SGLT2 inibitori: effetti collaterali e terapie concomitanti. Come comportarsi?

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Disclosures

Grant: Astra Zeneca

Advisory Board: Astra Zeneca, Boehringer Ingelheim, Mundipharma, sanofi

Speaker: Astra Zeneca, Boehringer Ingelheim, Lilly, Mundipharma, Novo, sanofi

Outline

Side effects

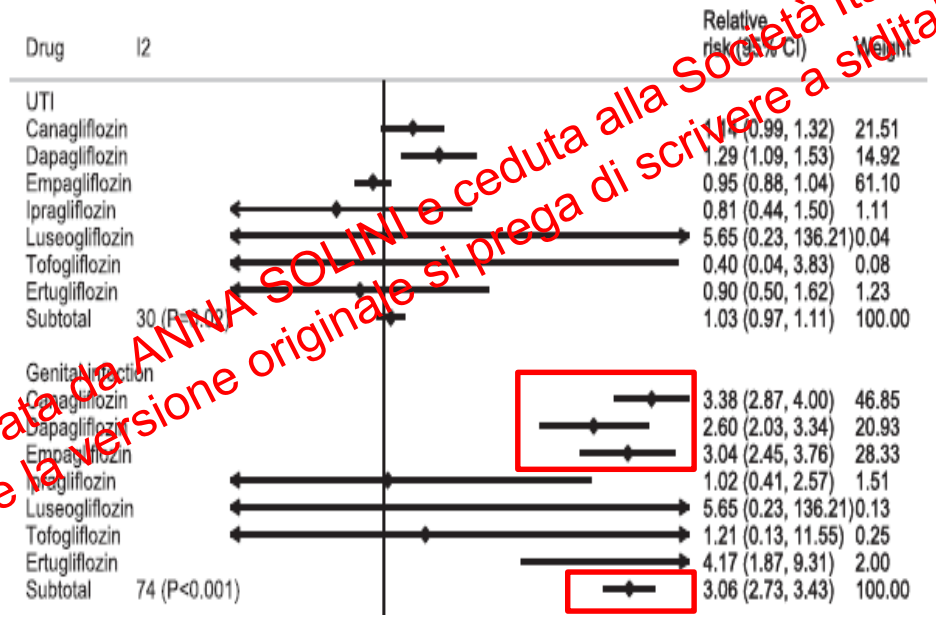
- Genital infections
- Fractures
- Lower limb amputations
- DKA

Concomitant treatments

- Insulin
- DPP-IV inh/GLP1 RA

Frequence of genital infections: a systematic review

Systematic review of 82 trials, 4 overviews and 6 regulatory reports



Radholm K, Diabetes Res Clin Pract 2018

Genital infections in metanalyses of clinical trials with SGLT2 inh compared with placebo or active comparators

All SGLT2 inh	Canagliflozin	Dapagliflozin	Empagliflozin
Vasilakou 2013 OR 3.5 [a] OR 5.1 [b]	***Young 2014*** RR 3.8 [a] RR 4.9 [b]	***Vasilakou 2013*** OR 3.5 [a] OR 4.8 [b]	***Liakos 2014*** OR 4.4 [a] OR 4.2 [b]
Puckrin 2018 RR 3.4 [a] RR 3.9 [b]	***Li 2017*** OR 5.0 [a] OR 5.3 [b]	***Li 2017*** OR 4.5 [a] OR 4.8 [b]	***Li 2017*** OR 3.9 [b]
Liu 2015 OR 4.2 [a] OR 5.7 [b]	***Chilelli 2018*** (retrospective observation) Incomplete voiding 6.3% Increased frequency of urination/ pollakiuria 43.8-73.6% Nocturia 25.0-50.0%		

a = vs placebo

b = vs active comparator

Modified from Scheen AJ, Expert Opin Drug Saf 2019

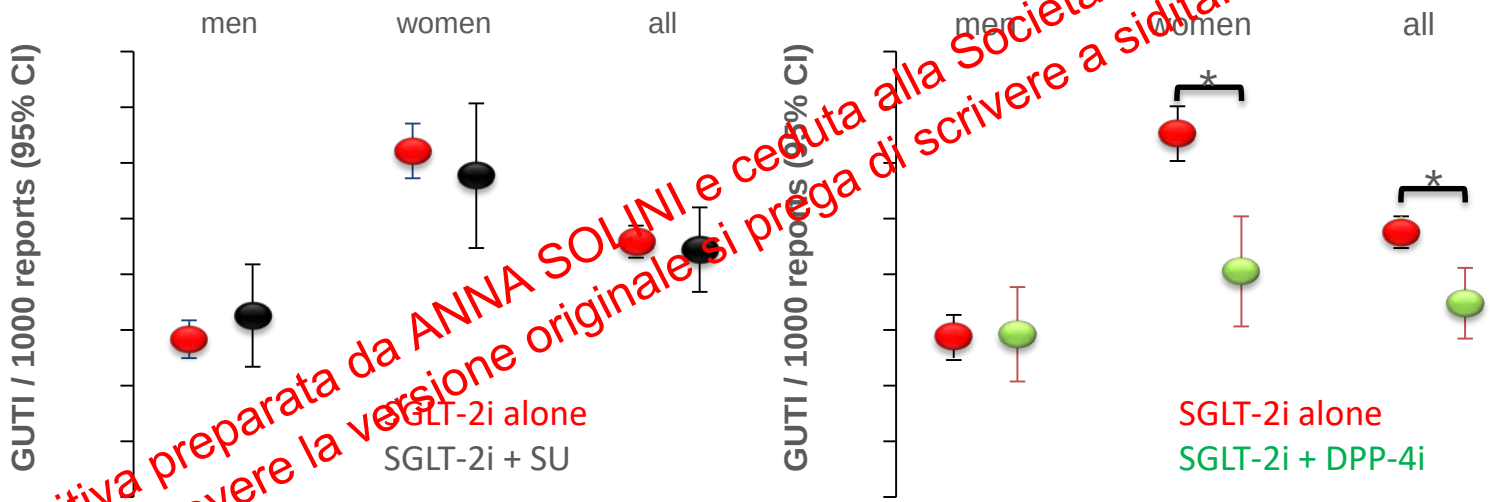
Comparative risk of GI vs other drugs

Propensity score-matched results on 129,994 women and 156,074 men

	No. of patients [b]	HR (95% CI)	Excess risk (95% CI) [c]
SGLT2 inhibitors versus DPP4 inhibitors (primary analysis)			
Women			
Genital infections (composite)	129 994	2.80 (2.63, 2.99)	87.6 (79.1, 96.7)
Candidal genital infections		3.15 (3.05, 3.27)	53.1 (46.4, 60.4)
Men			
Genital infections (composite)	156 074	2.66 (2.30, 3.08)	11.9 (9.4, 15.0)
Candidal genital infections		3.35 (2.28, 4.91)	2.4 (1.3, 4.1)
SGLT2 inhibitors versus GLP1 receptor agonists			
Women			
Genital infections (composite)	142 992	2.91 (2.73, 3.10)	91.0 (82.4, 100.3)
Candidal genital infections		3.60 (3.28, 3.95)	55.5 (48.7, 62.9)
Men			
Genital infections (composite)	139 398	2.85 (2.42, 3.35)	12.9 (9.9, 16.4)
Candidal genital infections		3.28 (2.18, 4.94)	2.5 (1.3, 4.2)
SGLT2 inhibitors versus DPP4 inhibitors, age ≥ 60 y			
Women			
Genital infections (composite)	37 764	4.45 (3.83, 5.17)	90.0 (73.9, 108.7)
Candidal genital infections		5.28 (4.28, 6.52)	54.6 (41.8, 70.4)
Men			
Genital infections (composite)	43 078	3.30 (2.56, 4.25)	18.5 (12.6, 26.2)
Candidal genital infections		4.31 (2.16, 8.59)	3.4 (1.2, 7.8)

