SID
Società Italiana di Diabetologia
fondata nel 1964

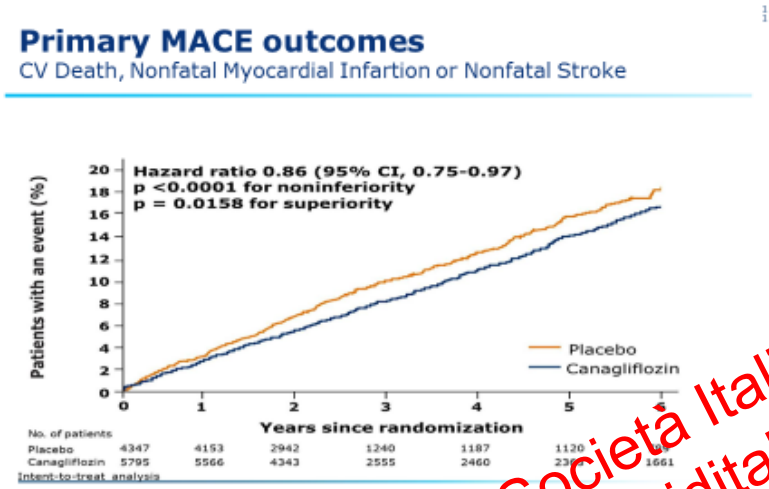
Sicurezza d'uso degli SGLT2 inibitori e strategie di miglioramento della sicurezza

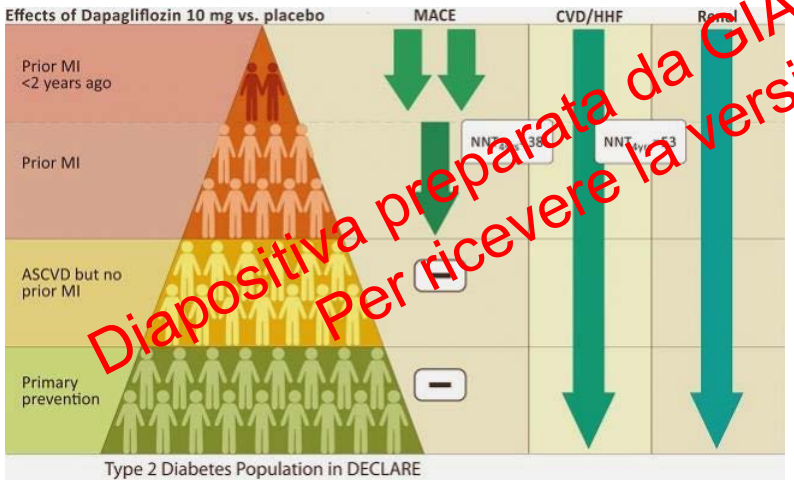
Gian Pio Sarice

SGLT2 INIBITORI

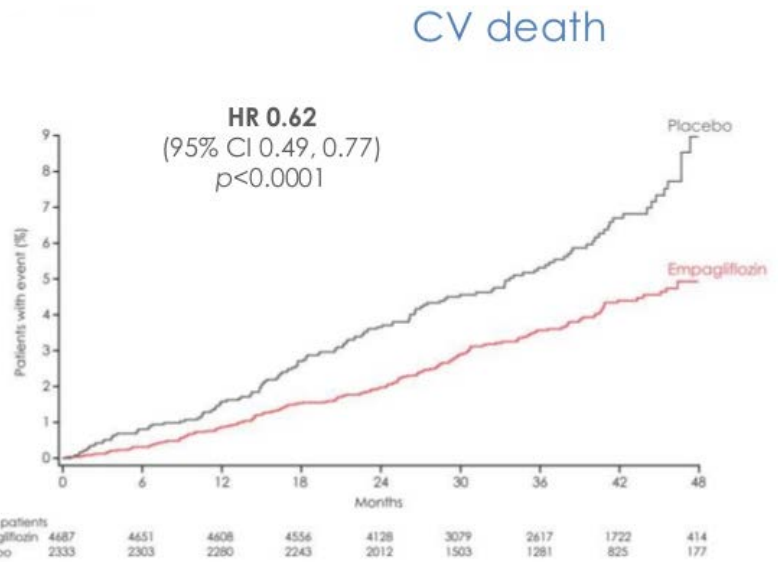
e progressione della **malattia renale** nel **diabete tipo 2**

CANVAS Program





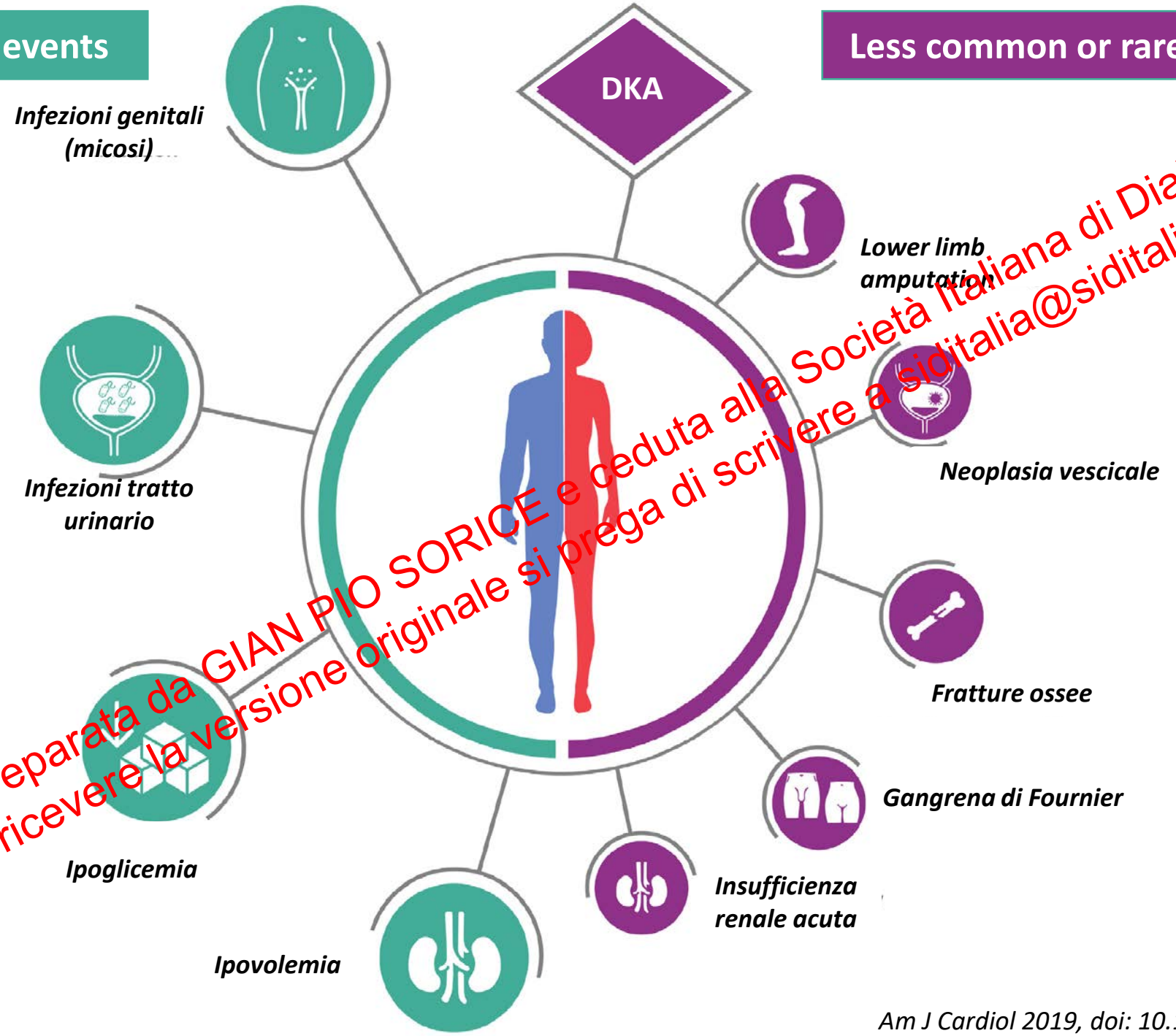
DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events



