Sicurezza d'uso degli SGLT2 inibitori e strategie di miglioramento dell'outcome sicurezza

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La Dr.ssa Benedetta Maria Bonora dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Boehringer Ingelheim
- Eli Lilly
- Novartis
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

SGLT2i adverse events

- Genital tract infections
- Hypoglycaemia

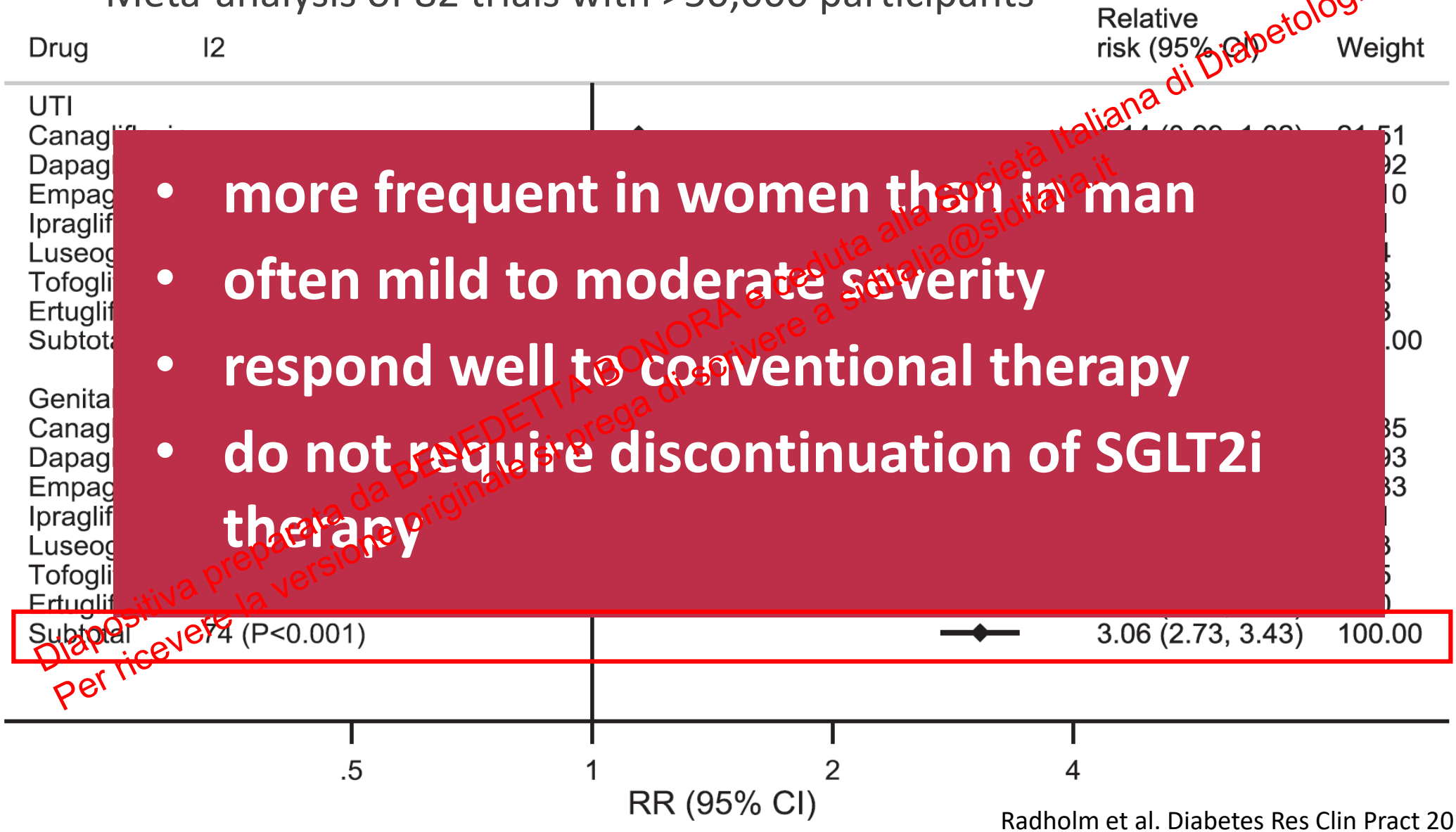
COMMON

- Volume depletion
- Acute kidney injury
- Diabetic ketoacidosis
- Fractures
- Lower limb amputations
- Fournier's gangrene

UNCOMMON

Genital tract infections (GTI) - RCT

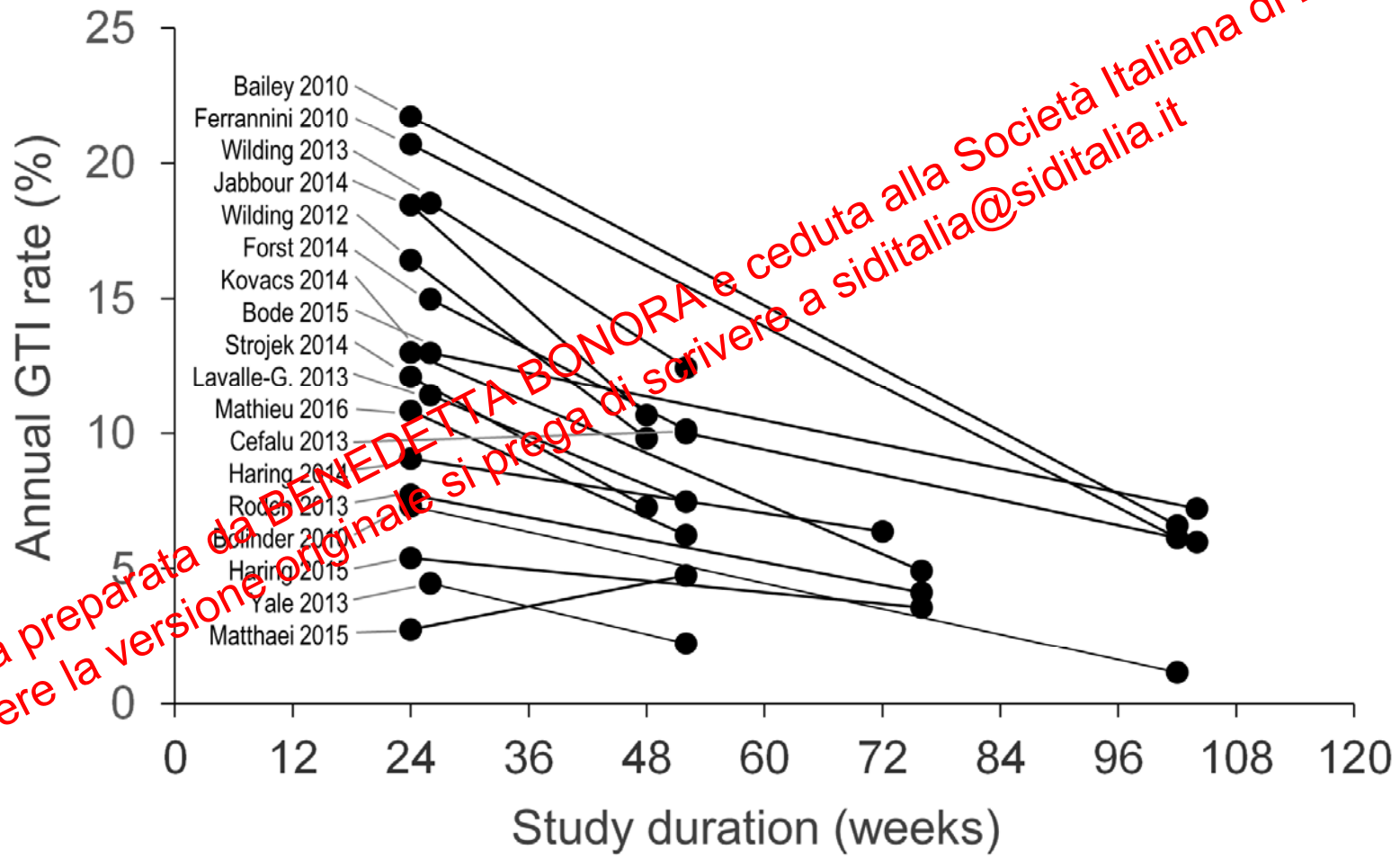
Meta-analysis of 82 trials with >50,000 participants



- more frequent in women than in man
- often mild to moderate severity
- respond well to conventional therapy
- do not require discontinuation of SGLT2i therapy