Chintan VD, Diabetes Obes Metab 2019

Frequency of genitourinary tract infections in the FDA AE reporting system



Fadini GP, Diabetes Obes Metab 2018

Fournier gangrene associated with SGLT2 inhibitors: a review of spontaneous postmarketing cases

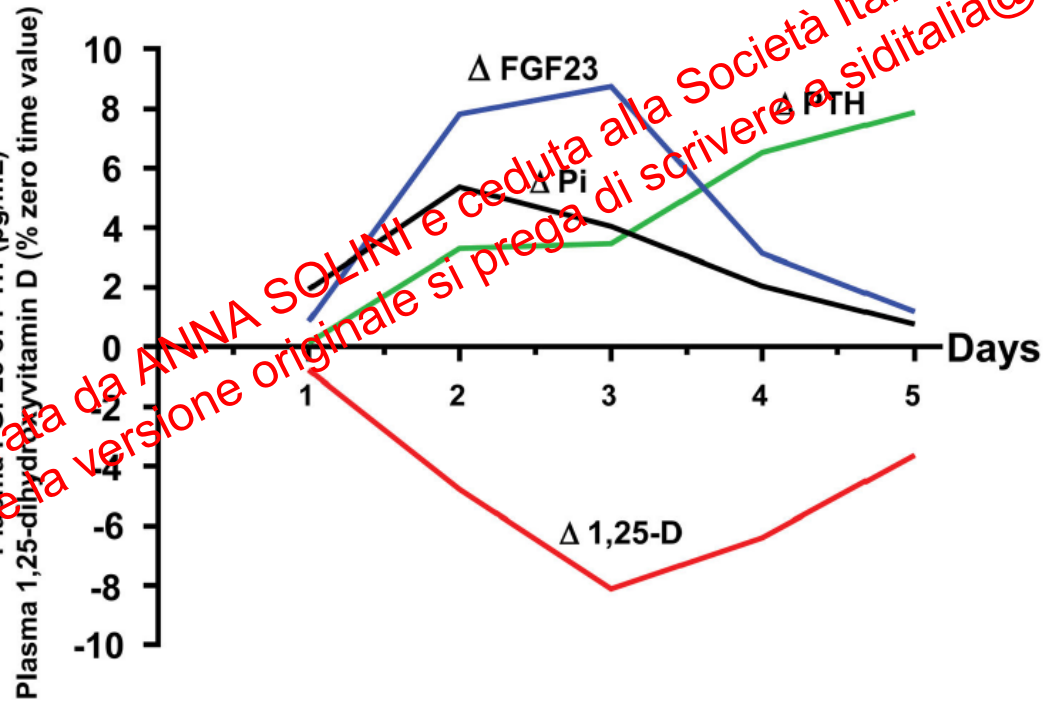
Characteristic	Value
Diabetes type	
Type 2 diabetes mellitus	22
Not specified	8
Not reported	25
SGLT2 inhibitor	
Canagliflozin	21
Dapagliflozin	16
Empagliflozin	18
Time to onset‡	
Median	4.5 mo
Range	5 d–49 mo
Serious outcomes	
Hospitalization (initial or prolonged)‖	53
Life-threatening	23
Disability	5
Death¶	3

Potential precipitating factors†**	
Urinary tract infection	2
Perineal hygiene difficulty	1
Recurrent genital fungal infection (self-treated)	1
Colostomy reversal (5 mo prior)	1
Concurrent colon cancer diagnosis	1

Bersoff-Matcha SJ, Ann Intern Med 2019

The combination of decreased 1,25-dihydroxy vitamin D and increased PTH levels may contribute to SGLT2 inhibitor-associated fracture risk

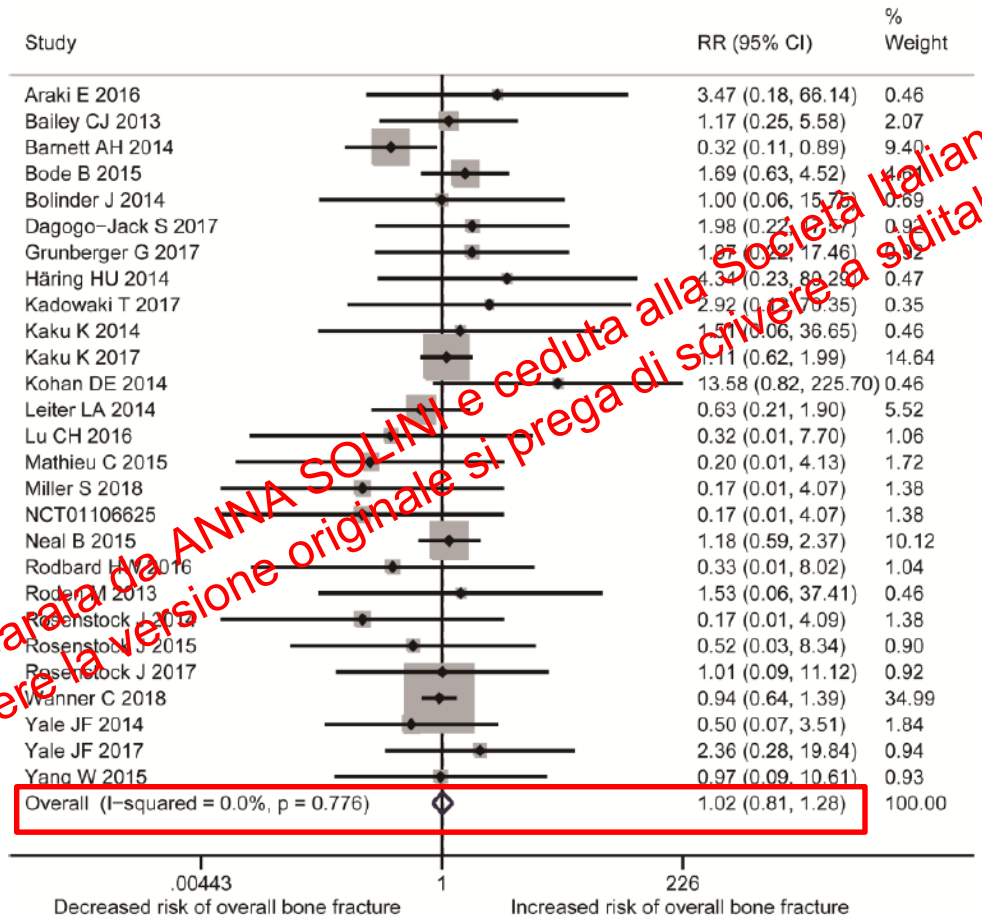
SGLT2i → ↑ Pi → ↑ FGF23 → ↓ 1,25-Vit D → ↑ PTH