EMPA-REG OUTCOME

Common adverse events

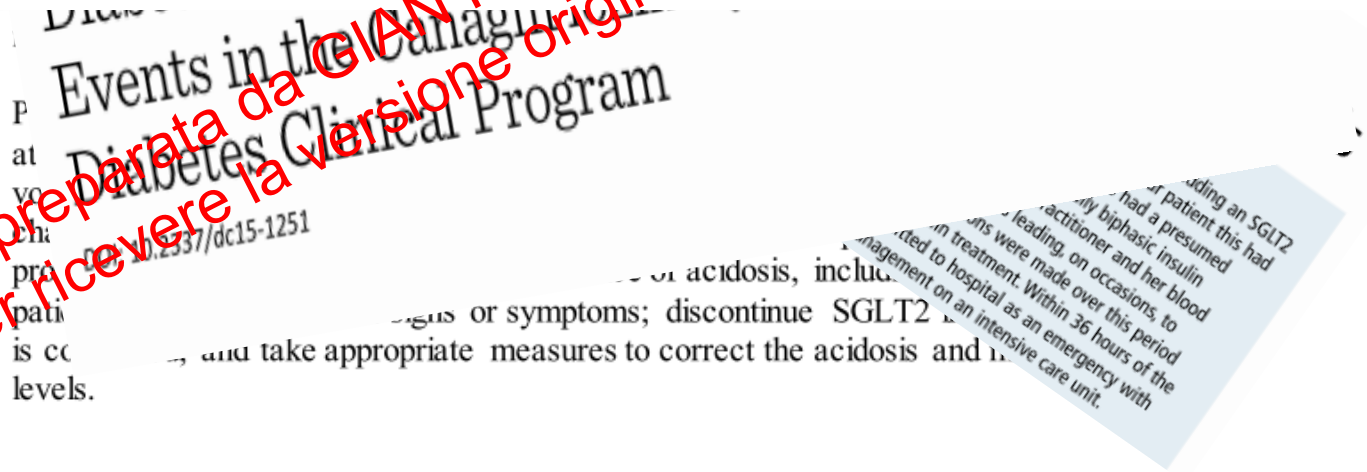
Less common or rare adverse events



Am J Cardiol 2019, doi: 10.1016/j.amjcard.2019.10.029

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors

Diabetes Care 2015;38:1638–1642 | DOI: 10.2337/dc15-1380



Events in the Management of Diabetes Clinical Program

DOI: 10.2337/dc15-1251

Case	Sex	Age (yrs)	T1/T2	Diabetes Duration (yrs)	Therapy	BMI (kgm^2)	Prior A1c (%)	PG (mg/dl)	pH	Where treated	Precipitating Factor/Insulin Dose Reduction
1	F	40	T1	17	MDI	26.5	11.4	220	6.9	ICU	URI/Yes
2	M	58	T2	2	N/A	26.5	9.8	150	7.12	ICU	Surgery/NA
3	F	27	T1	25	MDI	24.3	7.8	150 96	6.89	ICU OUTP	URI-Alcohol/Yes Alcohol/Yes
4	F	28	T1	6	CSII	25.9	8.0	224 158		ICU/ INPT	Alcohol/Yes Alcohol-exercise/Yes
5	F	31	T1	15	CSII	33.2	7.8	~125		OUTP	Exercise/Yes
6	F	55	T1	18	CSII	22	7.2	203		OUTP	GI/Unknown
7	F	26	T1	13	CSII+ GLP-1 RA	22	6.6	190 150 NA	7.15	ICU OUTP OUTP	None/NO
8	F	39	T1	26	CSII	26.1	7.0	233		ICU	URI/Yes
9	F	64	T2	6	BI+SU	32.8	7.8	169		ICU	Surgery/NA

BI, basal insulin, SU, sulfonylurea; GI, gastrointestinal, URI, upper respiratory tract infection, Inpt., inpatient; N/A, not available; Outpt., outpatient.

Peters A.L et al., Diabetes Care, 2015

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
HbA1c, %	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)
Time since diagnosis of type 2 diabetes, years			
≤5	423 (18.1)	406 (17.3)	434 (18.6)
>5 to 10	571 (24.5)	585 (24.9)	590 (25.2)
>10	1339 (57.4)	1354 (57.7)	1318 (56.3)
Glucose-lowering medication*			
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)
Sulphonylurea	992 (42.5)	985 (42.0)	1029 (43.9)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)
Mean daily dose, U**	65 (50.6)	65 (47.9)	66 (48.9)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

*Medication taken alone or in combination
**Placebo, n=1135; empagliflozin 10 mg, n=1132; empagliflozin 25 mg, n=1120

Peters A.L et al., Diabetes Care, 2015

DKA

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Diabetic ketoacidosis*	1 (<0.1%)	0.02	3 (0.1%)	0.05	1 (<0.1%)	0.02
Acute kidney injury†	155 (6.6%)	2.77	121 (5.2%)	2.07	125 (5.3%)	2.12
Events consistent with volume depletion§	115 (4.9%)	2.04	115 (4.9%)	1.97	124 (5.3%)	2.11
Serious events	24 (1.0%)	0.42	19 (0.8%)	0.32	26 (1.1%)	0.43
Events leading to discontinuation	7 (0.3%)	0.12	1 (<0.1%)	0.02	4 (0.2%)	0.07
Venous thrombotic events**	20 (0.9%)	0.35	9 (0.4%)	0.15	21 (0.9%)	0.35

Rate = per 100 patient-years

Patients treated with ≥1 dose of study drug

*Based on 4 MedDRA preferred terms. †Based on 1 standardised MedDRA query

§Based on 8 MedDRA preferred terms. **Based on 1 standardised MedDRA query

Peters A.L et al., Diabetes Care, 2015

DKA in the Canagliflozin T2 DM Clinical Program

	Patients with DKA (n = 12)	Patients without DKA (n = 17,584)
Sex, *n* (%)		
Male	9 (75.0)	7,182 (40.8)
Female	3 (25.0)	10,401 (59.2)
Age, years	69.5 (47, 78)	61.0 (20, 96)
Race, *n* (%)		
White	11 (91.7)	13,480 (76.7)
Black/African American	0	703 (4.0)
Asian	0	2,148 (12.2)
Other†	1 (8.3)	1,253 (7.1)
Ethnicity, *n* (%)		
Hispanic or Latino	2 (16.7)	3,118 (17.7)
Not Hispanic or Latino	10 (83.3)	14,385 (81.8)
Other‡	0	81 (0.5)
HbA_{1c}, %	8.9 (7, 11)	8.0 (5, 14)
HbA_{1c}, mmol/mol	74 (53, 97)	66 (31, 130)
BMI, kg/m^2	27.1 (23, 34)	31.3 (15, 73)
eGFR, mL/min/1.73 m^2	69.0 (33, 127)	79.0 (10, 227)
Duration of diabetes, years	13.5 (1, 29)	9.0 (0, 55)

Erondu N. at al.,Diabetes Care, 2015

DKA

Euglycemic Diabetic Ketoacidosis in a Patient With Type 2 Diabetes After Treatment With Empagliflozin

Paris Roach and Paul Skierczynski

Diabetes Care 2016;39:e3 | DOI: 10.2337/dc15-1797

….A 64-year-old woman with a 15-year history of type 2 diabetes ….. presented to the emergency room for evaluation of shortness of breath. She had been treated with insulin for 10 years (NPH 40 units twice daily and regular insulin 20 units with meals)…. At the time she started empagliflozin, she was taking liraglutide 1.8 mg per day, having discontinued insulin 3 weeks prior to presentation, to determine if her blood glucose could be controlled with liraglutide alone……. glucose measurements were in the low 200 mg/dL range on liraglutide alone, so treatment with empagliflozin 10 mg per day was initiated. Within 24 h of starting empagliflozin, she developed symptoms of weakness, joint pain, and mild confusion. After 4 days of treatment, she began to experience dyspnea on exertion and presented to the ER……

Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program

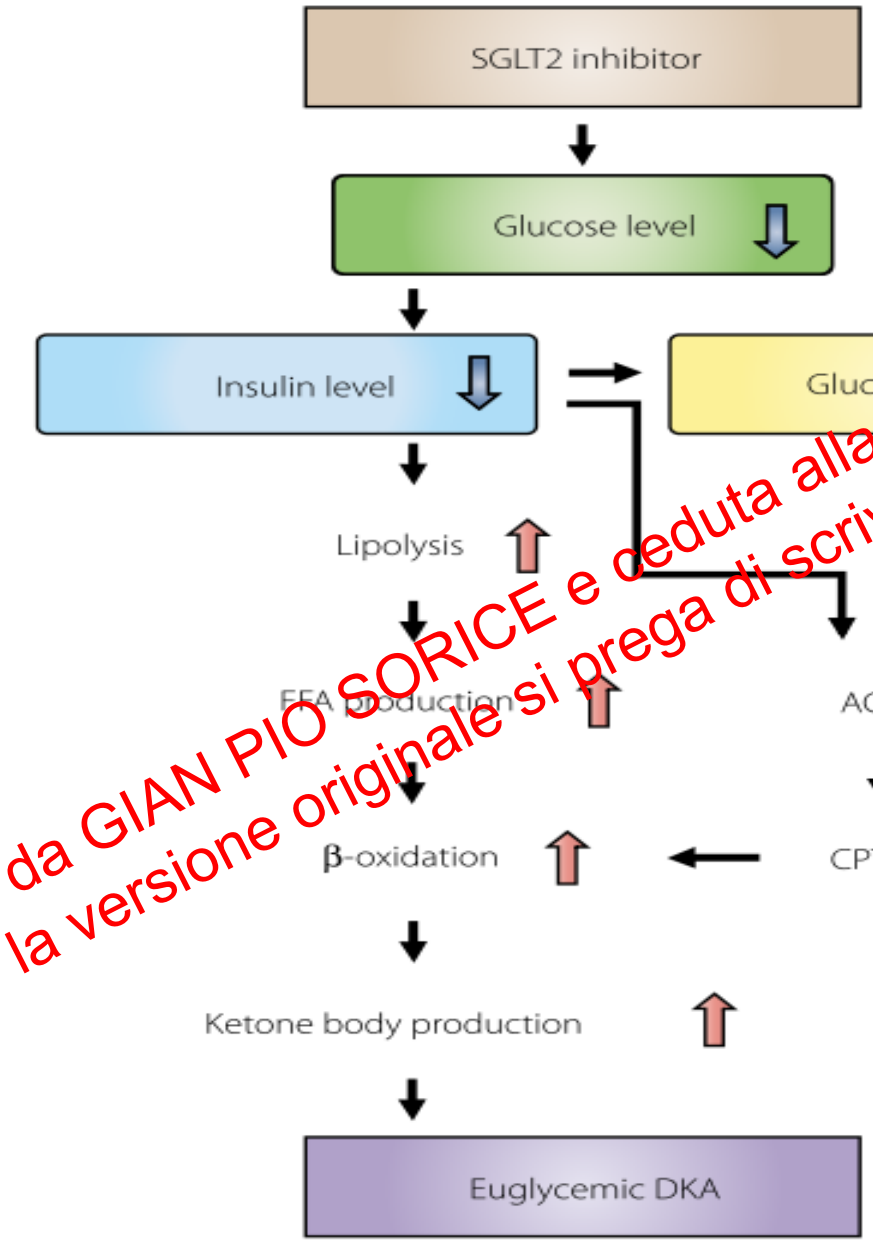
Ngozi Erondu, Mehul Desai, Kirk Ways, and Gary Meininger