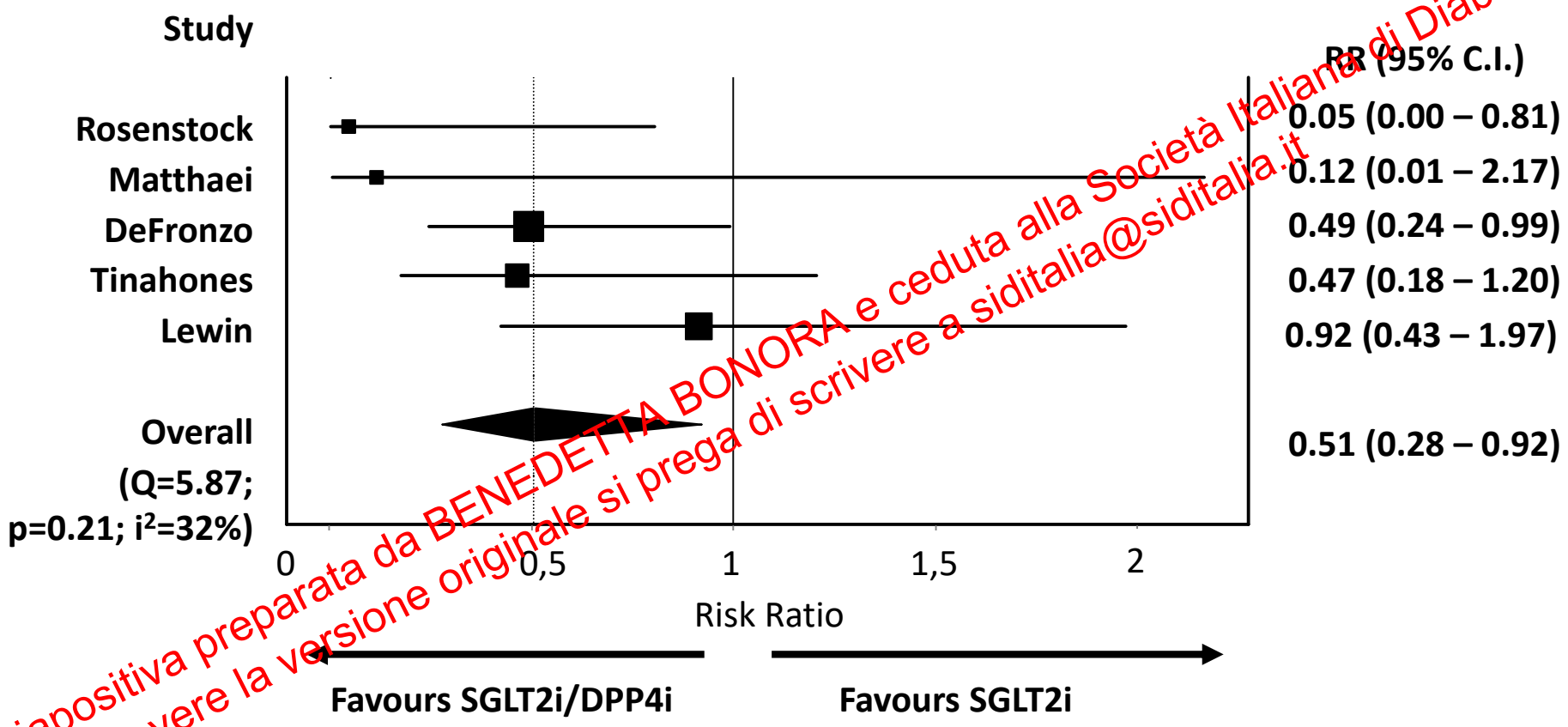
Radholm et al. Diabetes Res Clin Pract 2018

GTI and duration of follow-up



Fadini et al. DOM. 2018

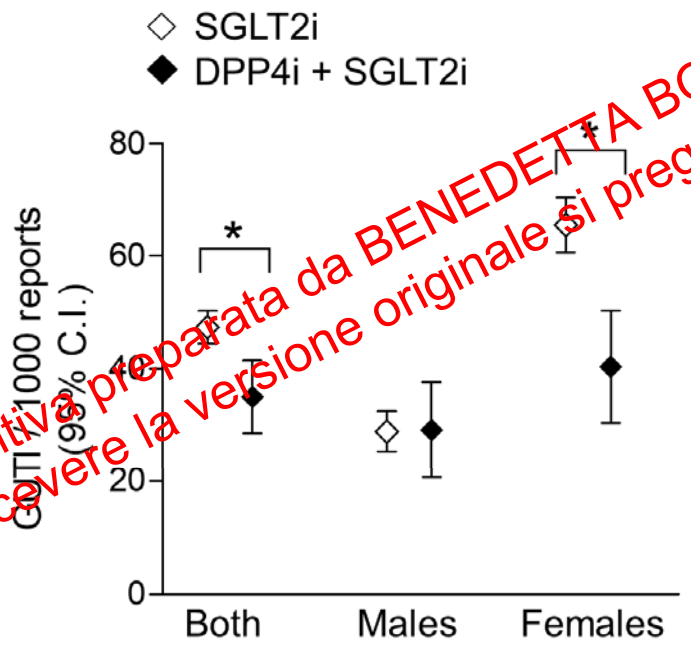
GTI - effects of SGLT2i/DPP4i association

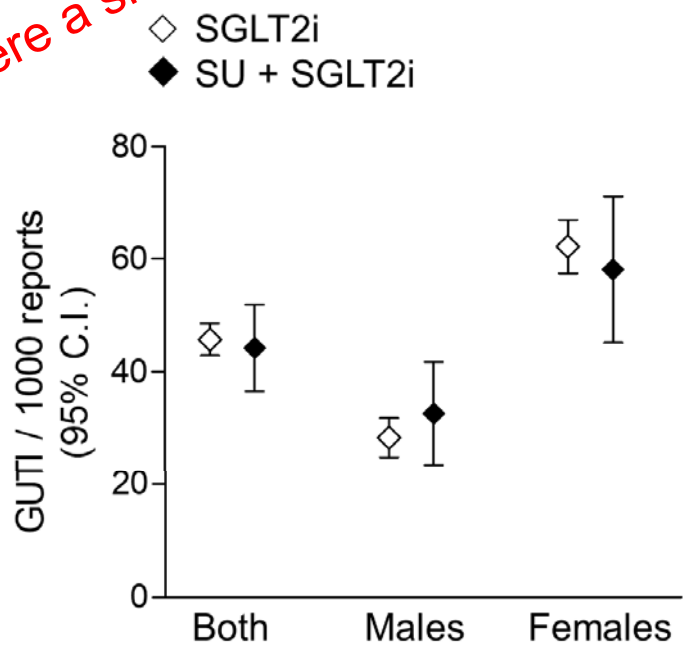


Fadini et al. DOM. 2018

GTI - effects of SGLT2i/AHAs association

Therapies	GTI RR (95% CI)
SGLT2i/GLP-1RA vs SGLT2i	0.85 (0.39-1.87)
SGLT2i/Met vs SGLT2i	0.99 (0.52-1.87)





Fadini et al. DOM. 2018

GTI - strategies to improve outcomes

- Genital hygiene
- Adequate idratation
- Avoid tight synthetic underwear
- For candidiasis, use topical antifungal agents (consider treating partner if recurrent infection)
- DPP4i may moderate the risk of GTI associated with SGLT2i use, independently from glycemic control, degree of glycosuria
- Direct action of DPP4i on yeasts, moulds, and bacteria?