Blau JE, Nat Rev Nephrol 2018

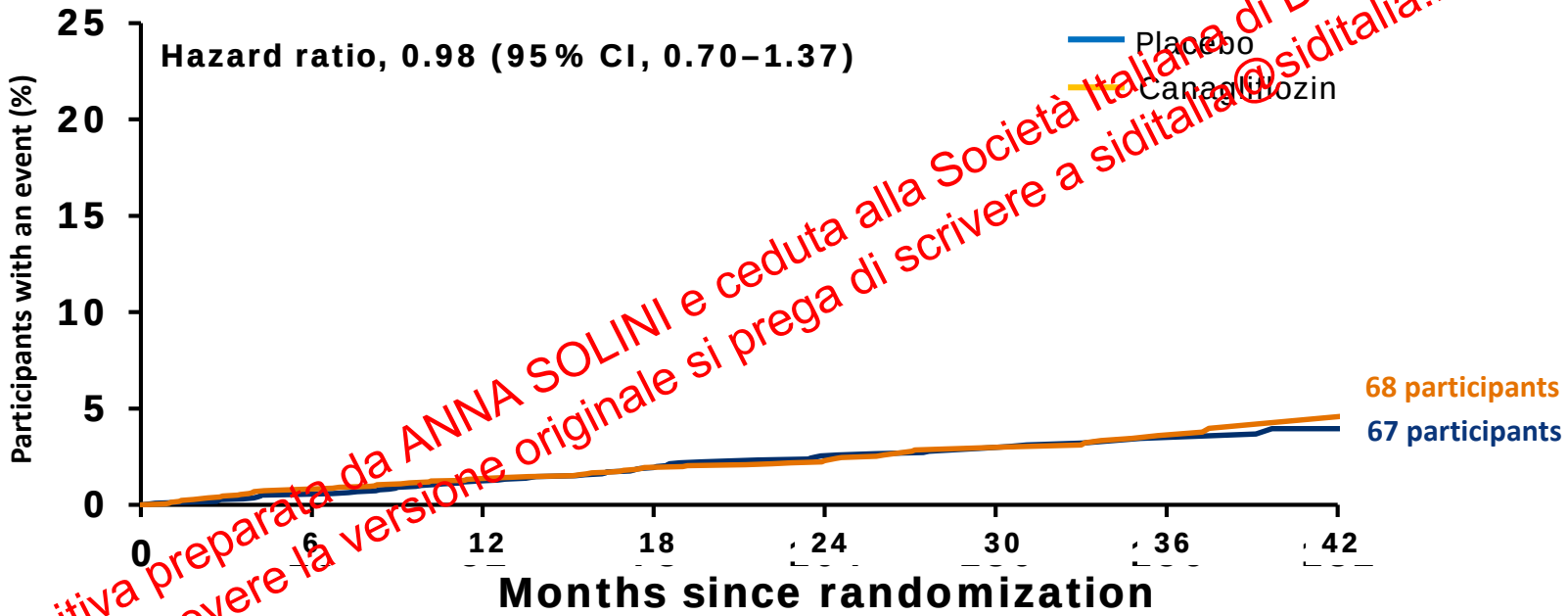
Bone fracture risk in SGLT2 inhibitors vs placebo

27 eligible RCTs
20,895 T2DM patients
64.22 weeks



Li X, Diabetes Metab Res Rev 2019

The CREDENCE Study: Fractures

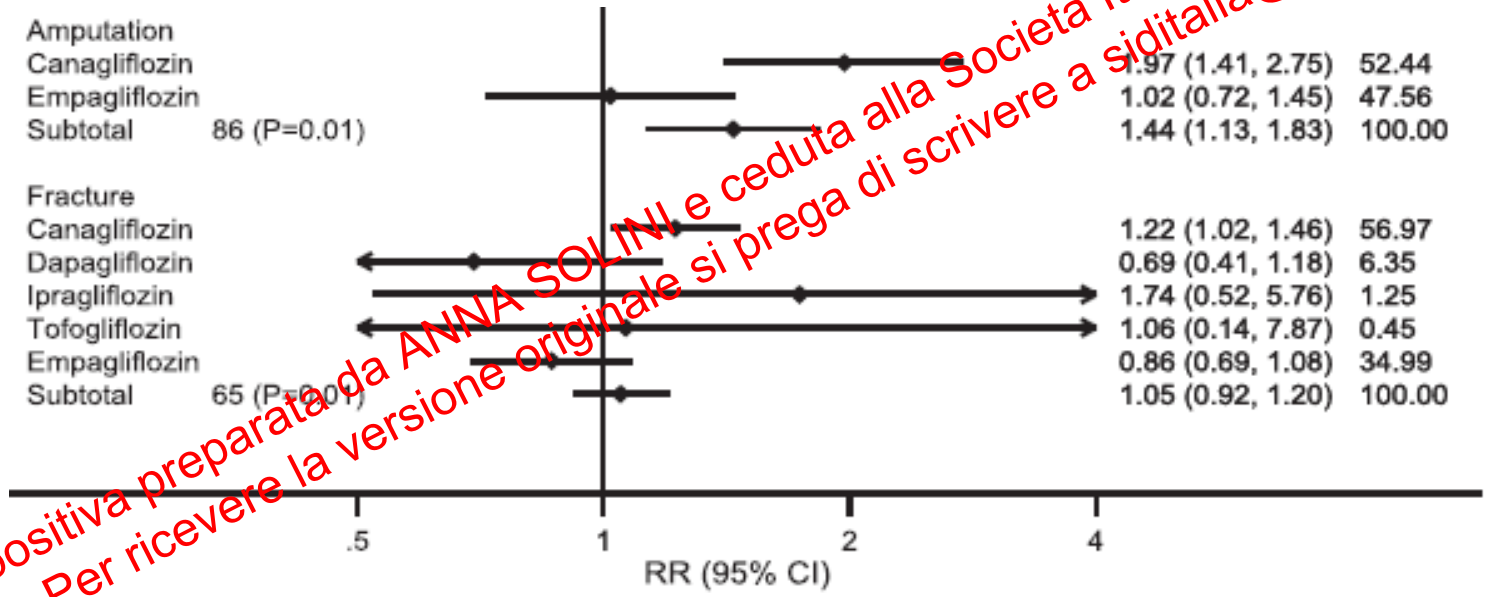


No. at risk								
Placebo	2197	2166	2128	2061	1769	1178	656	176
Canagliflozin	2200	2171	2121	2074	1785	1225	668	200

Perkovic V, N Engl J Med 2019

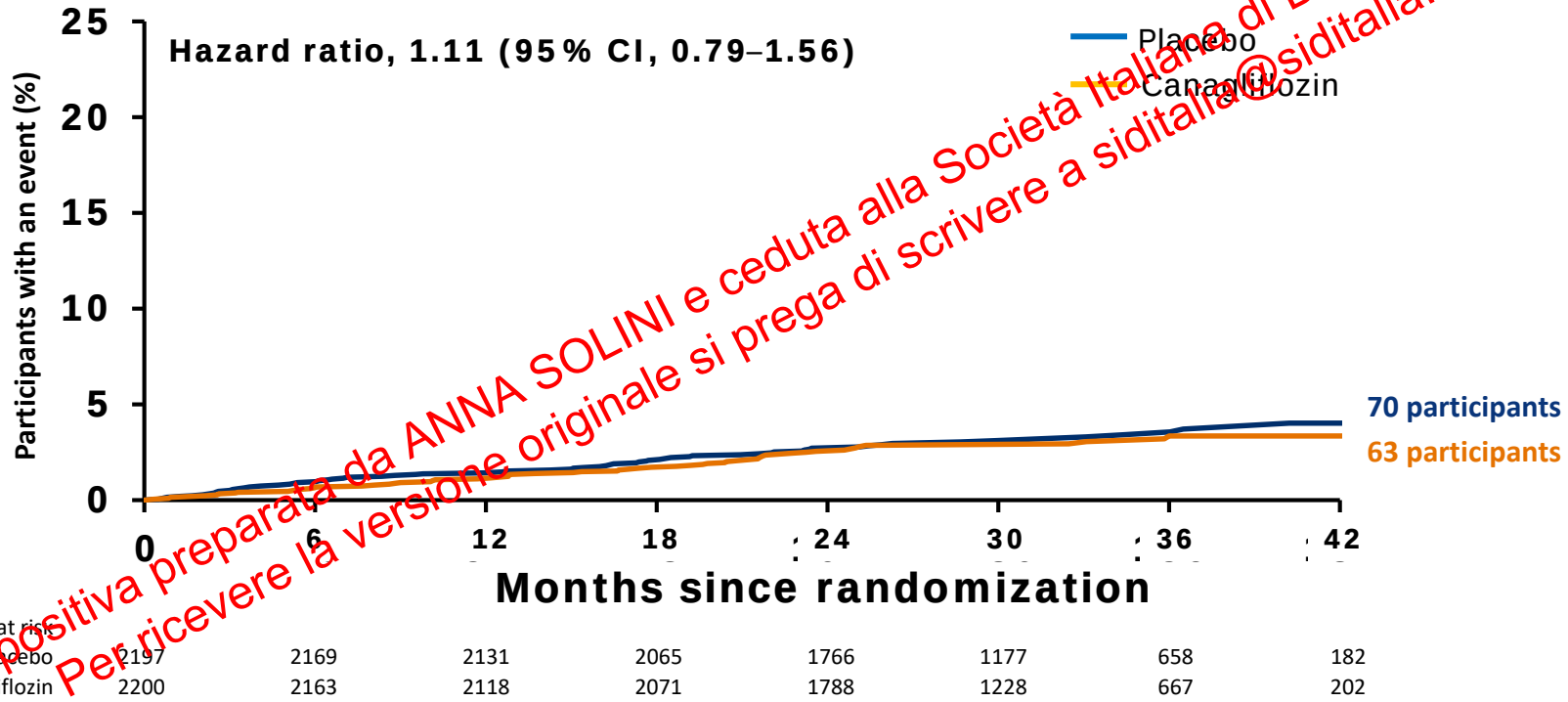
Frequence of amputations: a systematic review