Analyzed all serious adverse events of DKA, from 17.596 patients from RCT of canagliflozin through 11 May 2015

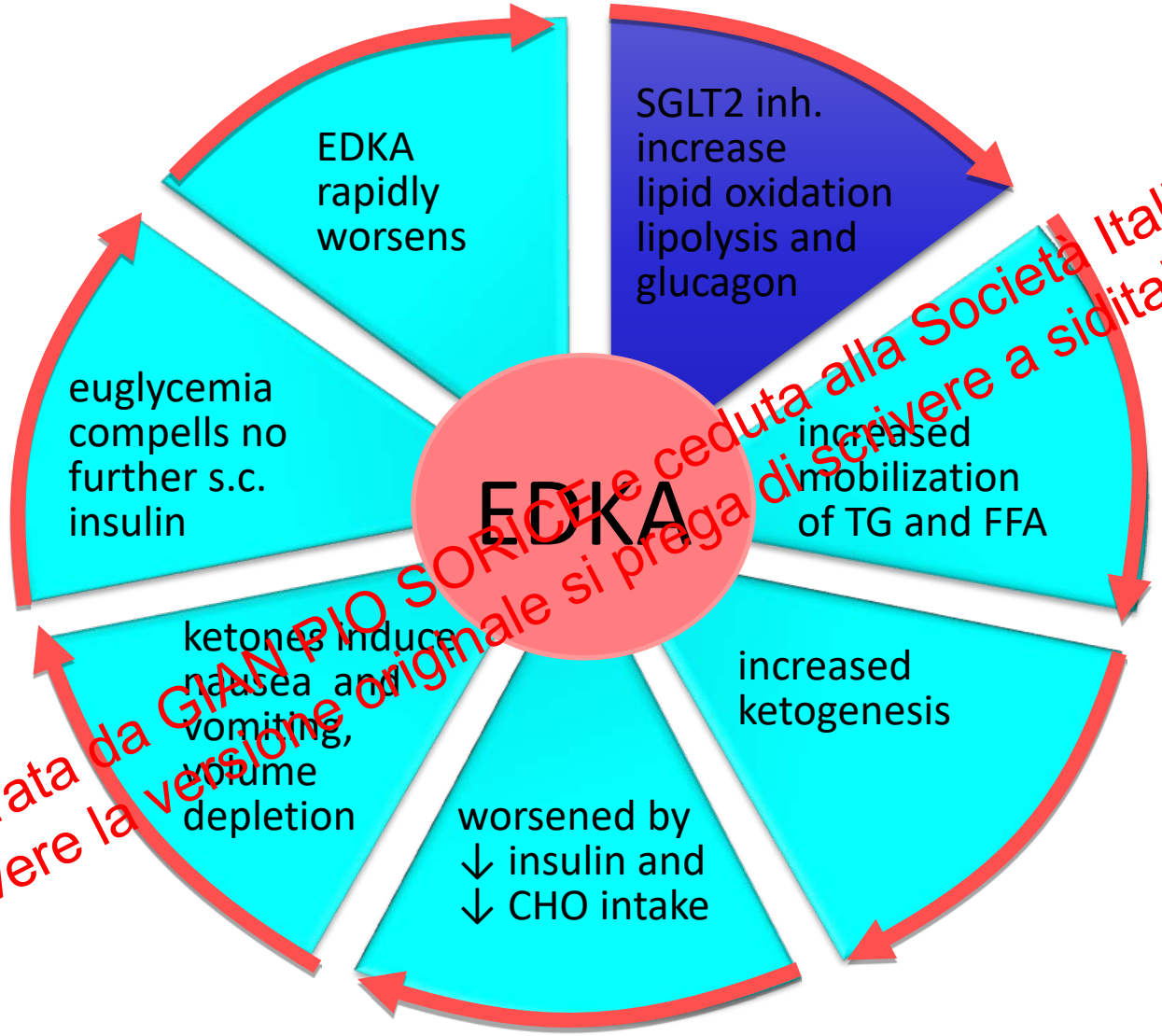
- DKA reported in 12 patients, 10 treated with canagliflozin (6 with 300 mg and 4 with 100 mg) and 2 with comparator, with an incidence rate of 0.522, 0.763, and 0.238 per 1.000 pt-years, respectively.
- Six out of the 10 treated with canagliflozin were reported to have LADA
- Most patients (8 out of the 10) were on insulin therapy. Half was non-compliant to insulin treatment
- Most patients (9 out of the 10) had blood glucose values >250 mg/dL
- Most patients had a known precipitating factor for DKA (MI, surgery, alcohol abuse, gastroenteritis, viral infection).

Majority of DKA occurs in people with diabetes who are **insulin deficient, i.e. long-standing T2D, LADA, and T1D**
Triggering factors include: surgery, extensive exercise, ilness, reduction in food intake and/or insulin doses, alcohol consumption
Symptoms such as abdominal pain, nausea, vomiting, fatigue, and dyspnea in patients on SGLT2 inhibitor should raise the suspect of DKA

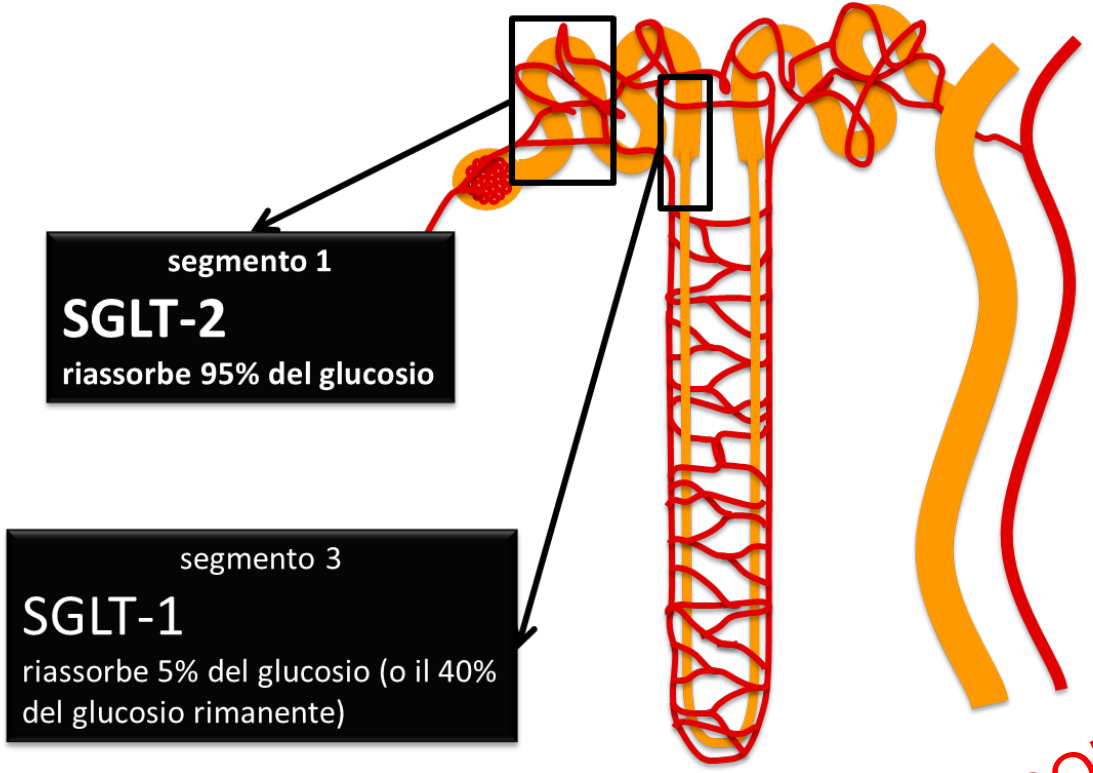
Diabetes Care 2015;38:1680–1686 | DOI: 10.2337/dc15-1251

