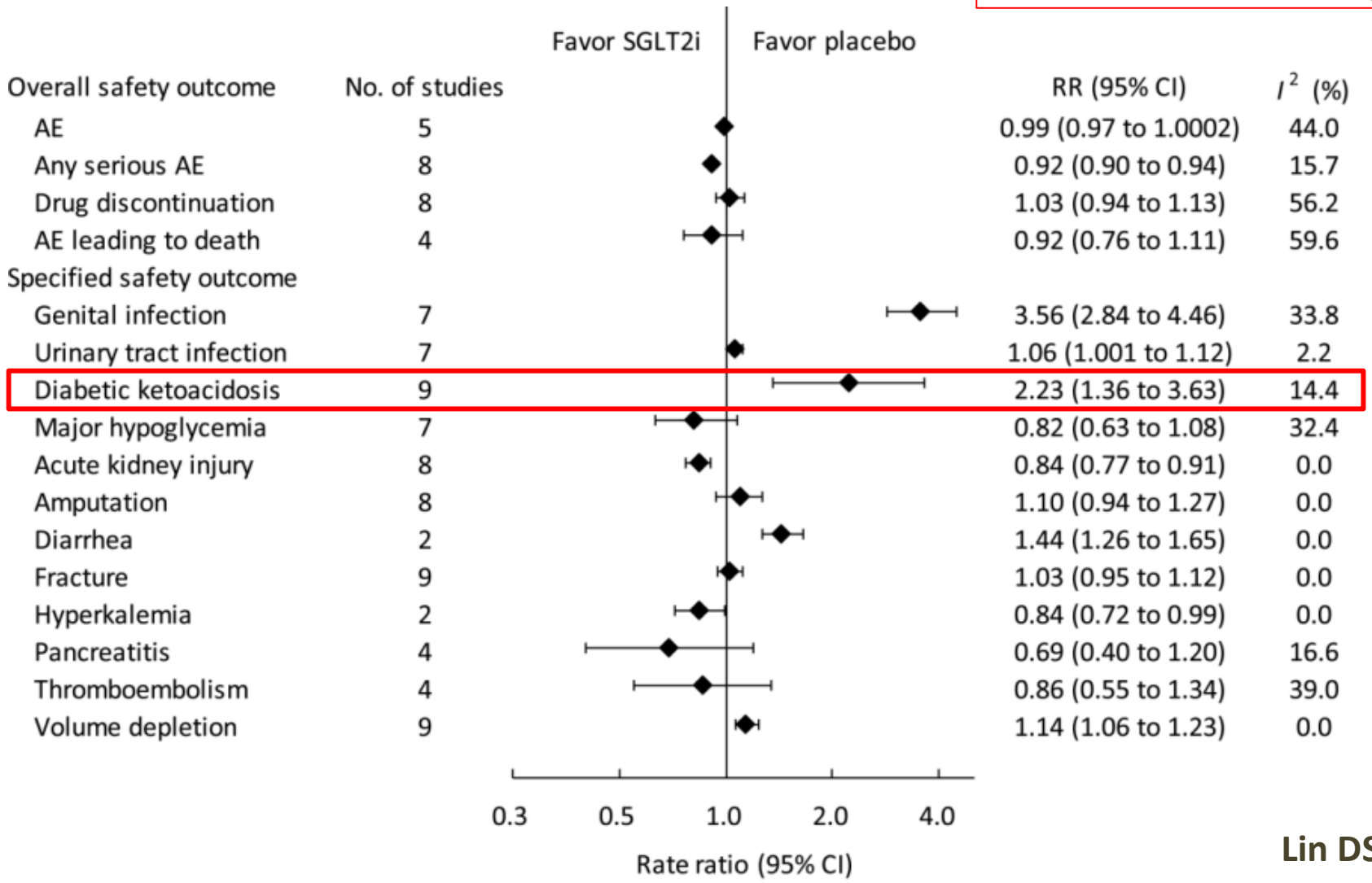
Urinary tract infections

- Studies show that SGLT2 inhibitors as a class **do not significantly raise the risk of UTI** when compared with placebo and active management with glitazones, incretins, metformin and sulfonylureas.
- **Why**: it is theorized that, while the effects of SGLT2 inhibitor-induced glycosuria create an environment favoring organism growth, these effects may be counterbalanced by the resulting osmotic diuresis, which improves urinary flow.
- **UTI incidence** in clinical trials from 4% to 9% from mild to moderate intensity, severe infections in up to 0.4% of patients.
- **When initiating an SGLT2 inhibitor**, practitioners should take note of history of UTIs and risk factors associated with complicated UTIs (obstruction, foreign body, incomplete voiding, vesicoureteral reflux, pregnancy, immunosuppression, UTIs in males, neurogenic bladder) and should consider choosing a non-dapagliflozin SGLT2 inhibitor, if worried.