Systematic review of 82 trials, 4 overviews and 6 regulatory reports



Radholm K, Diabetes Res Clin Pract 2018

The CREDENCE Study: lower extremity amputations



Perkovic V, N Engl J Med 2019

Risk of LEA in T2DM treated with SGLT2 inhibitors in the USA.

A retrospective cohort study

Crude incidence rate of BKLE amputation (n = 118,018 vs 226,623)

New users cohort	Number of exposed persons	Persons with amputation before exposure	Person-years at risk	Persons with BKLE amputation post-exposure	Incidence rate, per 1000 person-years
Overall					
SGLT2 inhibitors	119 567	225	140 145	171	1.22
Canagliflozin	73 024	139	95 42[illegible]	120	1.26
Dapagliflozin	39 117	76	38 541	37	0.96
Empagliflozin	24 433	55	17 930	25	1.39
Non-SGLT2 inhibitor AHA	226 623	722	283 406	530	1.87
High CV risk					
SGLT2 inhibitors	25 781	130	30 050	61	2.03
Canagliflozin	15 8[illegible]0	75	20 594	41	1.99
Dapagliflozin	8045	46	7829	10	1.28
Empagliflozin	5538	22	4098	14	3.42
Non-SGLT2 inhibitor AHA	48 483	357	58 903	194	3.29
Non-high CV risk					
SGLT2 inhibitors	93 786	105	110 095	110	1.00
Canagliflozin	57 174	64	74 827	79	1.06
Dapagliflozin	31 072	30	30 712	27	0.88
Empagliflozin	18 865	33	13 831	11	0.80
Non-SGLT2 inhibitor AHA	178 140	365	224 503	336	1.50

Yuan Z, Diabetes Obes Metab 2018

Some comments on the amputation risk

- Increased amputation risk was not noted in any other canagliflozin trial beside CANVAS, or other SGLT2 inhibitors.
- Potential explanations for the difference may lie in the baseline characteristics of the CANVAS population or the method of drug administration, molecular variation despite being from the same class; differences in amputation event ascertainment; varying populations; and chance.
- Moreover, the clinical benefit regarding MACE occurred during earlier phases of the study than did the adverse events, which occurred predominantly in the late phase of the study. This finding suggests the presence of other factors which may have led to the increased incidence of adverse events.
- Adverse events resulting from volume depletion, that might contribute to the circulatory failure in the distal peripheral arterial bed (see thiazides).
- An additional factor may be the relatively lower adherence with the study drugs in the CANVAS program discontinuation of the agent erased the potentially beneficial effects of the SGLT2 inhibitor on endothelial and metabolic function, causing an excess of distal peripheral arteriosclerosis and ischemia.

Prevention of adverse events with SGLT2 inhibitors

	At risk	Measures to prevent adverse event	
Genital mycotic infections	Women, prior candidiasis	Perineal hygiene, changing pads/tampons frequently, avoid tight synthetic underwear. With recurrent infection: consider treating partner	
Urinary tract infection	Prior UTI Neurogenic bladder, paraparesis, indwelling urinary catheter	Probably avoid SGLT2i in patients at very high risk	
Hypoglycaemia	Currently taking SU and/or insulin with current insulin or SU treatment, higher risk with prior hypoglycaemia, in elderly, or with impaired renal function	A1C <8.0 consider stopping or reducing dose of SU and or reducing insulin dose when initiating an SGLT2i Do not discontinue insulin	
Diabetic ketoacidosis	Acute illness, surgery, reduced oral intake, alcohol abuse or inappropriate reduction of insulin dosage	Stop SGLT2i with acute illness/surgery Maintain insulin if necessary, make only small adjustments to insulin dosage Beware DKA can present with normal or minimally increased blood glucose in patients receiving SGLT2i Do not use SGLT2i in patients with type 1 diabetes or with prior history of DKA	Advise patient of need for sick day strategy (Figure 2) with acute illness to reduce risk of DKA, acute kidney injury or symptomatic hypotension
Hypotension	SBP <100 mm Hg postural hypotension	Assess for volume depletion/hypotension (Figure 1) Consider reducing diuretic	
Acute kidney injury	Hypotension volume depletion	Stop SGLT2i with acute illness/surgery. Maintain euvolemia	
Fractures	Osteoporosis renal impairment	Avoid SGLT2i in patients at very high risk Use of vitamin D is of unproven benefit	
Amputations	Ischemic ulcers, neuropathy Peripheral vascular disease Lower limb ischemia Prior amputation	Avoid SGLT2i in patients with rest ischemia, ischemic ulcers, and prior amputations	

Fitchett D, Diabetes Obes Metab 2019

SGLT2 inhibitors and risk of serious adverse events: a nationwide register based cohort study

Outcome	No of events/No of events per 1000 patient years: SGLT2 inhibitors	GLP1 receptor agonists	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Lower limb amputation				
Intention-to-treat exposure definition	56/2.9	38/1.6		1.90 (1.25 to 2.87)
Additionally adjusted model	18/2.0	8/0.7		2.79 (1.19 to 6.55)
Varied grace period (30 days)	31/2.6	13/0.9		2.70 (1.41 to 5.17)
Adjusted for country	40/2.7	22/1.1		2.37 (1.40 to 4.00)
Bone fracture				
Intention-to-treat exposure definition	318/16.4	373/15.5		1.07 (0.92 to 1.24)
Additionally adjusted model	131/14.4	148/13.5		1.09 (0.86 to 1.39)
Varied grace period (30 days)	178/15.3	193/13.7		1.12 (0.91 to 1.37)
Adjusted for country	228/15.4	263/13.9		1.11 (0.93 to 1.33)
Varied outcome definition (fracture leading to hospital stay)	66/4.4	79/4.1		1.09 (0.78 to 1.51)
Excluding users of thiazolidinediones	223/15.2	256/13.6		1.12 (0.94 to 1.34)
Diabetic ketoacidosis				
Intention-to-treat exposure definition	23/1.2	11/0.6		1.95 (1.00 to 3.80)
Additionally adjusted model	12/1.3	6/0.5		2.13 (0.79 to 5.78)
Varied grace period (30 days)	17/0.9	6/0.4		1.99 (0.73 to 5.41)
Adjusted for country	19/1.1	11/0.6		2.14 (1.01 to 4.52)
Acute kidney injury				
Intention-to-treat exposure definition	55/2.8	76/3.1		0.90 (0.63 to 1.27)
Additionally adjusted model	25/2.7	48/4.3		0.72 (0.44 to 1.18)
Varied grace period (30 days)	26/2.2	42/3.0		0.73 (0.45 to 1.20)
Adjusted for country	34/2.3	62/3.2		0.68 (0.45 to 1.03)