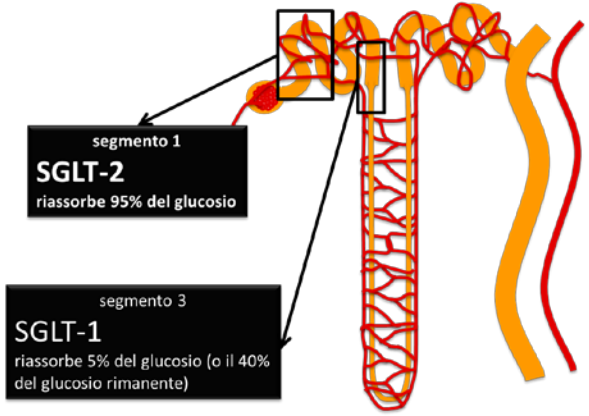


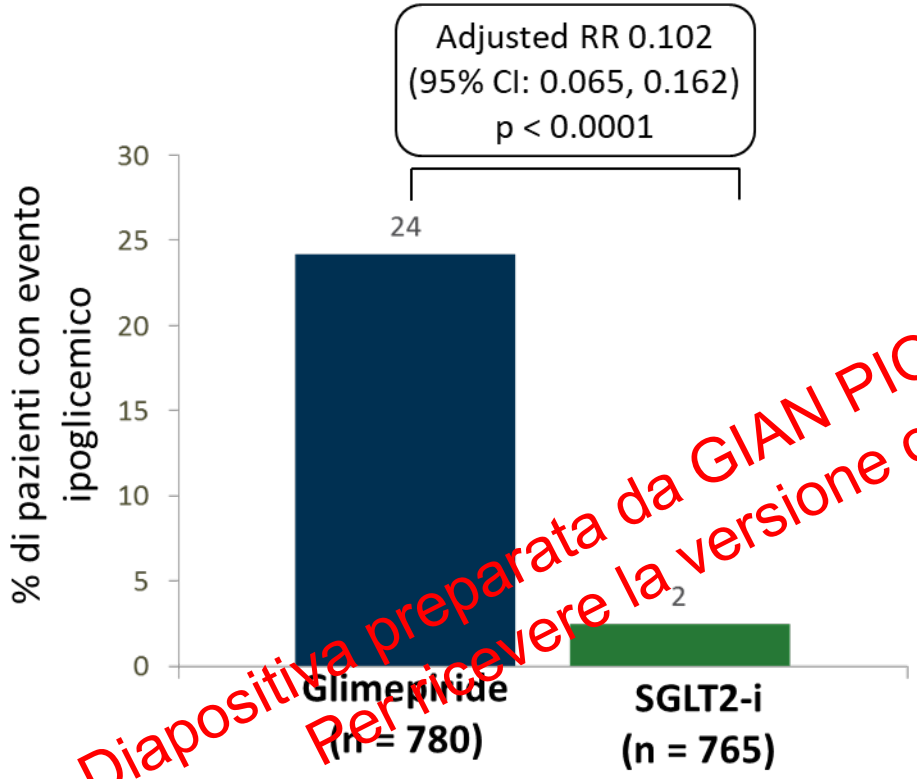
Ogawa and Sakaguch, J Diabetes Invest, 2015

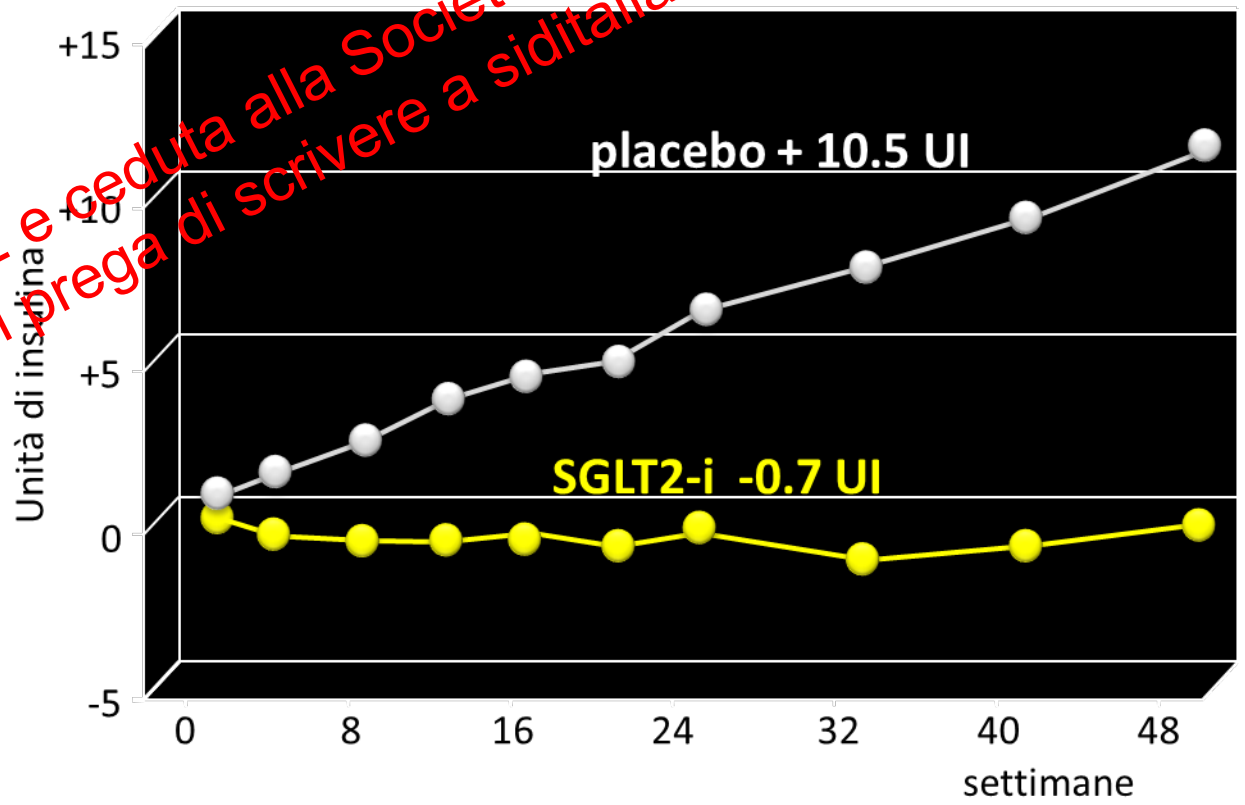


Modified from Rosenstock J and Ferrannini E Diabetes Care 38:1638, 2015



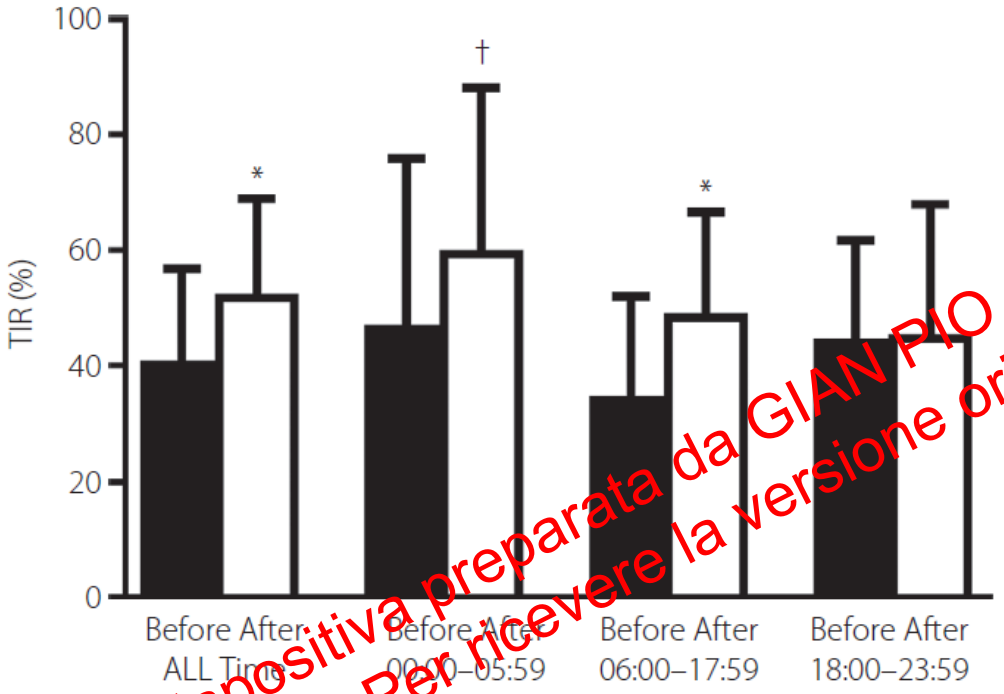


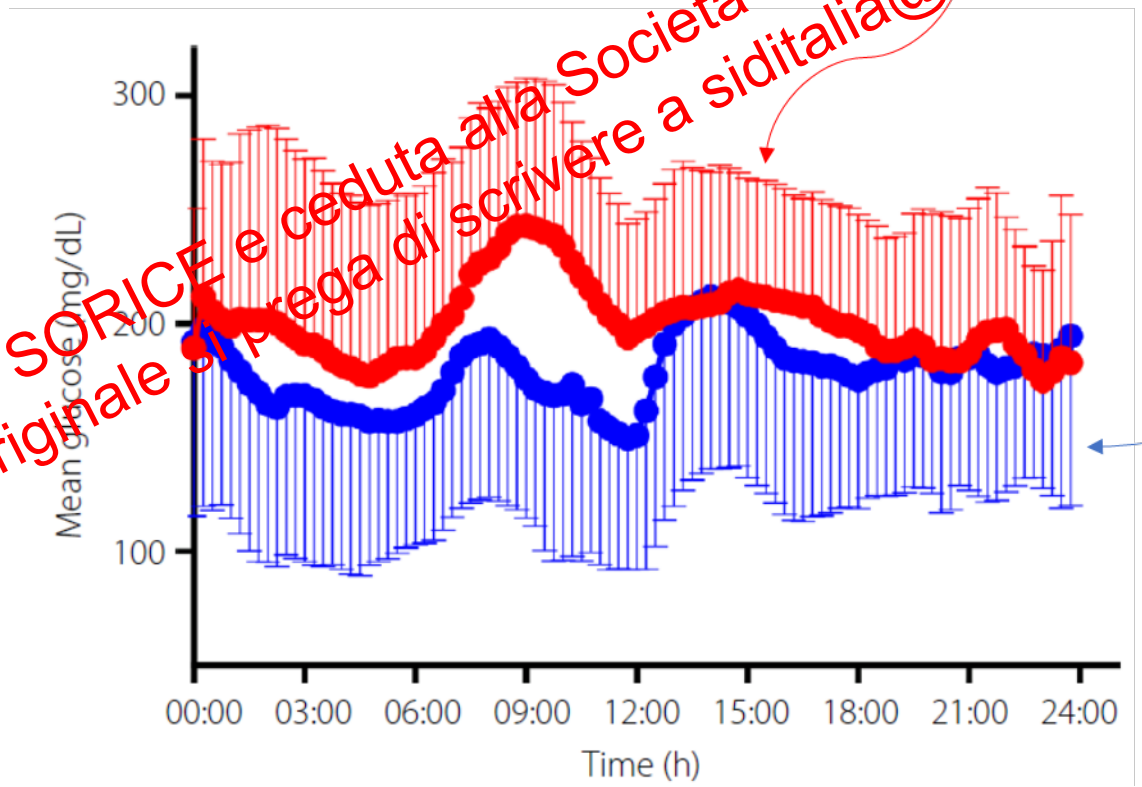




Ridderstråle M, et al. Lancet Diabetes Endocrinol. 2014;2:691–700.