Hypoglycaemia

- Meta-analysis of 38 trials with 23,997 participants
- SGLT2i vs placebo OR 1.28 (0.99-1.65); I^2 = 0%
- SGLT2i vs active comparator OR 1.01 (0.77-1.32); I^2 = 0%
- Incidence of hypoglycemia was low in most treatment groups, except for patients receiving a sulfonylurea or insulin as allocation treatment or background therapy

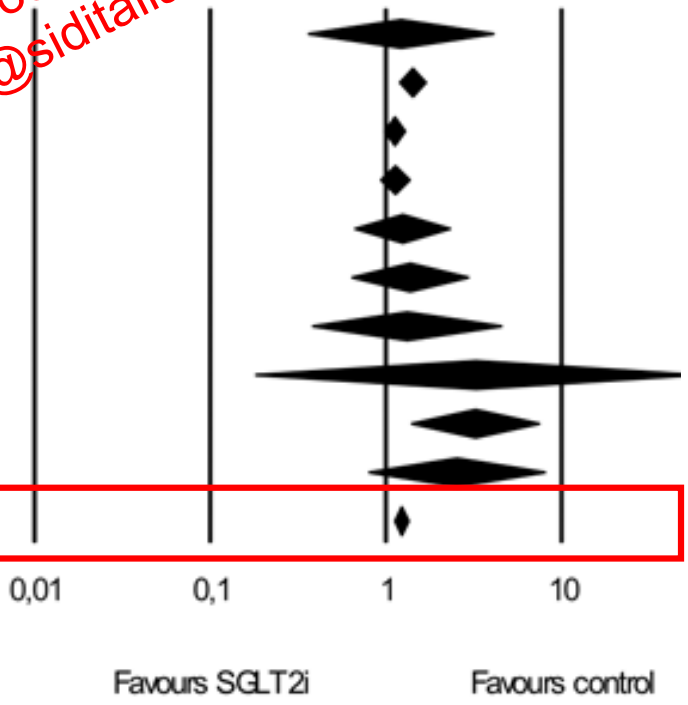
Consider reducing SU or insulin dose to reduce the risk of hypoglycaemia

Vasilakou et al. Ann Intern Med. 2013

Volume depletion - RCT

Meta-analysis of 92 trials with >80,000 participants

Group by Drug	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Vol. depl. AE / Total SGLT2i	Vol. depl. AE / Total Control
Bexagliflozin		1,192	0,356	3,990	0,285	0,776	6 / 157	5 / 155
Canagliflozin		1,392	1,177	1,648	3,851	0,000	465 / 10643	223 / 6762
Dapagliflozin		1,099	0,964	1,254	1,413	0,158	589 / 19108	469 / 16804
Empagliflozin		1,104	0,917	1,330	1,043	0,297	327 / 12339	73 / 6411
Ertugliflozin		1,217	0,656	2,258	0,623	0,533	49 / 3947	16 / 1407
Ipragliflozin		1,344	0,629	2,871	0,763	0,445	22 / 561	12 / 359
Luseogliflozin		1,288	0,375	4,433	0,402	0,687	15 / 659	4 / 235
Remogliflozin		3,190	0,128	57,229	0,788	0,431	7 / 164	0 / 33
Sotagliflozin		3,161	1,377	7,261	2,713	0,007	33 / 1485	7 / 1229
Tofogliflozin		2,482	0,787	7,826	1,551	0,121	23 / 643	3 / 192
Overall		1,201	1,100	1,311	4,094	0,000	1581 / 48776	912 / 32987



OR 1.20 (1.10-1.31)

Menne et al. PLoS Med. 2019

Volume depletion - background therapies

EMPA-REG OUTCOME

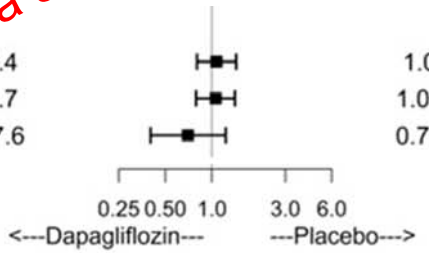
	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years
Volume depletion[c]						
Overall study population	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
ACEi/ARB yes	97 (5.2)	2.16	102 (5.4)	2.17	109 (5.7)	2.30
ACEi/ARB no	18 (3.9)	1.52	13 (2.9)	1.14	15 (3.4)	1.32
Any diuretic yes	67 (6.8)	2.90	66 (6.4)	2.65	69 (6.8)	2.82
Any diuretic no	48 (3.6)	1.44	49 (3.7)	1.47	55 (4.1)	1.61
CCB yes	39 (4.2)	2.03	37 (4.7)	1.90	44 (5.9)	2.32
CCB no	76 (4.9)	2.05	78 (5.0)	2.01	80 (5.0)	2.01
NSAID yes	14 (7.3)	3.39	13 (7.1)	2.89	21 (11.2)	4.54
NSAID no	101 (4.7)	1.94	102 (4.7)	1.90	103 (4.8)	1.91

Mayer et al. Kidney Int 2019

Volume depletion - age subgroups

DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

	Dapagliflozin		Placebo				
	n/N (%)	Rates per 1000 person- years	n/N (%)	Rates per 1000 person- years	Hazard ratio (95% CI)	p value	p interaction
Symptoms of volume depletion							
< 65 years	96/4626 (2.1%)	5.8	86/4619 (1.9%)	5.4	1.07 (0.8, 1.44)	0.6316	0.4046
65-< 75 years	96/3411 (2.8%)	8.0	90/3395 (2.7%)	7.7	1.06 (0.79, 1.41)	0.7076	
≥ 75 years	21/537 (3.9%)	12.1	31/535 (5.6%)	17.6	0.70 (0.40, 1.23)	0.2169	



Cahn et al. Diabetes Care 2020

Volume depletion - CKD patients

The NEW ENGLAND JOURNAL of MEDICINE

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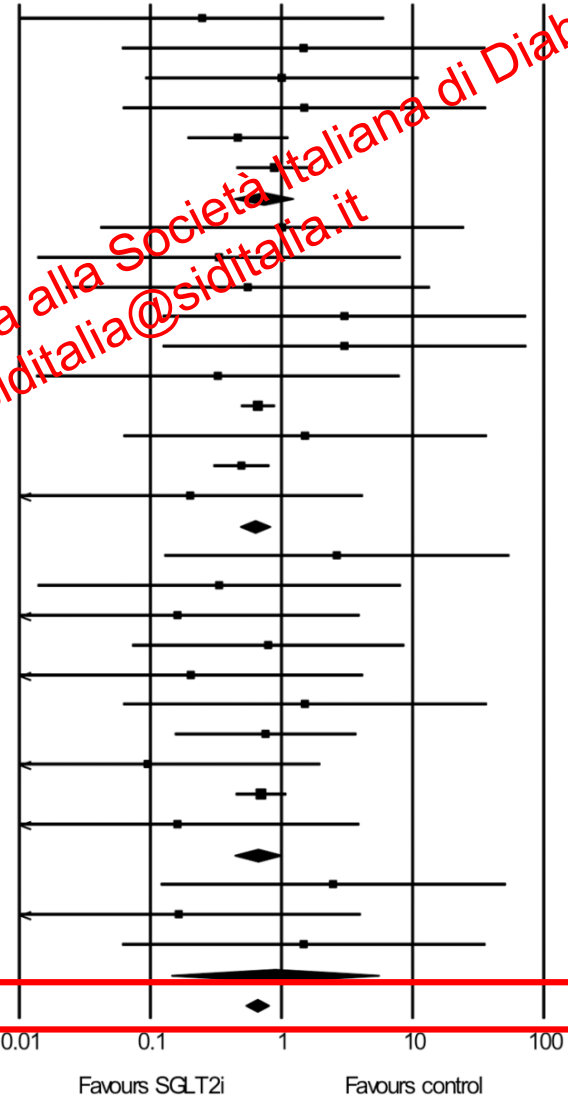
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)
	no./total no.		*events/ 1000 patient-yr*		
Volume depletion	144/2200	115/2197	28.4	23.5	1.25 (0.97–1.59)