Chandrashekar M, Int. J Urol, 2021

DIABETIC KETOACIDOSIS

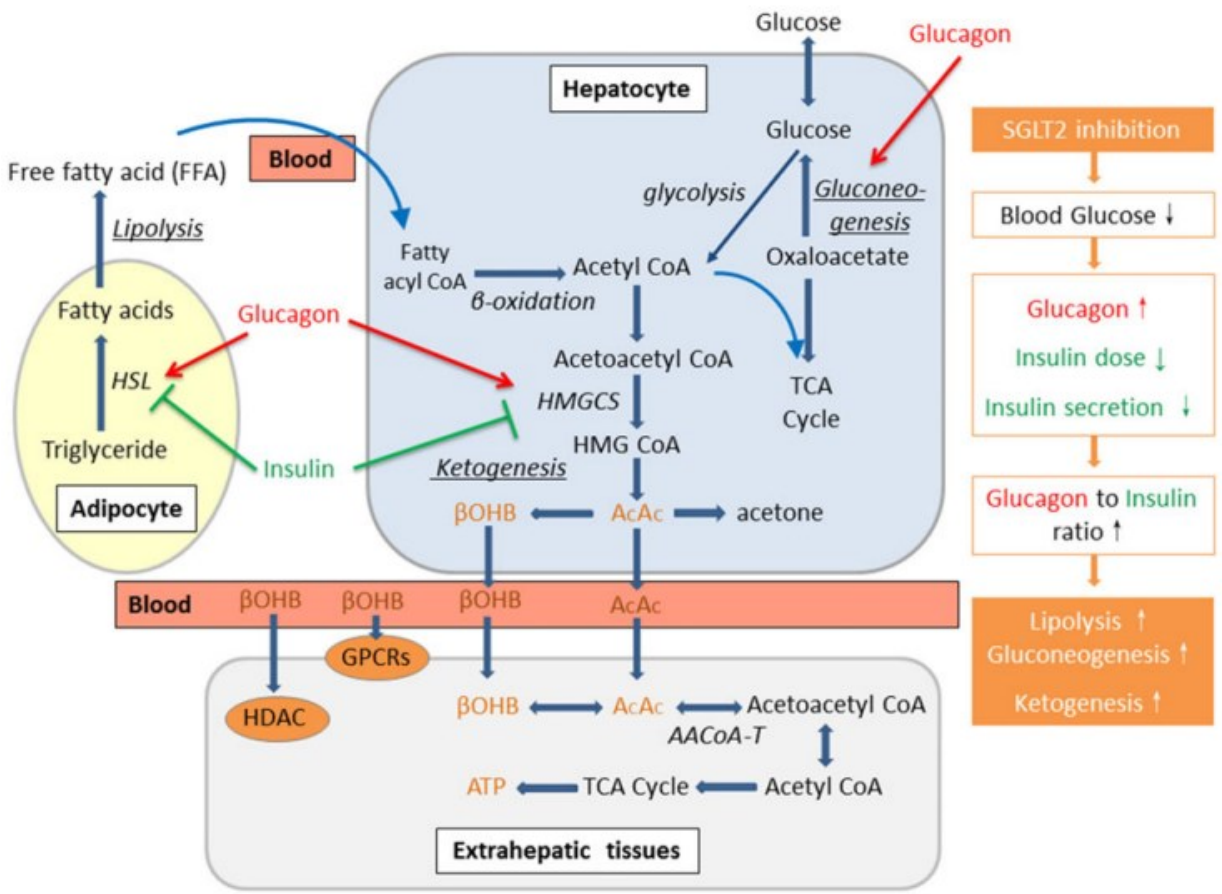
Clinical Adverse Events Associated with Sodium–Glucose Cotransporter 2 Inhibitors: A Meta-Analysis Involving 10 Randomized Clinical Trials and 71 553 Individuals Get access >