Wilding JPH, et al. Ann Intern Med 156:405; 2012





Diabetes Investig 2020; 11: 1230–1237

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [redacted]® safely and effectively. See full prescribing information for

[redacted] (canagliflozin) tablets, for oral use

Initial U.S. Approval: 2013

WARNING: LOWER LIMB AMPUTATION

See full prescribing information for complete boxed warning.

- **In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD [redacted] has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg. (5.1)**
- **Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2018
Warnings and Precautions (5.1, 5.7)	10/2018
Warnings and Precautions (5.5, 5.12)	Removal 10/2018

----------INDICATIONS AND USAGE----------

[redacted] is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)

Limitations of Use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose is 100 mg once daily, taken before the first meal of the day (2.2)
- Dose can be increased to 300 mg once daily in patients tolerating [redacted] 00 mg once daily who have an eGFR of 60 mL/min/1.73 [redacted] or greater and require additional glycemic control (2.2)
- Assess renal function before initiating and periodically thereafter (2.1)
- Limit the dose of [redacted] to 100 mg once daily in patients who have an eGFR of 45 to less [redacted] min/1.73 m² (2.3)
- Initiation or use of INVOKANA is not recommended if eGFR is below 45 mL/min/1.73 m² (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg, 300 mg (3)

----------CONTRAINDICATIONS----------

- Serious hypersensitivity reaction to [redacted] 4, 5.9)
- Severe renal impairment, ESRD, or on dialysis (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypotension: Before initiating [redacted] ssess volume status and correct hypovolemia in patients with renal impairment, the elderly, in

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [redacted] safely and effectively. See full prescribing information for

[redacted] (dapagliflozin) tablets, for oral use

Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Warnings and Precautions (5.6)	10/2018

INDICATIONS AND USAGE

[redacted] is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

DOSAGE AND ADMINISTRATION

- The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
- Dose can be increased to 10 mg once daily in patients tolerating [redacted] who require additional glycemic control. (2.1)
- Assess renal function before initiating [redacted] and periodically thereafter. (2.2)
- Initiation is not recommended in patients with an eGFR less than 60 mL/min/1.73 m². (2.2)
- Use of [redacted] s not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m². (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg and 10 mg (3)

CONTRAINDICATIONS

- History of serious hypersensitivity reaction to [redacted] (4)
- Severe renal impairment, end-stage renal disease, or dialysis. (4)

WARNINGS AND PRECAUTIONS

- *Hypotension:* Before initiating [redacted], assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1, 6.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinu [redacted] evaluate and treat promptly. Before

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [redacted] safely and effectively. See full prescribing information for

[redacted] (empagliflozin) tablets, for oral use

Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Contraindications (4)	12/2017
Warnings and Precautions (5)	10/2018

INDICATIONS AND USAGE

[redacted] is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,

to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitations of Use: Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg once daily (2.1)
- Assess renal function before initiating [redacted] E. Do not initiate [redacted] if eGFR is below 45 mL/min/1.73 m² (2.2)
- Discontinue [redacted] if eGFR falls persistently below 45 mL/min/1.73 m² (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 25 mg (3)

CONTRAINDICATIONS

- History of serious hypersensitivity reaction to empagliflozin or any of the excipients in J [redacted] (4)
- Severe renal impairment, end-stage renal disease, or dialysis (4)

WARNINGS AND PRECAUTIONS

- *Hypotension:* Before initiating J [redacted] assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue JA [redacted] evaluate and treat promptly.

Fattori di rischio per deplezione di volume:

- **Età > 75 anni**
- **eGFR<60 ml/min/1,73 m²**
- **Uso di diuretici dell'ansa**

Diabetes Res Clin Pract 2018 Jun

Effetto diuretico

Aumento della produzione di eritropoietina da parte dei fibroblasti a livello del tubulo renale prossimale

Ipovolemia

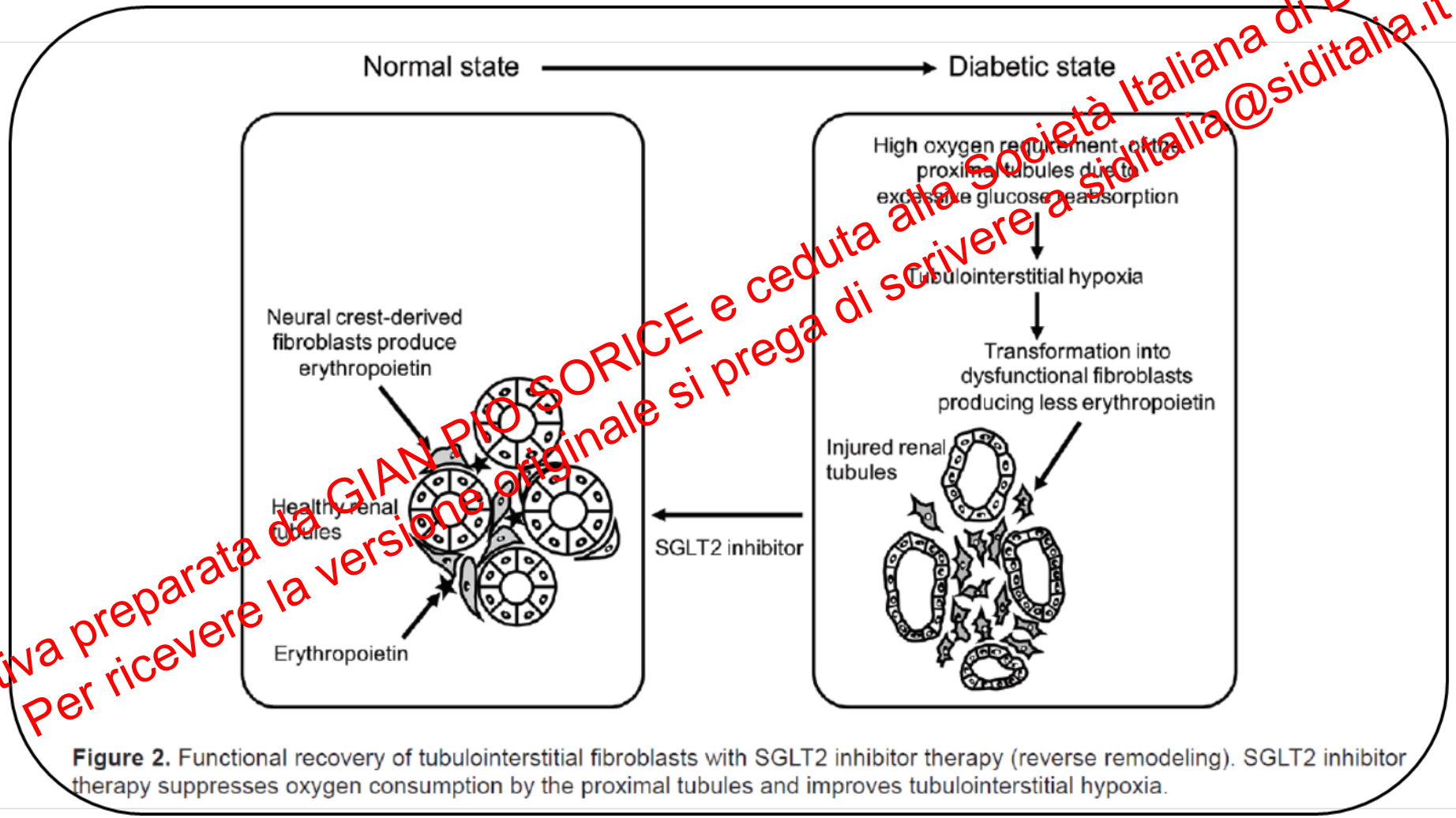


Figure 2. Functional recovery of tubulointerstitial fibroblasts with SGLT2 inhibitor therapy (reverse remodeling). SGLT2 inhibitor therapy suppresses oxygen consumption by the proximal tubules and improves tubulointerstitial hypoxia.