Serious acute kindey injury (AKI) - RCT

Group by Drug	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	AKI (SAE) / Total SGLT2i	AKI (SAE) / Total Control
Canagliflozin	CANTATA-D	0.249	0.010	6.114	-0.852	0.394	0 / 735	1 / 549
Canagliflozin	CANTATA-M	1.475	0.060	36.378	0.238	0.812	1 / 392	0 / 192
Canagliflozin	DIA3004	1.006	0.090	11.241	0.005	0.996	2 / 179	1 / 90
Canagliflozin	CANTATA-SU	1.496	0.061	36.795	0.247	0.805	1 / 968	0 / 482
Canagliflozin	CANVAS R	0.465	0.189	1.142	-1.670	0.095	7 / 2907	15 / 2905
Canagliflozin	CANVAS	0.882	0.446	1.747	-0.359	0.720	23 / 2886	13 / 1441
Canagliflozin		0.718	0.431	1.196	-1.273	0.203	34 / 8067	30 / 5659
Dapagliflozin	Bailey 2013	1.010	0.041	24.933	0.006	0.995	1 / 409	0 / 137
Dapagliflozin	NCT01042977	0.333	0.014	8.203	-0.672	0.501	0 / 482	1 / 483
Dapagliflozin	NCT00528372	0.553	0.022	13.706	-0.362	0.718	1 / 410	0 / 75
Dapagliflozin	NCT01031680	3.020	0.123	74.316	0.676	0.499	1 / 460	0 / 462
Dapagliflozin	CompoSIT-R	3.020	0.123	74.415	0.676	0.499	1 / 306	0 / 307
Dapagliflozin	NCT02551874	0.327	0.013	8.061	-0.683	0.494	0 / 324	1 / 319
Dapagliflozin	DECLARE-TIMI58	0.660	0.484	0.901	-2.622	0.009	67 / 8574	101 / 8569
Dapagliflozin	DEPICT-2	1.512	0.061	37.251	0.253	0.800	1 / 641	0 / 322
Dapagliflozin	DAPA-HF	0.495	0.299	0.819	-2.738	0.006	23 / 2373	46 / 2371
Dapagliflozin	DELIGHT	0.201	0.010	4.231	-1.032	0.302	0 / 146	2 / 148
Dapagliflozin		0.618	0.478	0.799	-3.867	0.000	95 / 14024	151 / 13143
Empagliflozin	EMPA-REG BASAL	2.643	0.126	55.373	0.626	0.531	2 / 324	0 / 170
Empagliflozin	EMPA-REG MONO	0.335	0.014	8.241	-0.669	0.503	0 / 448	1 / 451
Empagliflozin	NCT01734785	0.161	0.007	3.986	-1.115	0.265	0 / 222	1 / 108
Empagliflozin	EASE-2 and 3	0.792	0.072	8.760	-0.190	0.850	2 / 1221	1 / 484
Empagliflozin	EMPA-REG H2H-SU	0.203	0.010	4.244	-1.027	0.304	0 / 765	2 / 780
Empagliflozin	EMPA-REG MDI	2.110	0.061	37.245	0.252	0.801	1 / 375	0 / 188
Empagliflozin	EMPA-REG RENAL	0.756	0.152	3.771	-0.341	0.733	3 / 421	3 / 319
Empagliflozin	EMPA-REG MDI	0.095	0.005	1.998	-1.514	0.130	0 / 430	2 / 207
Empagliflozin	EMPA-REG OUTCOME	0.697	0.442	1.100	-1.551	0.121	45 / 4687	32 / 2333
Empagliflozin	NCT01422876	0.161	0.007	3.967	-1.117	0.264	0 / 551	1 / 267
Empagliflozin		0.649	0.433	0.974	-2.088	0.037	53 / 9444	43 / 5307
Ertugliflozin	VERTIS RENAL	2.480	0.118	51.973	0.585	0.558	2 / 313	0 / 154
Ertugliflozin	VERTIS FACTORIAL	0.165	0.007	4.061	-1.103	0.270	0 / 498	1 / 247
Ertugliflozin	VERTIS-SU	1.479	0.060	36.377	0.239	0.811	1 / 888	0 / 437
Ertugliflozin		0.878	0.143	5.404	-0.140	0.889	3 / 1699	1 / 838
Overall		0.642	0.527	0.784	-4.366	0.000	185 / 33234	225 / 24947

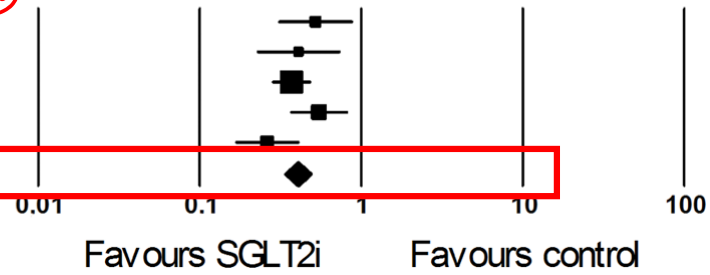


OR 0.64 (0.53-0.78)

Menne et al. PLoS Med. 2019

AKI - observational studies

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	AKI / Total SGLT2i	AKI / Total Control
Nadkarni 2017, Mt. sinai cohort	0.522	0.304	0.897	-2.355	0.019	22 / 372	40 / 372
Nadkarni 2017, Geisinger cohort	0.409	0.223	0.752	-2.881	0.004	15 / 1207	36 / 1207
Norhammar 2017	0.370	0.277	0.495	-6.731	0.000	52 / 3582	417 / 25746
Ueda 2018	0.547	0.360	0.832	-2.819	0.005	34 / 17213	62 / 17213
Cahn 2019	0.262	0.164	0.418	-5.618	0.000	23 / 5618	76 / 5604
	0.399	0.330	0.481	-9.599	0.000	146 / 33792	631 / 50142



OR 0.40 (0.33-0.48)

Menne et al. PLoS Med. 2019

AKI - background therapies

EMPA-REG OUTCOME

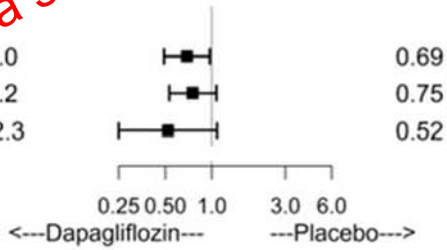
	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years
Acute renal failure[f]						
Overall study population	155 (6.6)	2.77	121 (5.2)	2.07	125 (5.3)	2.12
ACEi/ARB yes	131 (7.0)	2.93	101 (5.3)	2.14	113 (5.9)	2.38
ACEi/ARB no	24 (5.2)	2.13	20 (4.5)	1.76	12 (2.7)	1.05
Any diuretic yes	95 (9.6)	4.15	75 (7.2)	3.02	72 (7.1)	2.94
Any diuretic no	60 (4.5)	1.84	46 (3.5)	1.37	53 (4.0)	1.54
CCB yes	57 (7.3)	2.99	43 (5.5)	2.21	45 (6.0)	2.36
CCB no	98 (6.3)	2.65	78 (5.0)	2.00	80 (5.0)	2.01
NSAID yes	16 (8.5)	3.86	15 (8.2)	3.38	11 (5.9)	2.32
NSAID no	139 (6.5)	2.68	106 (4.9)	1.96	114 (5.3)	2.10

Mayer et al. Kidney Int 2019

AKI - age subgroups

DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

	Dapagliflozin		Placebo				
	n/N (%)	Rates per 1000 person- years	n/N (%)	Rates per 1000 person- years	Hazard ratio (95% CI)	p value	p interaction
Acute kidney injury							
< 65 years	58/4626 (1.3%)	3.5	80/4619 (1.7%)	5.0	0.69 (0.49, 0.97)	0.0319	0.6922
65-< 75 years	56/3411 (1.6%)	4.6	75/3395 (2.2%)	6.2	0.75 (0.53, 1.07)	0.1135	
≥ 75 years	11/537 (2%)	6.3	22/553 (4%)	12.3	0.52 (0.25, 1.08)	0.0778	



Cahn et al. Diabetes Care 2020

AKI - CKD patients

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Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)
	no./total no.		*events/ 1000 patient-yr*		
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)

Volume depletion/AKI

- Meta-analyses of RCT showed an increased risk of volume depletion in patients taking SGLT2i
- RCT and CVOTs did not detect an increased risk of acute kidney injury despite of background therapies acting on kidney hemodynamic
- The safety of SGLT2i was consistent regardless of age and renal function

Caution should be exercise in patients on anti-hypertensive therapy with a history of hypotension, in patients with borderline BP and in very elderly individuals. Stop SGLT2i in conditions that may lead to fluid loss (e.g. gastrointestinal illness).