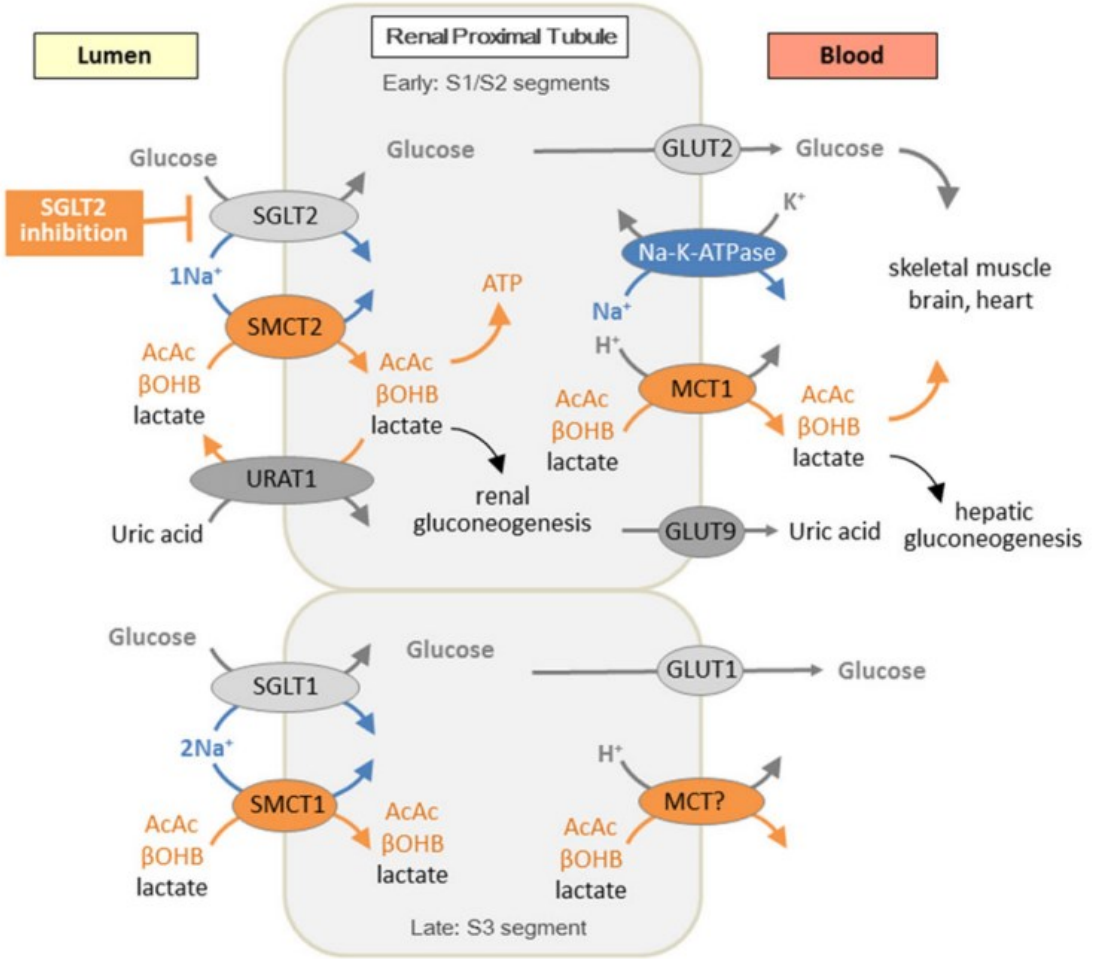


Lin DS, J Clin Endocrin Metabol, 2021

- **Pathogenesis** of DKA is triggered by relative or absolute insulin deficiency and subsequently increased ketogenesis, leading to metabolic acidosis. As iatrogenic-induced glucosuria is the consequence of SGLT2-inhibition, blood glucose levels may remain near to normoglycemic (euglycemic DKA – EDKA).
- **Clinical picture.** A correct diagnosis can be delayed when hyperglycemia is missing and when ketoacidosis presents with unspecific symptoms (such as the picture of an “acute abdomen”, severe pain and elevated tension (defense) of the abdominal wall, nausea, vomiting, weakness, tachypnea, and tachycardia).
- The most important parameters to diagnose EDKA are relative euglycemia (<250 mg/dl), anion gap acidosis (pH <7.30, bicarbonate <18 mEq/l) and the assessment of ketosis

Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: Basic mechanisms and therapeutic perspectives





Qiu H, Diabetes Metab Res Rev, 2017

- **DKA is a rare adverse effect** estimated to occur in 1-2.2 cases per 1000 person-years among SGLT2 users who have T2DM (in comparison to DKA incidence in T1DM of 4.6-8.0 cases per 1000 person—years)
- Reported **risk factors**
  - insulin deficiency: missed T1DM diagnosis, diabetes due to pancreatic disease
  - diet: prolonged fasting, reduced oral intake due to vomiting, very-low-calory or carbohydrate-restricted diet
  - metabolic stress: myocardial infarction, pancreatitis, intensive exercise, acute infection
  - surgery
    - basal insulin discontinuation and/or dose reduction before or after surgery
    - continuation of SGLT2-I medication perioperatively or withholding within 24– 48 h prior to elective interventions
    - bariatric surgery might be at special risk for because of surgical stress, perioperative diet changes, and prolonged fasting periods