Outcome	No of events/No of events per 1000 patient years: SGLT2 inhibitors	GLP1 receptor agonists	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Serious urinary tract infection				
Intention-to-treat exposure definition	125/5.4	147/6.1		1.06 (0.84 to 1.35)
Additionally adjusted model	42/4.6	70/6.3		0.81 (0.55 to 1.20)
Varied grace period (30 days)	64/5.5	87/6.2		0.88 (0.64 to 1.22)
Adjusted for country	80/5.4	114/6.0		0.89 (0.67 to 1.19)
Venous thromboembolism				
Intention-to-treat exposure definition	91/4.6	115/4.7		0.99 (0.75 to 1.30)
Additionally adjusted model	39/4.3	47/4.2		1.11 (0.72 to 1.71)
Varied grace period (30 days)	48/4.1	58/4.1		0.98 (0.67 to 1.44)
Adjusted for country	63/4.2	79/4.1		0.99 (0.71 to 1.38)
Acute pancreatitis				
Intention-to-treat exposure definition	29/1.5	29/1.2		1.27 (0.76 to 2.13)
Additionally adjusted model	15/1.6	13/1.2		1.47 (0.69 to 3.14)
Varied grace period (30 days)	17/1.4	16/1.1		1.35 (0.68 to 2.68)
Adjusted for country	20/1.3	23/1.2		1.15 (0.63 to 2.10)
Excluding users of DPP4 inhibitors	14/1.5	16/1.3		1.20 (0.58 to 2.48)

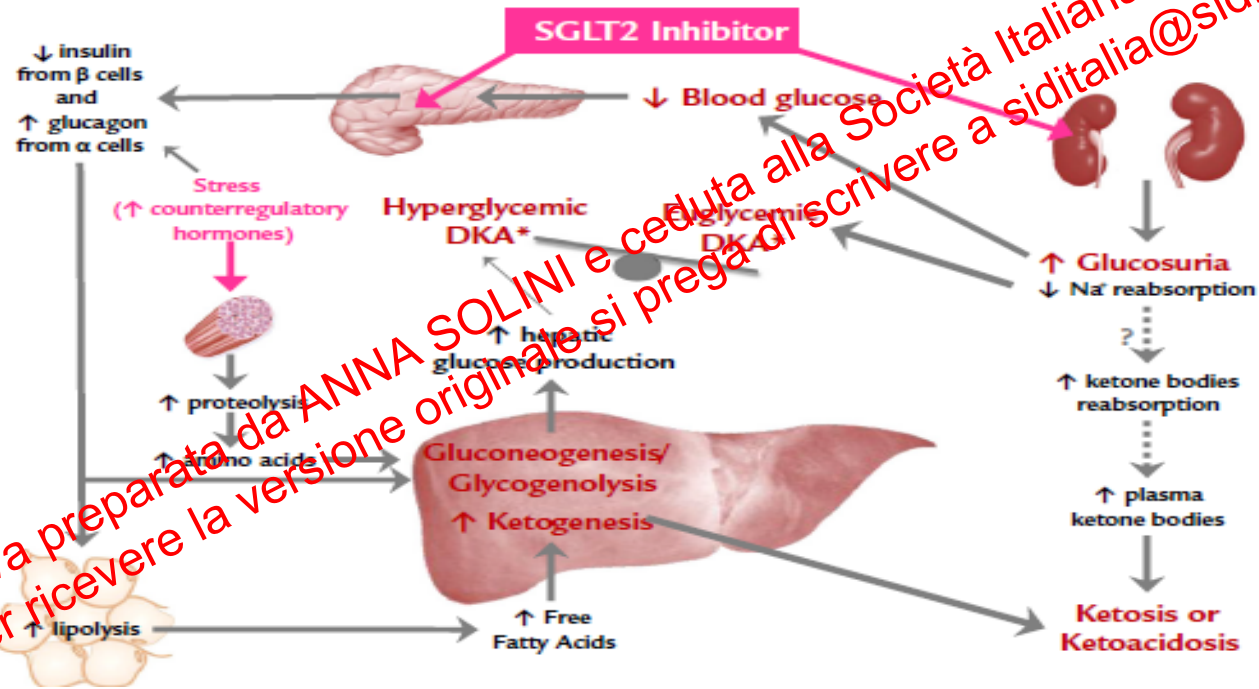
0.1 0.5 1 2 10

N= 17,213 vs 17,213

Propensity Score matching

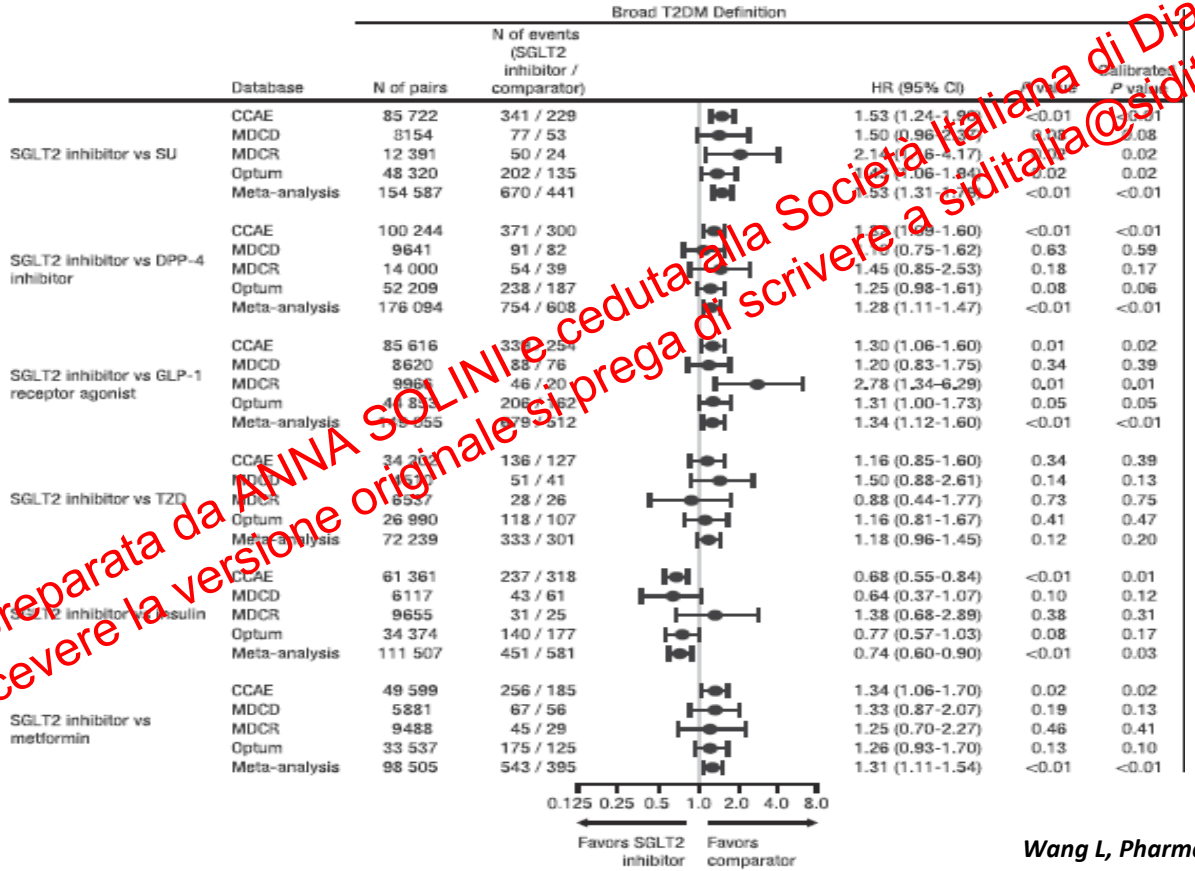
Ueda P, BMJ 2018

Mechanism of SGLT2 inhibitor-associated diabetic ketoacidosis



Goldenberg RM, Clin Ther 2016

HR of DKA for new users of SGLT2 inhibitors vs other hyperglycemic agents



Wang L, Pharmacoepidemiol Drug Saf 2019

Estimated risk of euglycemic diabetic ketoacidosis with SGLT2 inh compared with placebo or active comparators