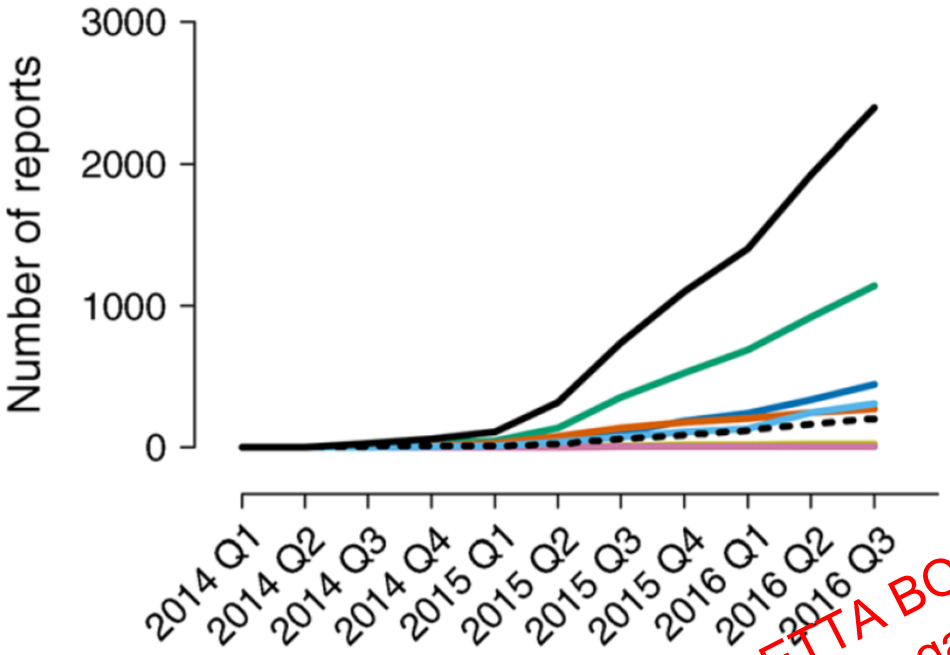
Diabetic ketoacidosis (DKA)

FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

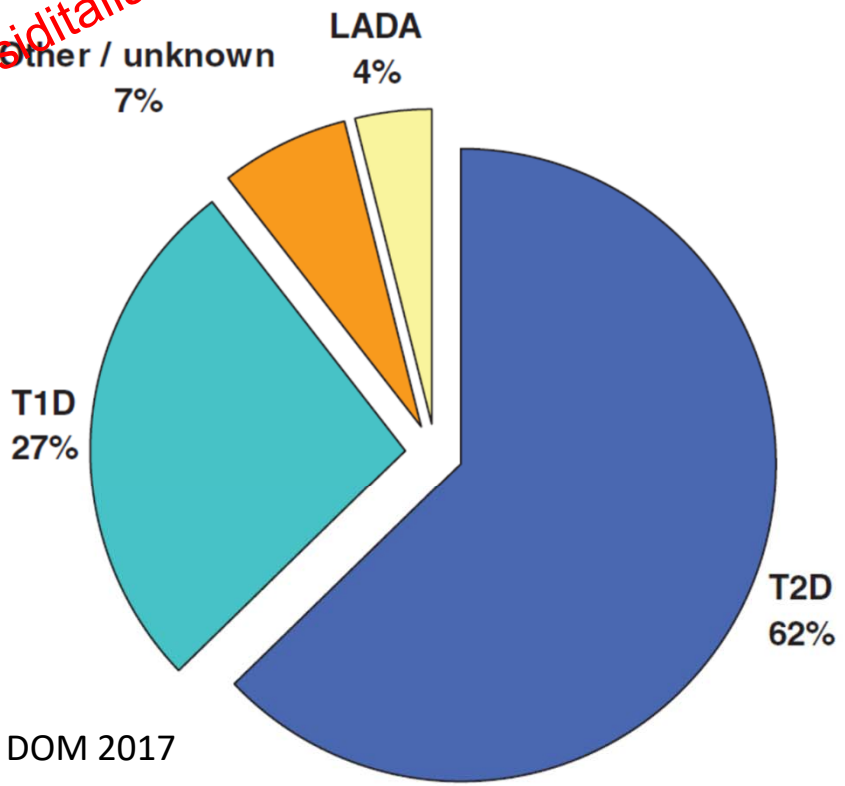
Safety Announcement

[5-15-2015] The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. We are continuing to investigate this safety issue and will determine whether changes are needed in the prescribing information for this class of drugs, called sodium-glucose cotransporter-2 (SGLT2) inhibitors.

DKA - FAERS and case report



Fadini et al. Diabetologia 2017



Bonora et al. DOM 2017

DKA - RCT in T2D

Pool analyses phase III trials

Treatment	Events/n° patients	Event rate per 1000 pt/anno
Cana 100 mg	4/5337	**0.52**
Cana 300 mg	6/5350	**0.76**
Comparator	2/6909	**0.24**
Empa 10 mg	5/4558	**0.6**
Empa 25 mg	2/5520	**0.2**
Comparator	5/5599	**0.4**
Dapa	1/5963	**0.16**

Bonora et al. DOM 2017

DKA - RCT and real world evidence (RWE)

Author	Studies	Comparison	n° of patients	HR (95% CI)
Meta-analyses				
Monami 2017	9 RCT	Placebo/AHA	15,553	**1.14 (0.45-2.88)**
Observational studies				
Wang 2017	US administrative database	AHA	30,196 pairs	**1.91 (0.95-4.11)**
Fralick 2017	US insurance database	DPP4i	38,045 pairs	**2.2 (1.5-2.9)**
Jensen 2017	Registers in Denmark	AHA	NA	**1.6 (0.7-3.5)**
Kim 2018	Korean Health Insurance database	DPP4i	56,325 pairs	**0.96 (0.58-1.57)**
Usuda 2018	Sweden and Denmark registers	GLP-1RA	17,213 pairs	**2.14 (1.01-4.52)**

Modified from Scheen et al. Expert Opin Drug Saf 2019

DKA - RCT in T1D

Treatment	Events/n° patients	Event rate 100 pt/years
Dapa 5 mg	11/277	**4.76**
Dapa 10 mg	10/296	**3.67**
Placebo	5/260	**2.15**

Dandona et al. Diabetes Care 2018

Treatment	Events/n° patients	Event rate 100 pz/anno
Empa 10 mg	21/491	**5.94**
Empa 25 mg	16/489	**5.05**
Placebo	6/484	**1.77**

Rosenstock et al. Diabetes Care 2018

DKA - strategies to improve outcomes

- To date, the exact rate of SGLT2i-associated DKA is difficult to establish
- SGLT2i-associated DKA episodes sometimes presented with relatively low glucose levels because of glycosuria (can delayed recognition and treatment)
- To minimize the risk:
  - Stop SGLT2i at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity
  - Stop immediately for emergency surgery or any extreme stress event or any situation that might precipitate DKA including illness
  - Avoid stopping insulin or decreasing the dose excessively
  - Avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets
  - Blood ketone testing if patient is feeling sick

Fractures

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA revises label of diabetes drug canagliflozin to include updates on bone fracture risk and new information on decreased bone mineral density

Safety Announcement

[9-10-2015] The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin related to the increased risk of bone fractures and added new information about decreased bone mineral density. Bone mineral density relates to the strength of a person's bones. To address these safety concerns, we added a new *Warning and Precaution* and revised the *Adverse Reactions* section of the drug labels.

Fractures - CANVAS

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value*
Low-trauma fracture (primary outcome)				
CANVAS	12.98	8.31	1.56 (1.18–2.06)	
CANVAS-R	7.87	10.30	0.76 (0.52–1.12)	
CANVAS Program	11.58	9.17	1.23 (0.99–1.52)	0.003
All fracture (secondary outcome)				
CANVAS	16.92	10.94	1.55 (1.21–1.97)	
CANVAS-R	11.42	13.23	0.86 (0.62–1.19)	
CANVAS Program	15.40	11.93	1.26 (1.04–1.52)	0.005

*P value for homogeneity between CANVAS and CANVAS-R.

Neal et al. N Engl J Med. 2017

Fractures - others CVOTs

EMPA-REG OUTCOME

	Empagliflozin (N=4,687)	Placebo (N=2,333)	Hazard ratio (95%CI)
	179 (3.8)	91 (3.9)	0.98 (0.76–1.25)

Zinman et al. N Engl J Med. 2015

DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59

Wiviott et al. N Engl J Med. 2019

CREDENCE™

	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)
	no./total no.		*events/ 1000 patient-yr*		
	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)

Perkovic et al. N Engl J Med. 2019

Fractures - RWE

Author	Studies	Comparison	n° of patients	HR (95% CI)
Toulis 2018	UK general practice electronic database	DAPA vs AHA	22,618	**0.89 (0.66-1.20)**
Ueda 2018	Sweden and Denmark register	SGLT2i vs GLP-1RA	17,213 pairs	**1.11 (0.93-1.33)**
Fralick 2019	2 US insurance database	Cana vs GLP-1RA	79,964 pairs	**0.98 (0.75-1.26)**

Cheng L et al. Diabetes & Metabolism 2019

Fractures - strategies to improve outcomes

- The use of canagliflozin has been associated with an increased risk of fractures in CANVAS trial but NOT in other clinical trial or in RWE studies
- Empagliflozin and dapagliflozin were not found to have an increased risk of fracture

Avoid SGLT2i (canagliflozin?) in patients at very high risk of fracture (history of osteoporotic fracture).