Diabetes Res Clin Pract 2018 Jun

Fratture ossee

Table 2. Adverse Events.* CANVAS Program N Engl J Med 2017;377:644-57

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06

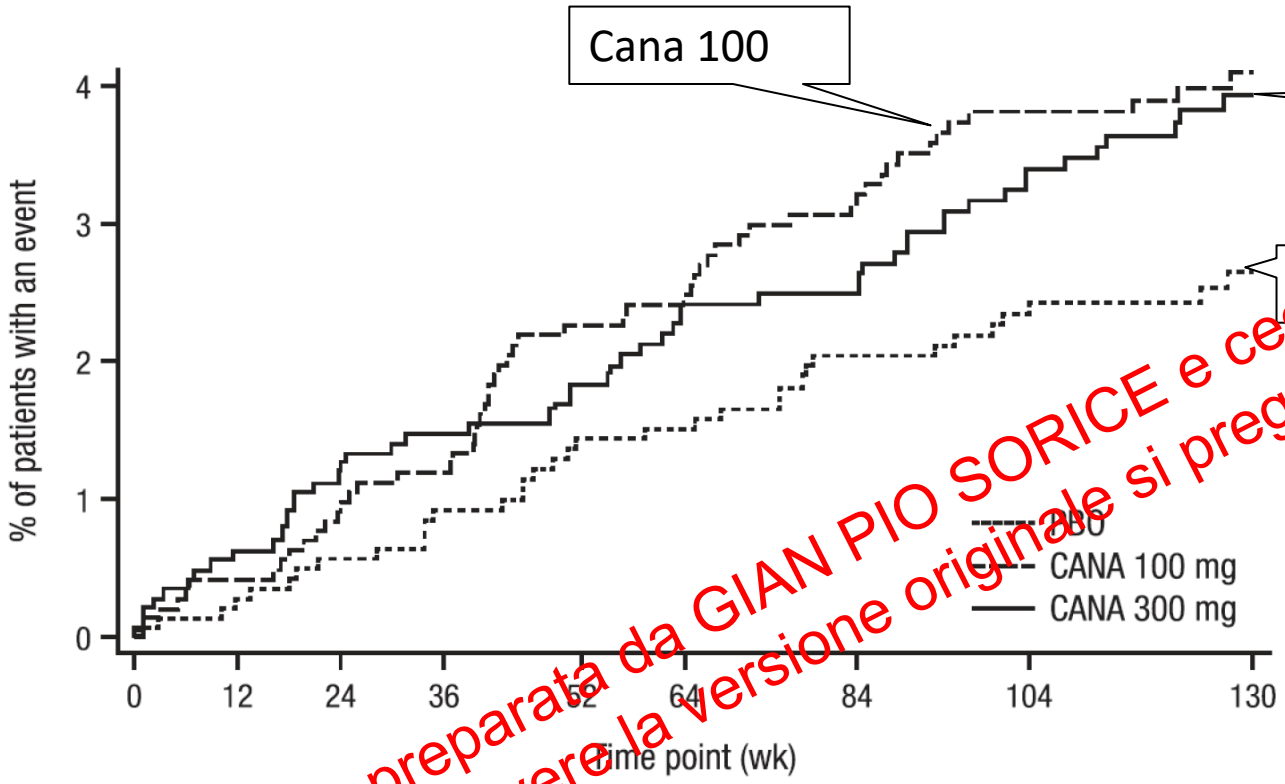
Table 2. Safety Events.* DECLARE–TIMI 58 DOI: 10.1056/NEJMoa1812389

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

Table 2. Adverse Events.* EMPA-REG OUTCOME N Engl J Med 2015;373:2117-28

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Bone fracture‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Fratture ossee

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

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[09-10-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana, Invokamet) 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 Invokana and Invokamet drug labels.

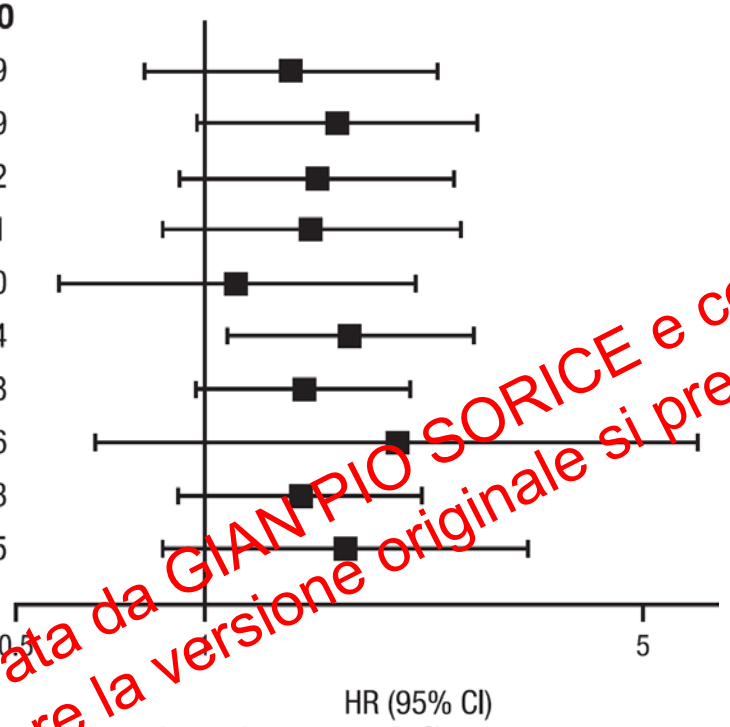
Health care professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin. Patients should talk to their health care professionals about factors that may increase their risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their health care professional.

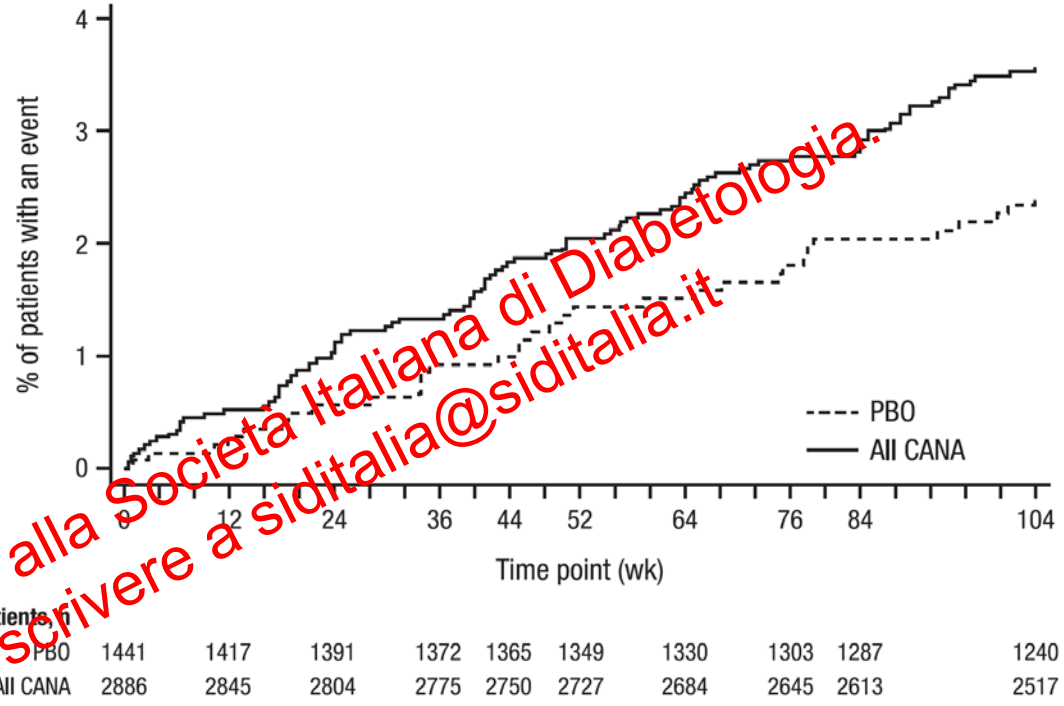
Fratture ossee

Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus

Nelson B. Watts, John P. Bilezikian, Keith Usiskin, Robert Edwards, Mehul Desai, Gordon Law, and Gary Meininger

Subgroup	Incidence, %	
	All CANA	PBO
Male	2.6	1.9
Female	6.5	3.9
<65 years of age	3.5	2.2
≥65 years of age	4.6	3.1
Duration of T2DM <10 years	3.4	3.0
Duration of T2DM ≥10 years	4.2	2.4
eGFR ≥60 mL/min/1.73 m²	4.0	2.8
eGFR <60 mL/min/1.73 m²	3.5	1.6
No fracture history	3.4	2.3
Fracture history	5.8	3.5





Conclusions: Fracture risk was increased with canagliflozin treatment, driven by CANVAS patients, who were older, with a prior history/risk of cardiovascular disease, and with lower baseline estimated glomerular filtration rate and higher baseline diuretic use. The increase in fractures may be mediated by falls; however, the cause of increased fracture risk with canagliflozin is unknown.