Recommendations for initiation and monitoring of SGLT2 inhibitor therapy (3)

- Careful prescription of an SGLT2 inhibitor in light of a **patient's risk factors for DKA**
- Reducing a **patient's insulin dose** cautiously when commencing an SGLT2 inhibitor, as excessive insulin dose reduction or cessation of insulin therapy can contribute to the risk of DKA
- **Informing patients** about the risk of SGLT2 inhibitor-associated DKA, including when to withhold an SGLT2 inhibitor, including acute illness with reduced oral intake (part of a **sick day management plan**), symptoms of DKA (nausea, vomiting, abdominal pain, tiredness, rapid breathing), and the need to seek medical attention if symptoms occur
- Cessation of an SGLT2 inhibitor≥3 days **prior to an operation** and only recommencing therapy when a patient is eating and drinking normally

Milder TY, Drug Safety, 2020

AMPUTATION

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001

Neal B, NEJM, 2017

- In a post-hoc analysis of CANVAS, multivariate modelling showed a number of baseline characteristics that were signifcantly associated with amputation during follow up, including male sex, prior amputation, peripheral vascular disease, neuropathy, albuminuria, and higher HbA1c
- **None of others RCTs** directly comparing SGLT2i vs placebo showed an increased risk of amputation
- Due to results of CANVAS Program, during the CREDENCE trial, there was a **protocol amendment** asking investigators to examine patients' feet and temporarily withhold the study drug if there was any active condition present that might lead to amputation

- Data from prospective or retrospective observational studies, cohort studies and subsequent meta-analysis comparing SGLT2i and other glucose lowering drugs (oGLD) gave conflicting results
  - (Chang HY, JAMA Int Med, 2018) non statistically significant increased risk with SGLT2i vs DPP-4i and GLP1-RAs; higher risk compared with sulfonylureas, metformin, or thiazolidinediones
  - (Yuan Z, Diabetes Obes Metab, 2018) no increased risk for canagliflozin vs with non-SGLT2 oGLD
  - (Ueda P, BMJ, 2018): increased risk Empagliflozin and Dapagliflozin vs GLP1-RAs
  - (Li CX, PLOS ONE, 2021) SGLT2i vs oGLD reduced risk of lower limb amputation
  - (Qiu M, J Diab Complicat, 2021) SGLT2i vs oGLD increased risk (especially canagliflozin vs GLP1-RAs), vs placebo no increased risk

- In summary, **whether** there is a definite increase in risk of lower limb amputation with canaglifozin treatment is unclear.
- Furthermore, **the mechanisms** underlying such a potential adverse efect are unknown. Postulated mechanisms include (1) volume depletion secondary to diuresis, and (2) an effect on calcium, magnesium, and vitamin D metabolism that may impair foot ulcer healing
- Based on available evidence to date, **we recommend** that clinicians provide education to patients about preventive foot care and perform regular foot screening, as well as avoiding canagliflozin in patients with an acute heightened risk of amputation (as per the CREDENCE protocol—history of amputation within past 12 months, active ulcer, osteomyelitis, gangrene, or critical leg ischaemia within 6 months)

Milder TY, Drug Safety, 2020

FRACTURE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
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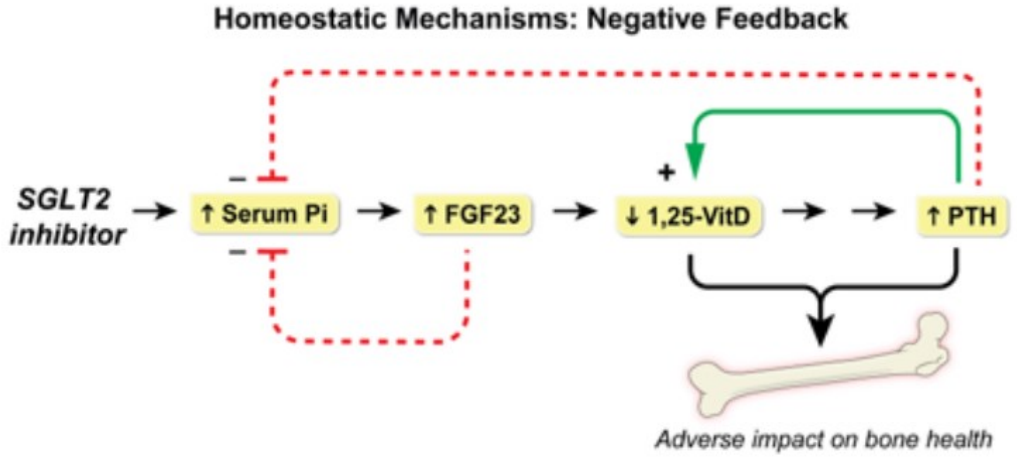
Infection of male genitalia§	34.9	10.8	<0.001