Amputations

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

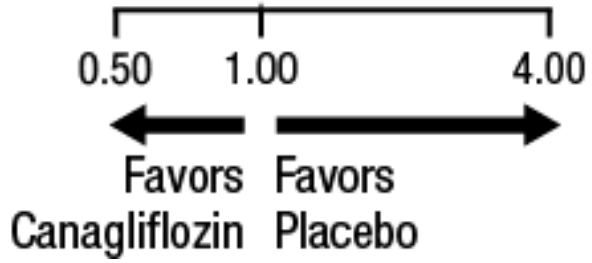
FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin

Patients taking canagliflozin should notify your health care professionals right away if you develop new pain or tenderness, sores or ulcers, or infections in your legs or feet. Talk to your health care professional if you have questions or concerns. Do not stop taking your diabetes medicine without first talking to your health care professional.

Health care professionals should, before starting canagliflozin, consider factors that may predispose patients to the need for amputations. These factors include a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Monitor patients receiving canagliflozin for the signs and symptoms described above and discontinue canagliflozin if these complications occur.

Amputations - CANVAS (1)

	Canagliflozin Event rate per 1000 patient-years	Placebo Event rate per 1000 patient-years	Hazard ratio (95% CI)
All amputation	6.30	3.37	1.97 (1.41–2.75)
Minor amputation	4.48	2.44	1.94 (1.31–2.88)
Toe	3.44	2.16	
Transmetatarsal	1.03	0.29	
Major amputation	1.82	0.93	2.03 (1.08–3.82)
Ankle	0.04	0.07	
Below-knee	1.16	0.64	
Above-knee	0.62	0.21	



Neal et al. N Engl J Med. 2017

Amputations - CVOTs

EMPA-REG OUTCOME

Empagliflozin		Placebo		Incidence rate ratio (95% CI)
n with event/N (%)	*Incidence rate/ 1,000 patient-yrs*	*n with event/N (%)*	*Incidence rate/ 1,000 patient-yrs*	
88/4,687 (1.9)	6.5	43/2,333 (1.8)	6.5	1.01 (0.70, 1.45)

Inzucchi et al. Diabetes Care 2018

DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
no. (%)			
123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53

Wiviott et al. N Engl J Med. 2019

CREDENCE™

Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)
no./total no.		*events/ 1000 patient-yr*		
70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)

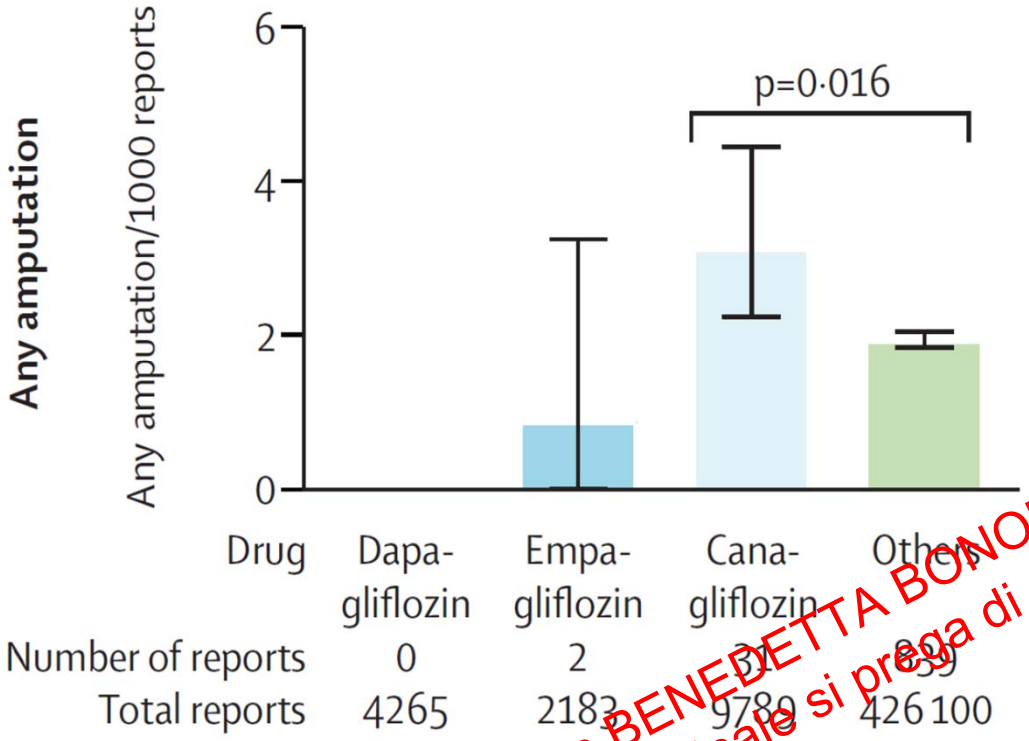
Perkovic et al. N Engl J Med. 2019

Amputations - RWE

Author	Studies	Comparison	n° of pts	HR (95% CI)
Udell 2017	US Department of Defense Military Health System	SGLT2i vs AHA	25,258 pairs	**1.99 (1.12-3.51)**
Ryan 2018	4 US insurance databases	Cana vs AHA	603,685	**0.75 (0.40-1.41)**
Adimadhyam 2018	US administrative database	SGT2i vs DPP4i	30,216 pairs	**1.38 (0.83-2.31)**
Yuan 2018	US administrative database	Cana vs AHA	63,845 pairs	**0.98 (0.68-1.41)**
Ueda 2018	Sweden and Denmark register	SGT2i vs GLP-1RA	17,213 pairs	**2.32 (1.37-3.91)**
Chang 2018	US insurance database	SGT2i vs DPP4i	144,892 pairs	**1.50 (0.85-2.67)**
Yang 2019	US insurance database	SGLT2i vs DPP4i	165,763	**1.69 (1.20-2.38)**

Modified from Scheen et al. Expert Opin Drug Saf 2019

Amputations - Pharmacovigilance reports



Fadini et al. Lancet Diab Endocrin 2017

	Reports of amputations (*n*) PRR (95% CI)		
	Lower limb	**Toe**	**All[a]**
SGLT-2 inhibitors	79 **5.55 (4.23, 7.29)**	62 **7.83 (5.64, 10.86)**	92 **5.95 (4.61, 7.67)**
Canagliflozin	56 **7.09 (5.25, 9.57)**	42 **8.91 (6.23, 12.74)**	67 **7.82 (5.92, 10.32)**
Dapagliflozin	10 1.81 (0.96, 3.41)	9 **2.62 (1.33, 5.14)**	11 1.79 (0.98, 3.27)
Empagliflozin	14 **4.96 (2.89, 8.50)**	12 **6.86 (3.80, 12.37)**	14 **4.43 (2.59, 7.58)**

Khouri et al. DOM 2018

Amputations - strategies to improve outcomes

- The use of canagliflozin has been associated with an increased risk of lower-limb amputation in CANVAS trial but NOT in other clinical trial (amputations were primarily at the level of the toe or metatarsal)
- Empagliflozin and dapagliflozin were not found to have an increased risk of amputations
- Real world data reported conflicting results
- Signals for empagliflozin and dapagliflozin begin to appear in pharmacovigilance reports

Avoid SGLT2i in patients with severe PAD, ischemic foot ulcers and history of amputations

Fournier's gangrene

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

Safety Announcement

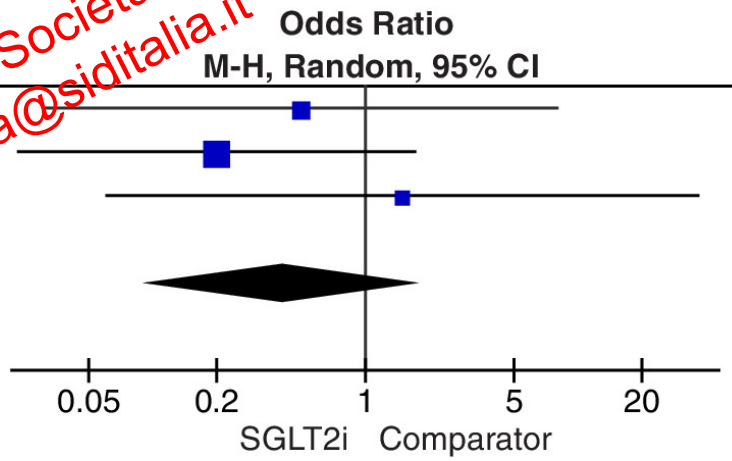
[8-29-2018] The U.S. Food and Drug Administration (FDA) is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.