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

Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin

Fratture ossee

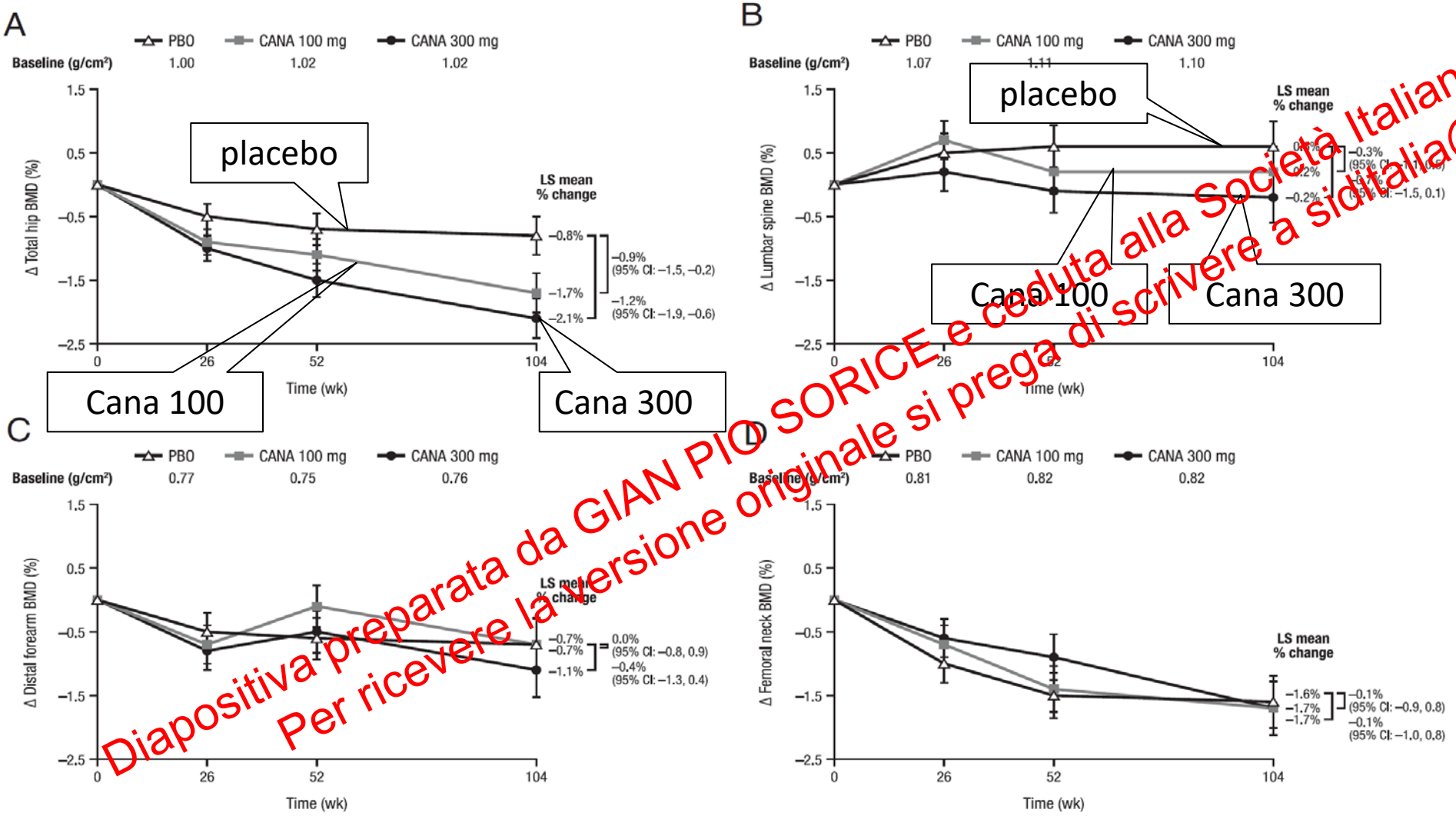
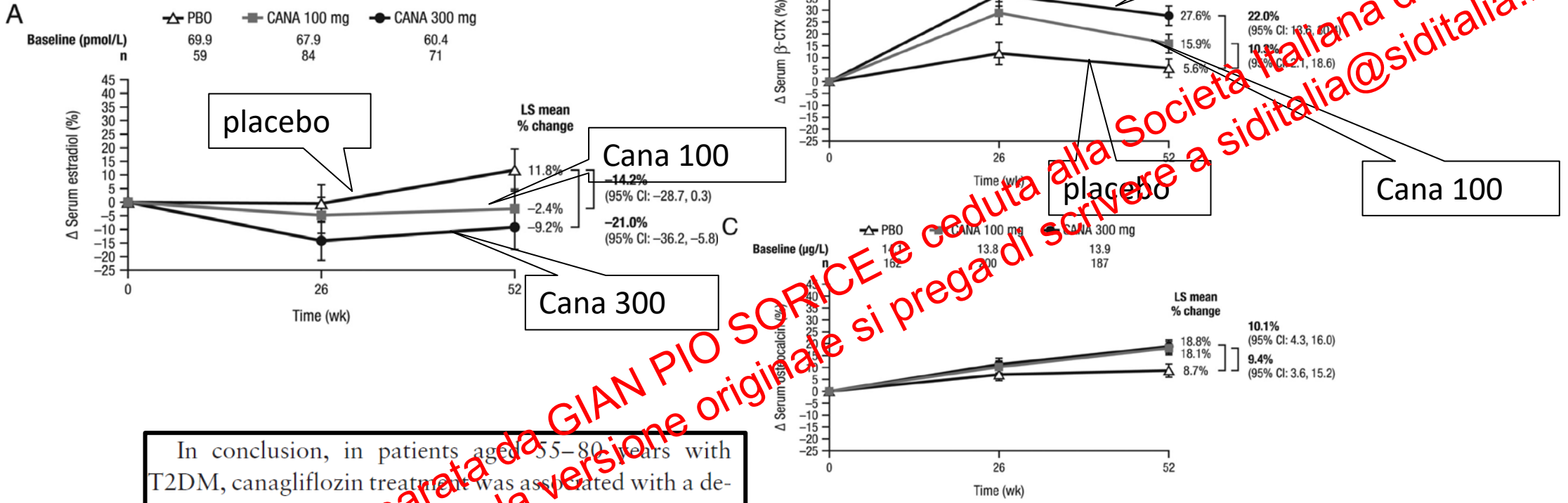


Figure 1. LS mean changes from baseline in BMD over 104 weeks for the (A) total hip, (B) lumbar spine, (C) distal forearm, and (D) femoral neck.[a,b] BMD, bone mineral density; CANA, canagliflozin; CI, confidence interval; LS, least squares; PBO, placebo; SE, standard error. [a]GE Lunar BMD values were converted to Hologic units. [b]Data are LS mean % change ± SE from baseline.

(*J Clin Endocrinol Metab* 101: 44–51, 2016)

Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin

Fratture ossee



In conclusion, in patients aged 55–80 years with T2DM, canagliflozin treatment was associated with a decrease in total hip BMD and increases in bone resorption and formation biomarkers that are of uncertain clinical significance, particularly in the context of no significant BMD changes in other skeletal sites or in volumetric BMD and bone strength. The changes in total hip BMD as well as the increases in bone biomarkers observed with canagliflozin treatment may be, in part, related to weight loss.

(*J Clin Endocrinol Metab* 101: 44–51, 2016)

Fratture ossee

Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control

Kidney International (2014) **85,** 962–971

Donald E. Kohan[1], Paola Fioretto[2], Weihua Tang[3] and James F. List[3]

Table 5 | Adverse and special interest events through week 104

	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg
n	84	83	85
Adverse event	77 (91.7)	80 (96.4)	77 (90.6)
Related adverse event	39 (46.4)	39 (47.0)	41 (48.2)
Adverse event leading to discontinuation	22 (26.2)	16 (19.3)	11 (12.9)
At least one serious adverse event	26 (31.0)	21 (25.3)	26 (30.6)
Deaths	5 (6.0)	2 (2.4)	3 (3.5)
Adverse events of special interest			
Suggestive of urinary tract infection	12 (14.3)	11 (13.3)	12 (14.1)
Suggestive of genital tract infection	3 (3.6)	8 (9.6)	7 (8.2)
Renal impairment or failure (total)	6 (7.1)	2 (2.4)	8 (9.4)
Blood creatinine increased	3 (3.6)	0	5 (5.9)
Renal impairment	0	1 (1.2)	2 (2.4)
Renal failure chronic	1 (1.2)	0	1 (1.2)
Renal failure	1 (1.2)	1 (1.2)	0
Renal failure acute	1 (1.2)	0	0
Hypotension/dehydration/hypovolemia	5 (6.0)	8 (9.6)	11 (12.9)
Fracture	0	5 (6.0)	8 (9.4)
Hypertension	6 (7.1)	3 (3.6)	5 (5.9)
Micturition urgency	0 (0)	5 (6.0)	2 (2.4)
Hyperkalemia	13 (15.5)	10 (12.0)	8 (9.4)
Events of hypoglycemia			
Total patients with hypoglycemia	43 (51.2)	38 (45.8)	33 (38.8)
Major episode of hypoglycemia [a]	4 (4.8)	0	2 (2.4)

ORIGINAL RESEARCH

Pooled Safety and Tolerability Analysis of Empagliflozin in Patients with Type 2 Diabetes Mellitus

Ona Kinduryte Schorling · Douglas Clark · Isabella Zwiener · Stefan Kaspers · Jisoo Lee · Hristo Iliev