References	Study	Comparator	Results HR (95%CI)
Meta-analysis of RCT			
Monami, 2017	8 RCTs	Placebo	1.22 (0.461-3.210)
Observational studies			
Wang, 2017	US insurance database	Other GLAs	1.91 (0.945-4.11)
Jensen, 2017	Danish nationwide study	Other GLAs	1.6 (0.7-3.5)
Fralick, 2017	US insurance database	DPP-IV inhibitors	2.2 (1.4-3.6)
Kim, 2018	Korean Health Insurance	DPP-IV inhibitors	0.95 (0.58-1.57)
Ueda, 2018	Nationwide registers (Sweden and Denmark)	GLP-1 RAs	2.14 (1.01-4.52)
Pharmacovigilance reports			
Fadini, 2017	US FDA	Other GLAs	**7.9 (7.5-8.4)**
Blau, 2017	US FDA	DPP-IV inhibitors	**~14 (all) ~7 (T2DM)**
Ado Moumouni, 2018	WHO VigiBase	Other GLAs	**OR=15.5 (12.8-18.7)**

Scheen AJ, Expert Opin Drug Saf 2019

Outline

Side effects

- Genital infections
- Lower limb amputations
- Fractures
- DKA

Concomitant treatments

- Insulin
- DPP-IV inh/GLP1 RA

SGLT2 inhibition and risk of DKA developing in the community and during hospital admission

A retrospective cohort study performed in all the hospitals of Melbourne and Geelong (5 million inhabitants) in 2015-2017

DKA: 162 events

Incidence of DKA in confirmed T2DM exposed or unexposed to SGLT2 inhibition during a 26-mo audit period

Fasting status and potential precipitating events for DKA development

		SGLT2i (n = 37)	Non-SGLT2i (n = 125)	*P* Value
Insulin	24 (65)	70 (56)		0.45
Metformin	32 (87)	81 (65)		0.014
Sulfonylurea	7 (19)	28 (22)		0.82
DPP4 inhibitor	6 (16)	14 (11)		0.40
GLP-1 analog	2 (5)	1 (1)		0.13
Thiazolidinedione	1 (3)	2 (2)		0.54
α-Glucosidase inhibitor	2 (5)	1 (1)		0.13

Surgery	15 (41)	3 (2)	<0.001
Major[a]	12	2	
Minor[b]	3	1	
Infection	10 (27)	51 (41)	0.18
Nonadherence to medication	5 (14)	19 (15)	1.0
Illness (e.g., AMI, stroke)	4 (11)	19 (15)	0.61
Alcohol	1 (3)	5 (4)	1.0
Glucocorticoids	1 (3)	3 (2)	1.0
None apparent	4 (11)	23 (18)	0.33

Hamblin PS, J Clin Endocrinol Metab 2019

Recommendations for patients with T1D initiated on SGLT inhibitor adjunct therapy

- ✓ Not recommended for poorly compliant patients with HbA1c>7.5mmol/mol (9%) and history of DKA
- ✓ Consider increased DKA risk in patients on insulin-pump therapy
- ✓ Use lowest available dose of SGLT inhibitor required to achieve clinical benefit
- ✓ Reduce prandial insulin by 10-20% initially and adjust doses of prandial and basal insulin based on frequent pre-and postprandial glucose monitoring
- ✓ Reassess insulin carbohydrate ratios once established on SGLT inhibitor
- ✓ Provide blood ketone meter and advise on DKA diagnosis and management
- ✓ Advise blood ketone testing if patient is feeling sick and blood glucose is >9 mmol/L
- ✓ Advise stopping SGLT inhibitor during intercurrent illness or conditions where there is fluid loss or reduced fluid intake
- ✓ Advise about increased risk of genital mycotic infections and/or diarrhoea

McCrimmon RJ, Diabetologia 2018

Precipitants for SGLT2 inhibitor-associated DK and actions to prevent its occurrence

The insulin dose should be maintained, and supplemental insulin may be necessary

Precipitant	Action(s) regarding SGLT2 inhibitor
Acute illness (eg, infection, gastroenteritis, myocardial infarction/stroke)	Hold at onset; restart when feeling well and able to eat and drink
Bariatric surgery	Hold while on preoperative low-carbohydrate diet; revaluate post-operatively
Major surgical procedures	Hold 3 days before surgery; restart when feeling well and able to eat and drink
Risk of dehydration (eg, extensive exercise, preparing for colonscopy)	Hold until able to maintain hydration
Low-carbohydrate diet	Hold until normal diet resumes
Excessive alcohol intake	Stop immediately; reassess at a later date

Sick-day strategy of temporary discontinuation of medications in the event of an acute illness, major surgery or trauma

Sick Day Medication List

If people with diabetes become ill and are unable to maintain adequate fluid intake, or have an an acute decline in renal function (eg due to GI upset or dehydration) they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function

- ACE inhibitors
- ARBs
- Direct renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

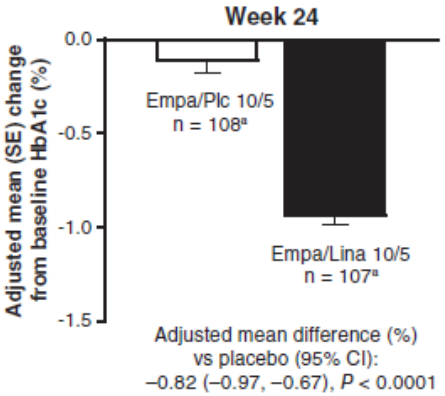
B) Have reduced clearance and increase risk for adverse effects

- Metformin
- Sulphonylureas (glicazide, glimeprimide, glyburide)

S	sulphonylureas
A	ACE inhibitors
D	diuretics, direct renin inhibitors
M	metformin
A	angiotension receptor blockers
N	nonsteroidal anti-inflammatory
S	SGLT2 inhibitors

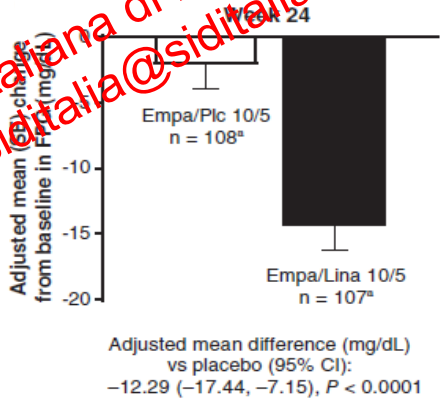
Diabetes Canada
Can J Diabetes 2018

Efficacy and safety of the combination empagliflozin+linagliptin in T2DM japanese subjects



HbA1c

FPG



Adverse event	Part A (24 weeks with FDC)		Part B (52 weeks with FDC)	
	Empa/Plc 10/5 (*n* = 108)	Empa/Lina 10/5 (*n* = 107)	Empa/Plc 25/5 (*n* = 116)	Empa/Lina 25/5 (*n* = 116)
≥ 1 AE	64 (59.3)	53 (49.5)	86 (74.1)	94 (81.0)
≥ 1 Serious AE	3 (2.8)	1 (0.9)	1 (0.9)	2 (1.7)
≥ 1 Drug-related AE	16 (14.8)	13 (12.1)	23 (19.8)	33 (28.4)
≥ 1 AE leading to discontinuation	5 (4.6)	2 (1.9)	3 (2.6)	4 (3.4)
≥ 1 Serious AE	4 (3.7)	1 (0.9)	8 (6.9)	6 (5.2)
Death	0 (0)	0 (0)	0 (0)	0 (0)

Kaku K, Diabetes Obes Metab 2019

Safety of empagliflozin plus linagliptin

Table 1. Compilation of key data on adverse events (AEs) from phase III trials with the combination of empagliflozin 10 mg (E10) and 25 mg (E25) plus linagliptin 5 mg (L5) vs individual components.