Fournier's gangrene - RCT

Study or Subgroup	SGLT2i Events	SGLT2i Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
Neal 2017 [14]	1	2886	1	1442	29.3%	0.50 [0.03, 7.99]
Wiviott 2018 [12]	1	8574	5	8569	48.8%	0.20 [0.02, 1.71]
Zinman 2015 [13]	1	4687	0	2333	22.0%	1.49 [0.06, 36.68]
Total (95% CI)		**16 147**		**12 344**	**100.0%**	**0.41 [0.09, 1.82]**
Total events	3		6			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.08$, df = 2 (P = 0.58); $I^2 = 0\%$

Test for overall effect: Z = 1.18 (P = 0.24)



Silverii GA. Diabetes Obes Metab. 2020

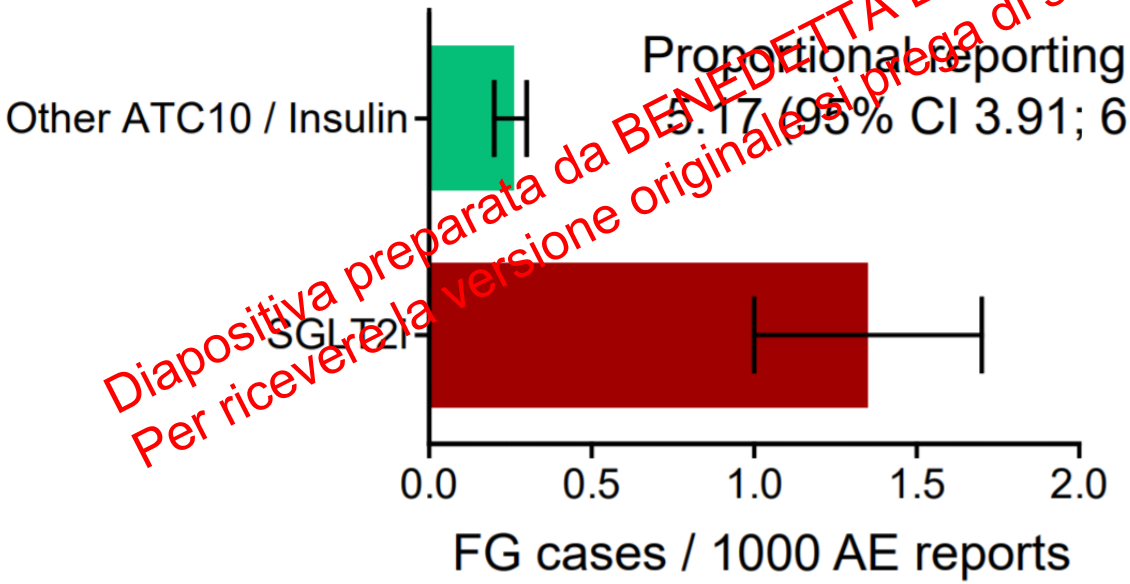
Fournier's gangrene - RWE

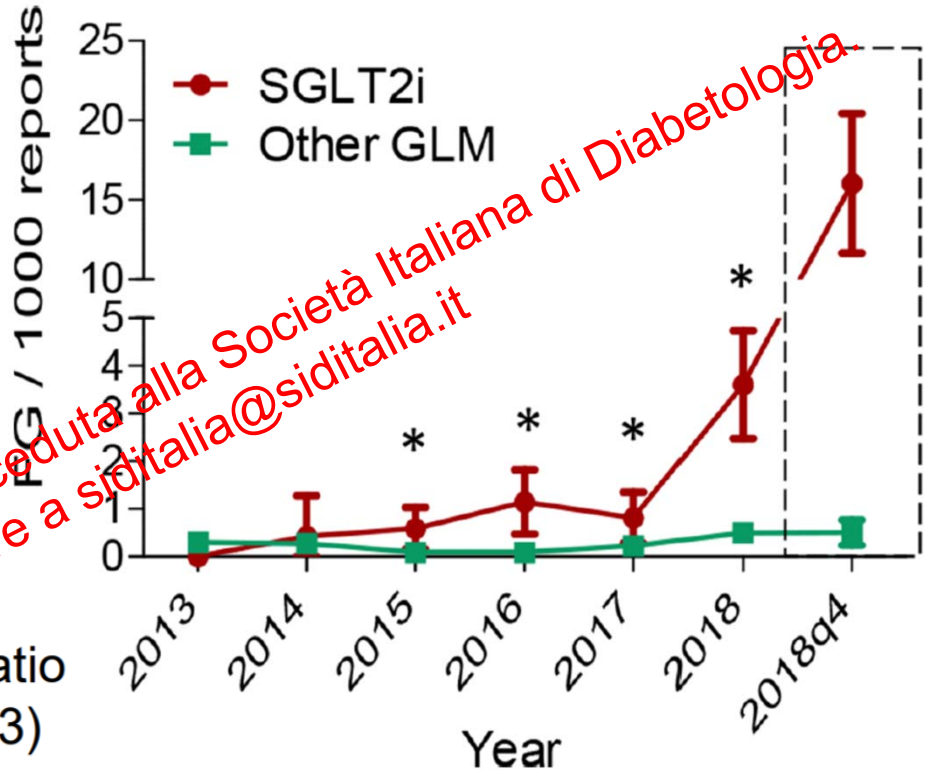
Author	Studies	Comparator	n° of patients	HR (95% CI)
Dave 2019	3 US insurance databases	DPP4i	498,843	**1.73 (0.87-3.42)**
Petruski-Ivleva 2019	US insurance database	AHA	67,994	**0.99 (0.35-2.81)**
Wang 2020	2 US administrative databases	AHA or insulin	1,296 pairs	**0.55 (0.25-1.18)**

Dave CV et al. AMA Intern Med. 2019
Petruski-Ivleva N et al. DOM 2020
Wang T et al. Diabetes Ther. 2020

Fournier's gangrene - Pharmacovigilance reports

- 64 cases (47 FG, 17 cases of other severe AEs of the genital area)
- 77% in men
- 3 patients trated with systemic immunosuppressive drugs (psoriasis)





Fadini GP et al. BMJ Open Diabetes Res Care. 2019

Fournier's gangrene - strategies to improve outcomes

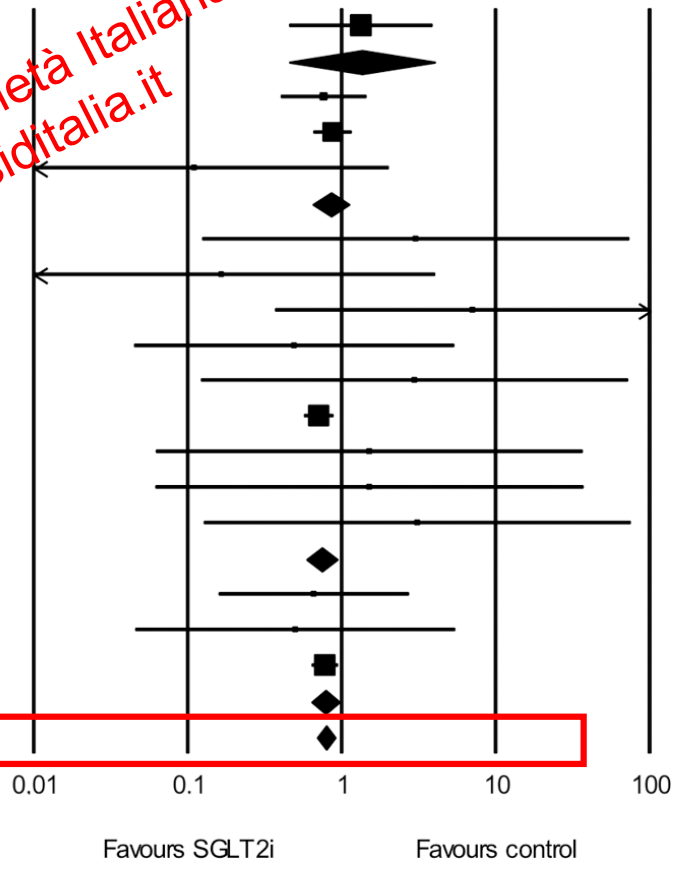
- Extremely rare but can be life threatening and fatal
- Immunosuppressed states may increase the risk such as genital or urine tract infection, poorly controlled diabetes, severe obesity, poor hygienic habits