Neal B, NEJM, 2017

Review

The Off-Target Effects, Electrolyte and Mineral Disorders of SGLT2i

- **Increased bone fragility and risk of fracture are features of both type 1 diabetes and T2D** and may be caused by poor bone quality and abnormal bone microarchitecture.
- **It is plausible that SGLT2i entail an increased phosphate-dependent sodium reabsorption in the proximal tubule** caused by decreased glucose-dependent sodium reabsorption.



- **This combined pattern of reduced 1,25(OH)2D and increased PTH and FGF-23 levels likely contribute to the increased fracture risk associated with SGLT2i.**

Cianciolo G, Molecules, 2020

- **Meta-analyses and population-based studies** of SGLT2 inhibitor therapy have largely not demonstrated an increased risk of fracture
- A **possible relationship between falls** (potentially caused by volume depletion) **and fractures** cannot be excluded.
- However, given the changes in mineral metabolism and the results of the CANVAS Program, **longer-term data are needed with respect to risk of fracture**.
- **This issue is of relevance to the population of patients with CKD**, who have or are at risk of CKD–mineral and bone disorder (CKD-MBD).

Milder TY, Drug Safety, 2020

SGLT2-i in Kidney Transplant patients

Table 1. Summary of studies in kidney transplant recipients treated with Sodium-Glucose-Transporter-2 (SGLT2) inhibitors

Study	n	Type of SGLT2 inhibitor	Follow-up (weeks)	HbA1c	Uric acid	Weight	Blood pressure	Hct	Album-inuria	UTI/ candida[2]
Rajasekeran *et al.* [32]	10	Dapagliflozin	<12 mo	↓	n.a.	↓	↓	↑	n.a.	→
Schwaiger *et al.* [37▪]	14	Empagliflozin	12 mo	n.a.	↓	↓	↓	→	→	→
Mahling *et al.* [36]	10	Empagliflozin	<12 mo	↓	↓	↓	↓	↑	n.a	→
Shah *et al.* [33]	24	Canagliflozin	>6 mo	↓	n.a.	↓	↓	n.a.	n.a.	→
Attallah *et al.* [31]	8	Empagliflozin	12 mo	↓	n.a.	↓	n.a.	n.a.	↓	→
Kong *et al.* [34]	42	Dapagliflozin	>12 mo	↓	n.a.	↓	↓	n.a.	→	→
AlKindi *et al.* [35]	8	Empa- and dapagliflozin	12 mo	↓	n.a.	↓	↓	n.a.	n.a.	→
Halden *et al.* [30▪▪]	44	Empagliflozin	24 w	↓	↓	↓	↓	↑	→	→

n.a., not assessed; UTIs, urinary tract infections.
[1]Reduced blood pressure and/or reduction in blood pressure medication.
[2]UTI or mycotic infection as in control group or in less than 13% of cases.

Jenssen TG, Curr Opin Nephrol Hypertens, 2021

Sodium-Glucose Cotransporter 2 Inhibitors and Kidney Transplantation: What Are We Waiting For?

Niralee Patel,[1] Judy Hindi,[2] and Samira S. Farouk[2]

- Overall, these studies did not find significantly higher rates of infection with SGLT2 inhibitor use.
- BUT
- In some cases, however, UTI did lead to **SGLT2 inhibitor discontinuation**.
- **General inclusion criteria used:**
  - No significant history of genital mycotic infections, urosepsis, recurrent UTI
  - UTI-free period of 6 months prior to SGLT2 inhibitor initiation
  - Patients at least 1-year posttransplantation with well-controlled diabetes and stable kidney function

Patel N, KIDNEY360, 2021

Table 2. Characteristics of the "ideal" sodium-glucose cotransporter 2 inhibitor candidate with a kidney transplant

Proposed Characteristics for the "Ideal" Sodium-Glucose Cotransporter 2 Inhibitor Candidate with Kidney Transplant
At least 6–12 mo after KT with stable kidney function
No recent episode of KT rejection or need for increased immunosuppression within 6–12 mo
No history of recurrent UTI or genital infection and 6-mo UTI-free period prior to initiation
No history of recurrent or persistent hypotension or recurrent episodes of volume depletion
No history of peripheral vascular disease
Stable BP

KT, kidney transplantation; UTI, urinary tract infection.

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