	Lewin et al [28]					D'Onofrio et al [29]				
Background therapy	Diet and exercise					Metformin				
	E10+ L5	E25+ L5	E10	E25	L5	E10+ L5	E25 + L5	E10	E25	L5
n	136	136	135	135	135	135	134	137	140	128
One or more AEs	99 (72.8)	103 (75.7)	110 (81.5)	93 (68.9)	97 (70.9)	94 (69.1)	98 (71.5)	96 (68.6)	103 (73.0)	91 (68.9)
One or more drug-related* AEs	14 (10.3)	23 (16.9)	16 (11.9)	22 (16.3)	17 (12.6)	23 (16.9)	18 (13.1)	26 (18.6)	26 (18.4)	15 (11.4)
One or more severe AEs	8 (5.9)	8 (5.9)	11 (8.1)	10 (7.4)	1 (0.7)	9 (6.6)	11 (8.0)	7 (5.0)	4 (2.8)	8 (6.1)
One or more serious AEs	7 (5.1)	6 (4.4)	10 (7.4)	9 (6.7)	2 (1.5)	9 (6.6)	6 (4.4)	6 (4.3)	10 (7.1)	8 (6.1)
Deaths	1 (0.7)	0	1 (0.7)	2 (1.5)	0	1 (0.7)	0	1 (0.7)	0	0
Confirmed hypoglycaemia ^	0	0	1 (0.7)	1 (0.7)	1 (0.7)	3 (2.2)	5 (3.6)	2 (1.4)	5 (3.5)	3 (2.3)
Events consistent with UTI+	21 (15.4)	17 (12.5)	22 (16.3)	14 (10.4)	14 (10.4)	13 (9.6)	14 (10.2)	16 (11.4)	19 (13.5)	20 (15.2)
Male	5 (3.8)	4 (3.0)	6 (9.2)	3 (3.8)	2 (2.7)	2 (2.4)	2 (2.7)	3 (3.7)	2 (3.0)	3 (4.5)
Female	16 (25.8)	13 (20.3)	16 (22.9)	11 (19.3)	12 (20.0)	11 (21.2)	12 (18.8)	13 (22.0)	17 (22.7)	17 (26.2)
Events consistent with GI‖	4 (2.9)	8 (5.9)	7 (5.2)	6 (4.4)	4 (3.0)	8 (5.9)	3 (2.2)	11 (7.9)	12 (8.5)	3 (2.3)
Male	1 (1.4)	5 (6.9)	2 (3.1)	1 (1.3)	1 (1.3)	2 (2.4)	2 (2.7)	5 (6.2)	3 (4.5)	2 (3.0)
Female	3 (4.8)	3 (4.7)	5 (7.1)	5 (8.8)	3 (5.0)	6 (11.5)	1 (1.6)	6 (10.2)	9 (12.0)	1 (1.5)
Nasopharyngitis	5 (3.7)	10 (7.4)	9 (6.7)	5 (3.7)	8 (5.9)	11 (8.1)	8 (5.8)	7 (5.0)	9 (12.0)	12 (9.1)
Pancreatitis #	0	1 (0.7)	0	0	0	0	0	0	0	1 (0.8)
Hypersensitivity reactions †	1 (0.7)	2 (1.5)	2 (1.5)	2 (1.5)	0	1 (0.7)	1 (0.7)	0	0	1 (0.8)

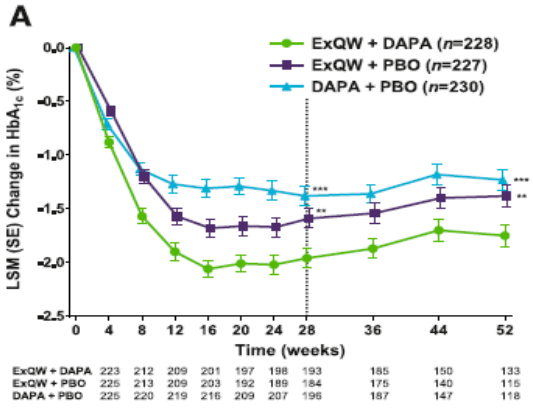
Data are n (%). UTI: urinary tract infections. GI: genital infections. *As assessed by the investigator. ^Plasma glucose ≤ 70 mg/dL (3.9 mmol/L) and/or requiring assistance. + Based on: 77 MedDRA preferred terms [29], 77 preferred terms [30]. ‖Based on: 89 MedDRA preferred terms. #Based on: 1 standardized MedDRA query and 1 preferred term. † Based on 3 standardized MedDRA queries.

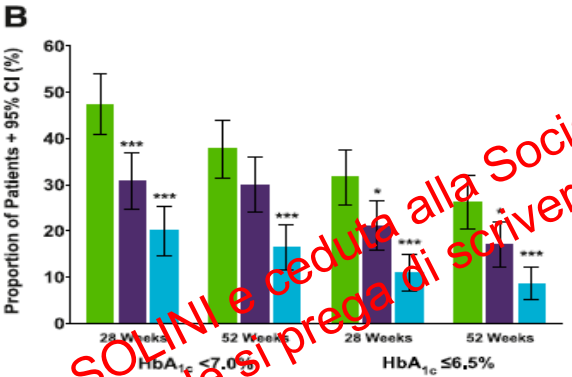
HYPO

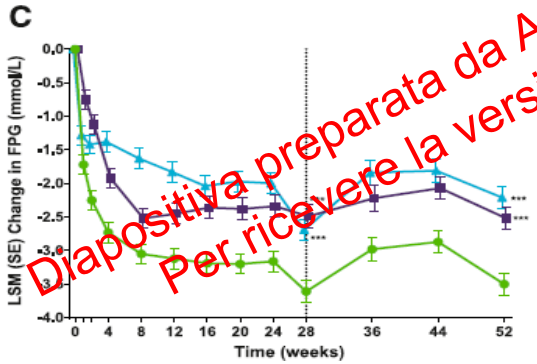
GI

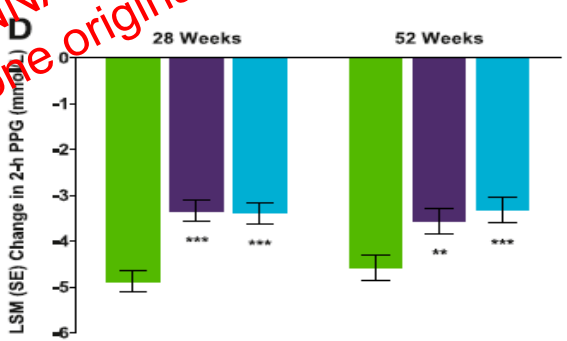
Molina-Vega M, Exp Opin Drug Saf 2018

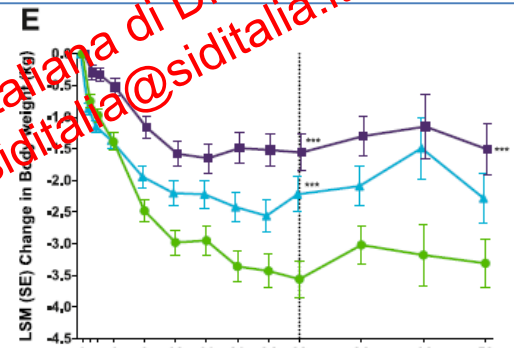
Exenatide once weekly + dapagliflozin: the DURATION-8 trial