- Perineal hygiene
- Attention in the case of any symptoms of subcutaneous infection around the genitals (pain, tenderness, erythema, and/or swelling in the genital or perineal area), accompanied with high fever
- If suspected, prompt hospitalization, treatment with broad-spectrum antibiotics, and if required, surgical debridement are crucial

Grazie per l'attenzione
e saluti da Padova

AKI all events - RCT

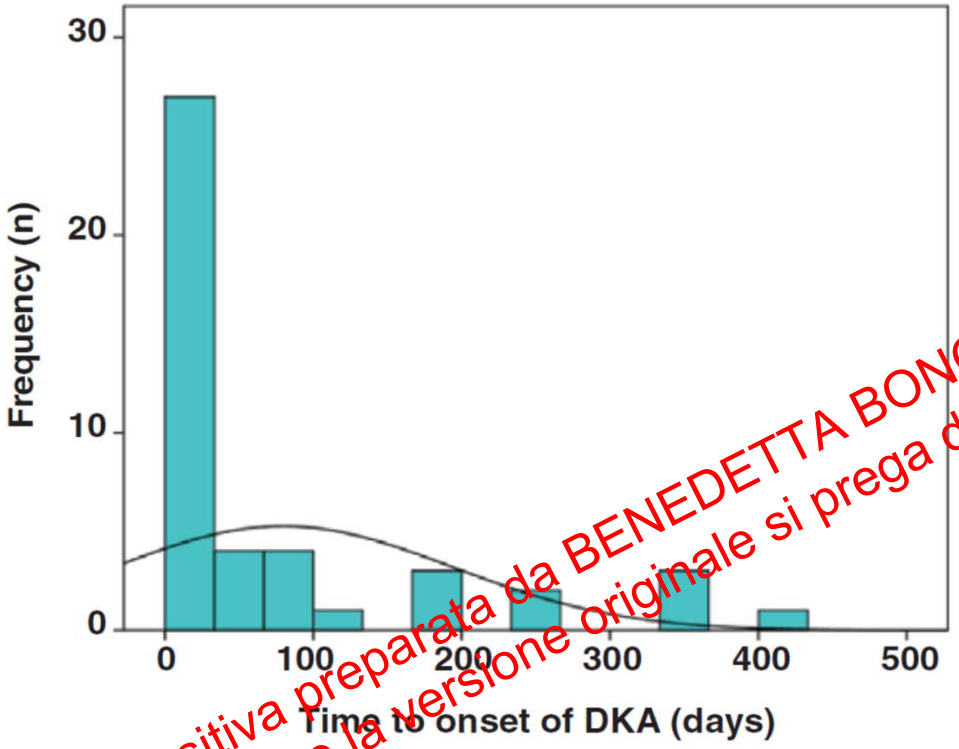
Group by Drug	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	AKI (SAE or AE) / Total SGLT2i	AKI (SAE or AE) / Total Control
Bexagliflozin	NCT02715258	1.333	0.452	3.936	0.521	0.602	8 / 157	6 / 155
Bexagliflozin		1.333	0.452	3.936	0.521	0.602	8 / 157	6 / 155
Canagliflozin	CANVAS	0.764	0.397	1.468	-0.808	0.419	23 / 2886	15 / 1441
Canagliflozin	CREDENCE	0.871	0.648	1.171	-0.913	0.361	86 / 2200	98 / 2197
Canagliflozin	SUSTAIN-8	0.110	0.006	2.050	-1.479	0.139	0 / 394	4 / 394
Canagliflozin		0.837	0.640	1.095	-1.296	0.195	109 / 5480	117 / 4033
Dapagliflozin	NCT00660907	3.022	0.123	74.406	0.677	0.499	1 / 406	0 / 408
Dapagliflozin	NCT00663260	0.165	0.007	4.099	-1.099	0.272	0 / 168	1 / 84
Dapagliflozin	NCT01031680	7.077	0.365	137.385	1.293	0.196	3 / 460	0 / 462
Dapagliflozin	DURATION-8	0.491	0.044	5.456	-0.579	0.563	1 / 230	2 / 227
Dapagliflozin	NCT02284893	2.974	0.121	73.387	0.666	0.505	1 / 232	0 / 229
Dapagliflozin	DECLARE-TIMI58	0.710	0.563	0.894	-2.904	0.004	125 / 8574	175 / 8569
Dapagliflozin	2014-004599-49	1.512	0.061	37.251	0.253	0.800	1 / 541	0 / 272
Dapagliflozin	MB102029	1.513	0.061	37.549	0.253	0.800	1 / 168	0 / 84
Dapagliflozin	2010-019797-32	3.100	0.126	76.383	0.692	0.489	1 / 302	0 / 311
Dapagliflozin		0.733	0.584	0.919	-2.692	0.007	134 / 11081	178 / 10646
Empagliflozin	EASE-2 and 3	0.659	0.157	2.769	-0.569	0.569	5 / 1221	3 / 484
Empagliflozin	PIONEER 2	0.500	0.045	5.536	-0.565	0.572	1 / 409	2 / 410
Empagliflozin	EMPA-REG OUTCOME	0.778	0.633	0.958	-2.368	0.018	246 / 4687	155 / 2333
Empagliflozin		0.773	0.630	0.949	-2.464	0.014	252 / 6317	160 / 3227
Overall		0.780	0.684	0.890	-3.709	0.000	503 / 23035	461 / 18060

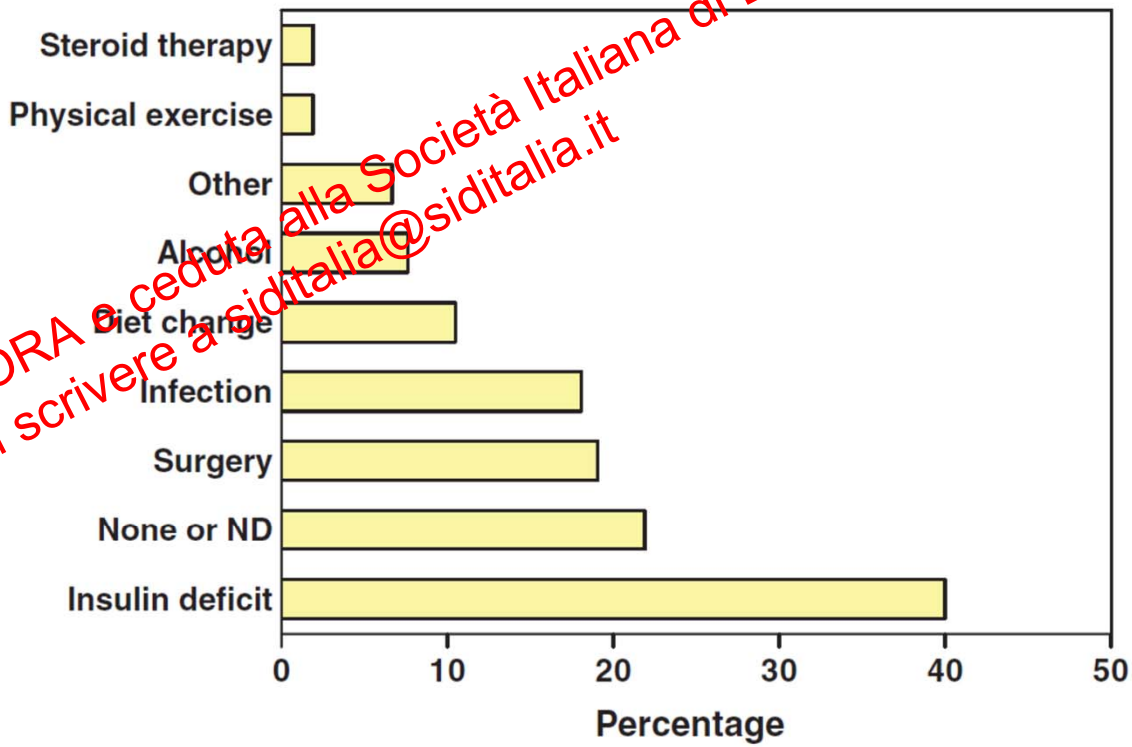


OR 0.78 (0.69-0.89)

Menne et al. PLoS Med. 2019

DKA - case report





Bonora et al. DOM 2017

Amputations - CANVAS (2)

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)
History of amputation			
Yes	96.30	59.16	2.15 (1.11–4.19)
No	4.68	2.48	1.88 (1.27–2.78)
History of peripheral vascular disease			
Yes	12.09	8.16	1.39 (0.80–2.40)
No	5.20	2.41	2.34 (1.53–3.58)

Neal et al. N Engl J Med. 2017