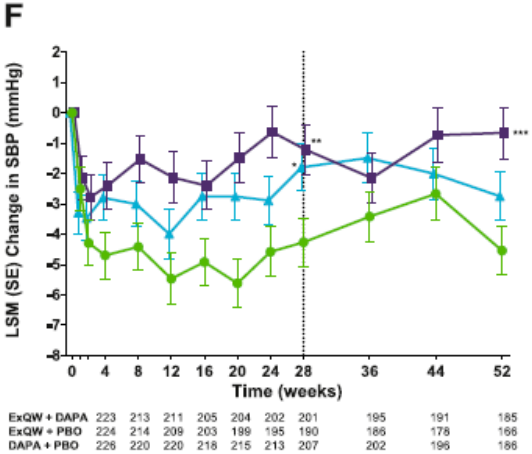






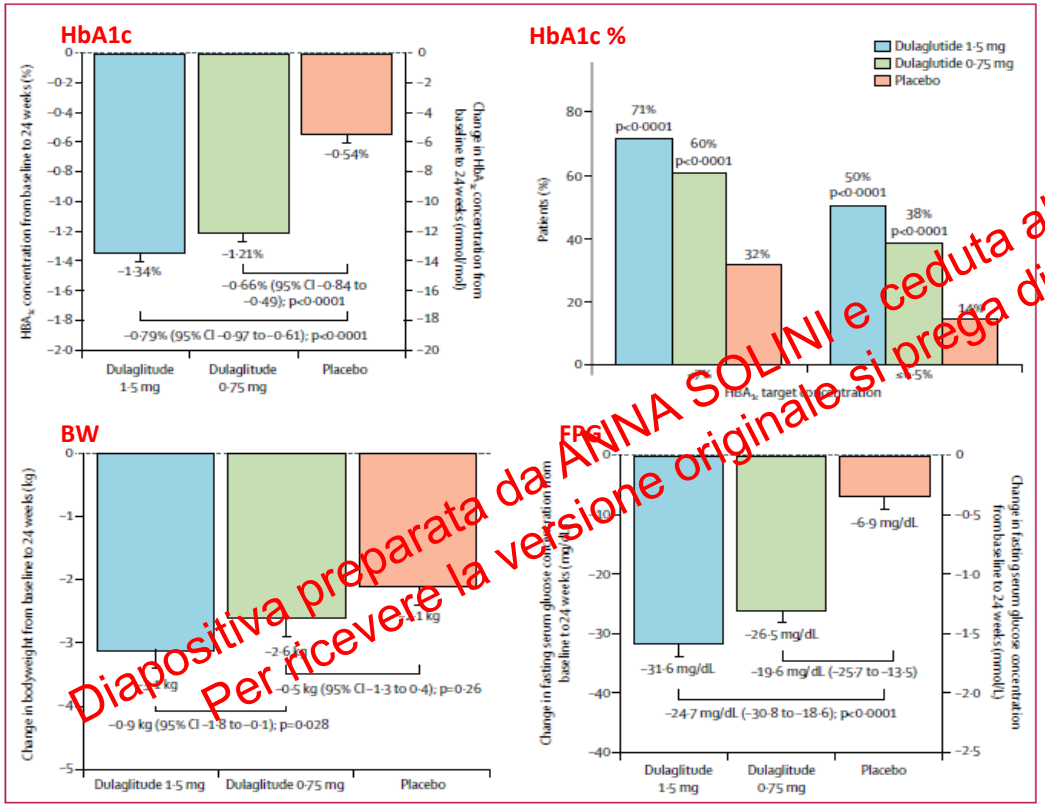


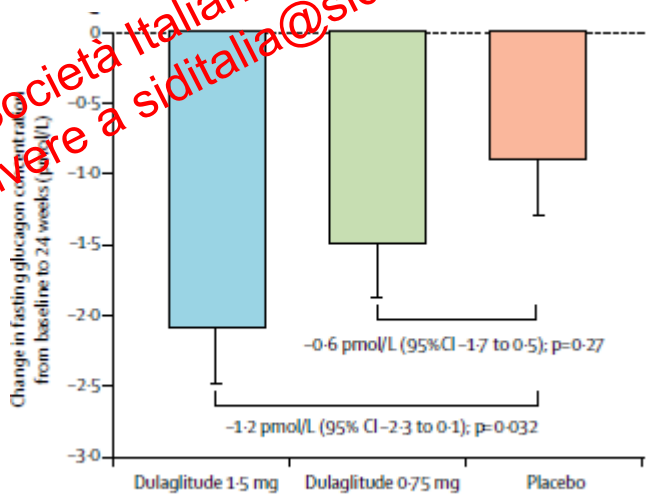




Jabbour SA, Diabetes Care 2018

Dulaglutide as add-on to SGLT2 inhibitors: the AWARD 10 study





Ludvik B, Lancet Diabetes Endocrinol 2018

Adverse events during the AWARD 10 study

	Dulaglutide 1·5 mg (n=142)	Dulaglutide 0·75 mg (n=141)	Placebo (n=140)
Deaths	2 (1%)	0	0
Serious adverse events	5 (4%)	3 (2%)	5 (4%)
Adjudication confirmed			
Pancreatic events	0	0	0
Cardiovascular events	0	0	3 (2%)
Cardiovascular death	0	0	0
Non-fatal myocardial infarction	0	0	2 (1%)
Unstable angina	0	0	1 (1%)
Renal and urinary disorders	1 (1%)	3 (2%)	4 (3%)
Treatment-emergent adverse events (patients with ≥1 adverse event)	95 (67%)	83 (59%)	84 (60%)
Treatment-emergent adverse events (≥5% of patients in either group)			
Gastrointestinal disorders	46 (32%)	29 (21%)	24 (17%)
Nausea	21 (15%)	7 (5%)	5 (4%)
Diarrhoea	8 (6%)	14 (10%)	4 (3%)
Other			
Back pain	15 (11%)	12 (9%)	10 (7%)
Headache	8 (6%)	5 (4%)	13 (9%)
Study or study-drug discontinuation or both, due to adverse events	4 (3%)	0	0

	Dulaglutide 1·5 mg (n=142)	Dulaglutide 0·75 mg (n=141)	Placebo (n=140)
Pancreatic enzymes, LOCF, units per L			
Pancreatic amylase	4·0 (1·0 to 7·0)	4·0 (−1·0 to 8·0)	0·0 (−3·0 to 3·0)
Lipase	7·0 (−3·0 to 16·0)	5·0 (−4·0 to 12·0)	−1·0 (−8·0 to 5·0)
Patients with enzyme concentrations ≥1 x ULN			
Pancreatic amylase	12 (9%)	10 (7%)	6 (4%)
Lipase	29 (20%)	22 (16%)	18 (13%)
Patients with enzyme concentrations ≥3 x ULN			
Pancreatic amylase	1 (1%)	0	0
Lipase	3 (2%)	1 (1%)	1 (1%)
Adverse events of interest associated with SGLT2 inhibitors			
Amputation	0	0	0
Diabetic ketoacidosis	0	0	0
Hypotensive episodes or syncope	0	1 (1%)	1 (1%)
Genital Infections	0	0	1 (1%)
Fractures	1 (1%)	1 (1%)	1 (1%)

Data are n (%) or median (IQR). LOCF=last observation carried forward. SGLT2=sodium-glucose co-transporter-2. ULN=upper limit of normal.

Ludvik B, Lancet Diabetes Endocrinol 2018

A final comment

The impressive CV and renal protection exerted by these drugs will enormously enlarge their use in T2DM patients with and without previous CV disease.

In this view, their performance in combination with incretins appears clinically rewarding.

This implies a deep knowledge of the rare, but extremely severe complications related to their use.

Rareness should be balanced against severity and fatality

Pay particular attention in primary care

Consider closer monitoring of rare severe AEs