Table 6 continued

	Placebo (n = 4904)		EMPA 10 mg (n = 4858)		EMPA 25 mg (n = 5057)		EMPA 10/25 mg (n = 10,177)	
	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs	n (%) or n/N (%)	Rate/100 pt-yrs
Diabetic ketoacidosis (narrow BIcMQ[b])	4 (0.1)	0.03	4 (0.1)	0.05	2 (< 0.1)	0.02	6 (0.1)	0.04
Urinary tract carcinogenicity[c] (BIcMQ)	9 (0.2)	0.11	10 (0.2)	0.12	13 (0.3)	0.16	23 (0.2)	0.14
Onset after 6 months' treatment	7 (0.1)	0.12	8 (0.2)	0.13	10 (0.3)	0.16	18 (0.3)	0.15
Liver injury (SMQ)	157 (3.2)	2.02	109 (2.2)	1.36	135 (2.7)	1.65	247 (2.4)	1.51
Bone fractures (BIcMQ)	134 (2.7)	1.72	121 (2.5)	1.52	107 (2.1)	1.30	233 (2.3)	1.42
Pancreatitis (SMQ)	11 (0.2)	0.14	8 (0.2)	0.10	7 (0.1)	0.08	15 (0.1)	0.09
Amputation risk (ITT population)	46 (0.9)	0.52	46 (0.9)	0.51	49 (1.0)	0.54	95 (0.9)	0.52
Minor	27 (0.6)	0.30	36 (0.7)	0.40	40 (0.8)	0.44	76 (0.8)	0.41
Major	19 (0.4)	0.21	10 (0.2)	0.11	9 (0.2)	0.10	19 (0.2)	0.10

The effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on mineral metabolism and bone in patients with type 2 diabetes mellitus

Maria Alba, John Xie, Albert Fung & Mehul Desai

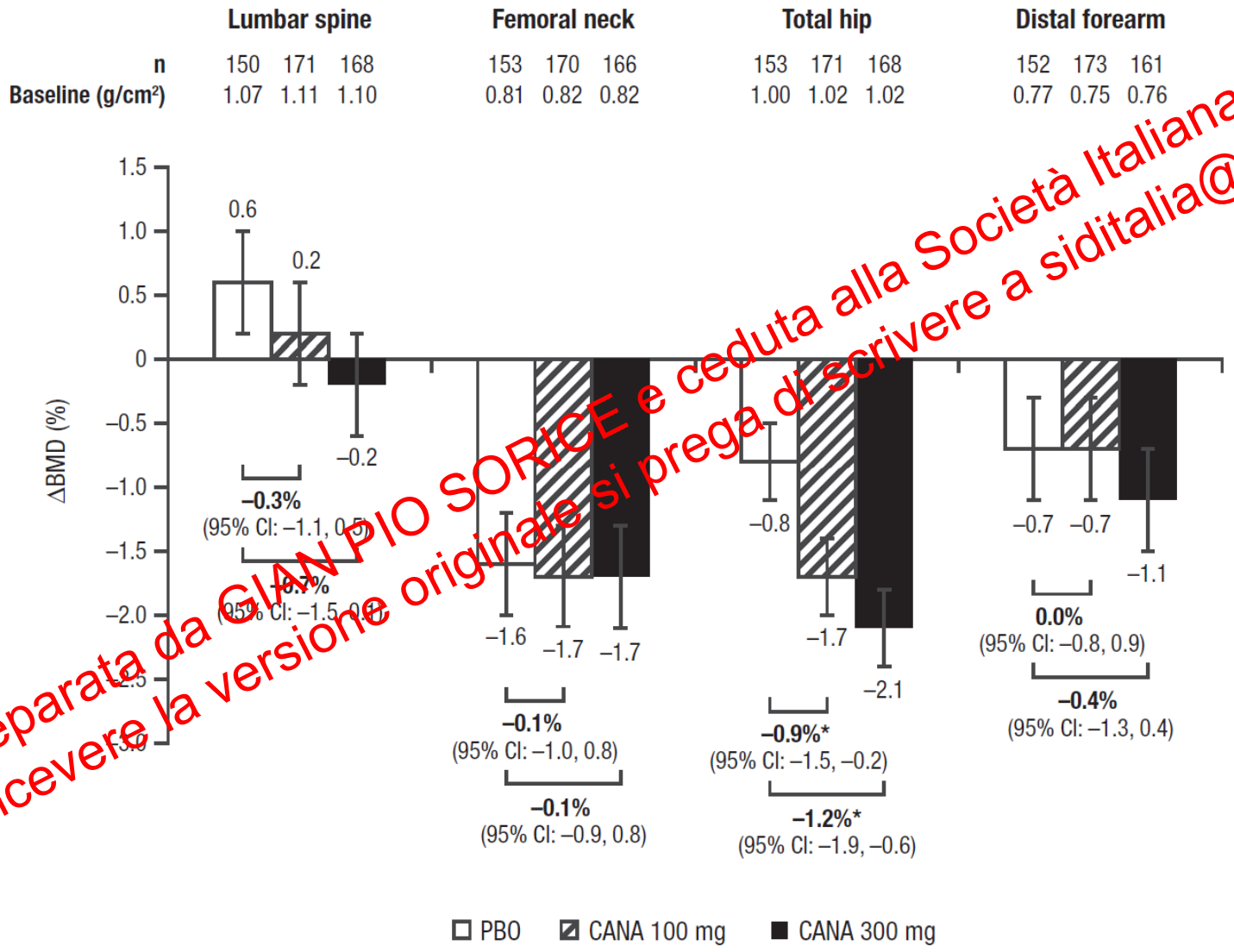


Figure 4. Change from baseline in BMD with canagliflozin at Week 104 (study in older patients)[36]. BMD, bone mineral density; CI, confidence interval; PBO, placebo; CANA, canagliflozin. *95% CI for the difference versus PBO excludes 0.

Current Medical Rsearch and Opinion, 2016; 32:8; 1375-85

Fratture ossee

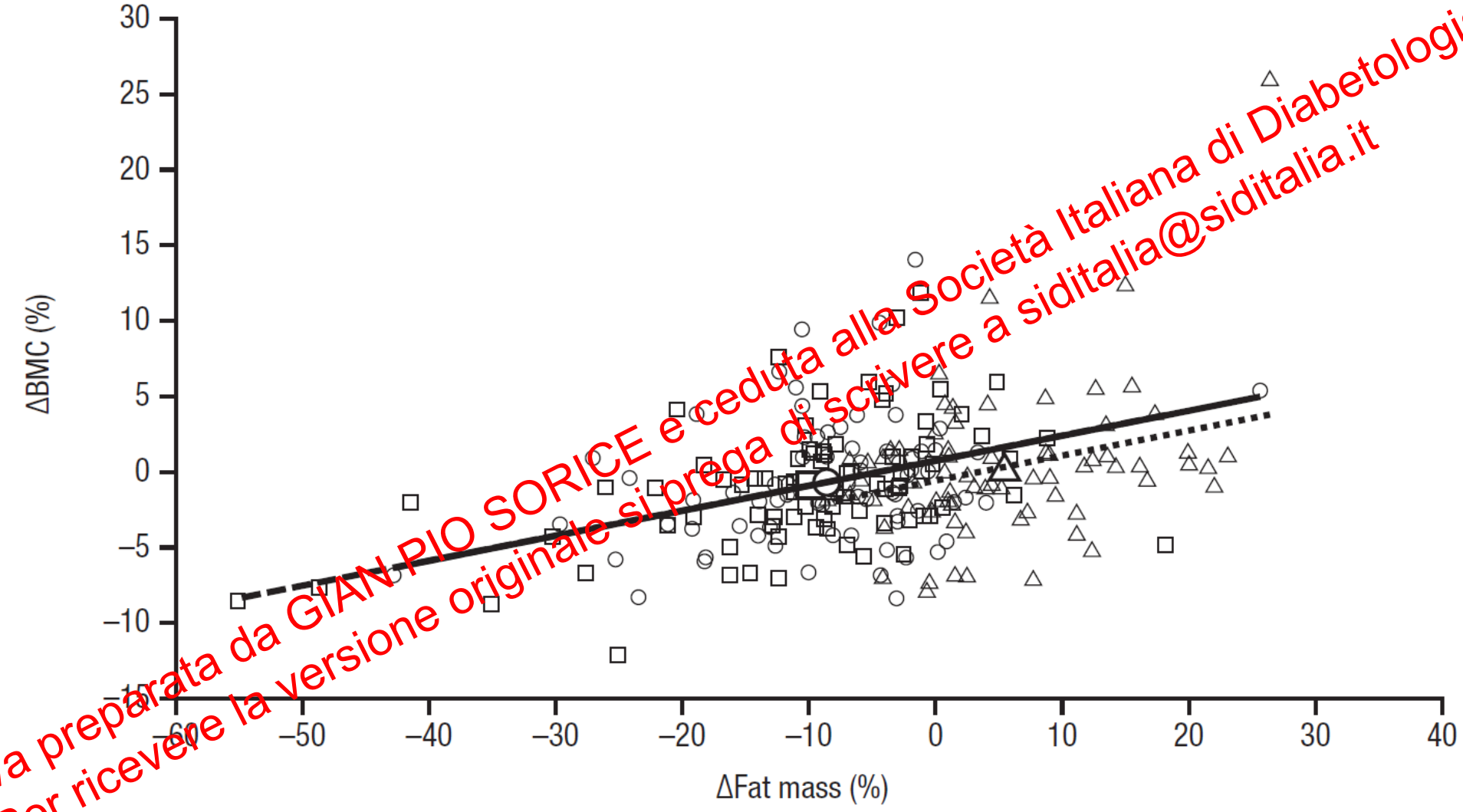


Figure 6. Relationship between weight loss and BMC with canagliflozin treatment (add-on to MET vs GLIM study and study in older patients). BMC, bone mineral content; GLIM, glimepiride; CANA, canagliflozin; PBO, placebo; LS, least squares; CI, confidence interval; MET, metformin.

Current Medical Rsearch and Opinion, 2016; 32:8; 1375-85

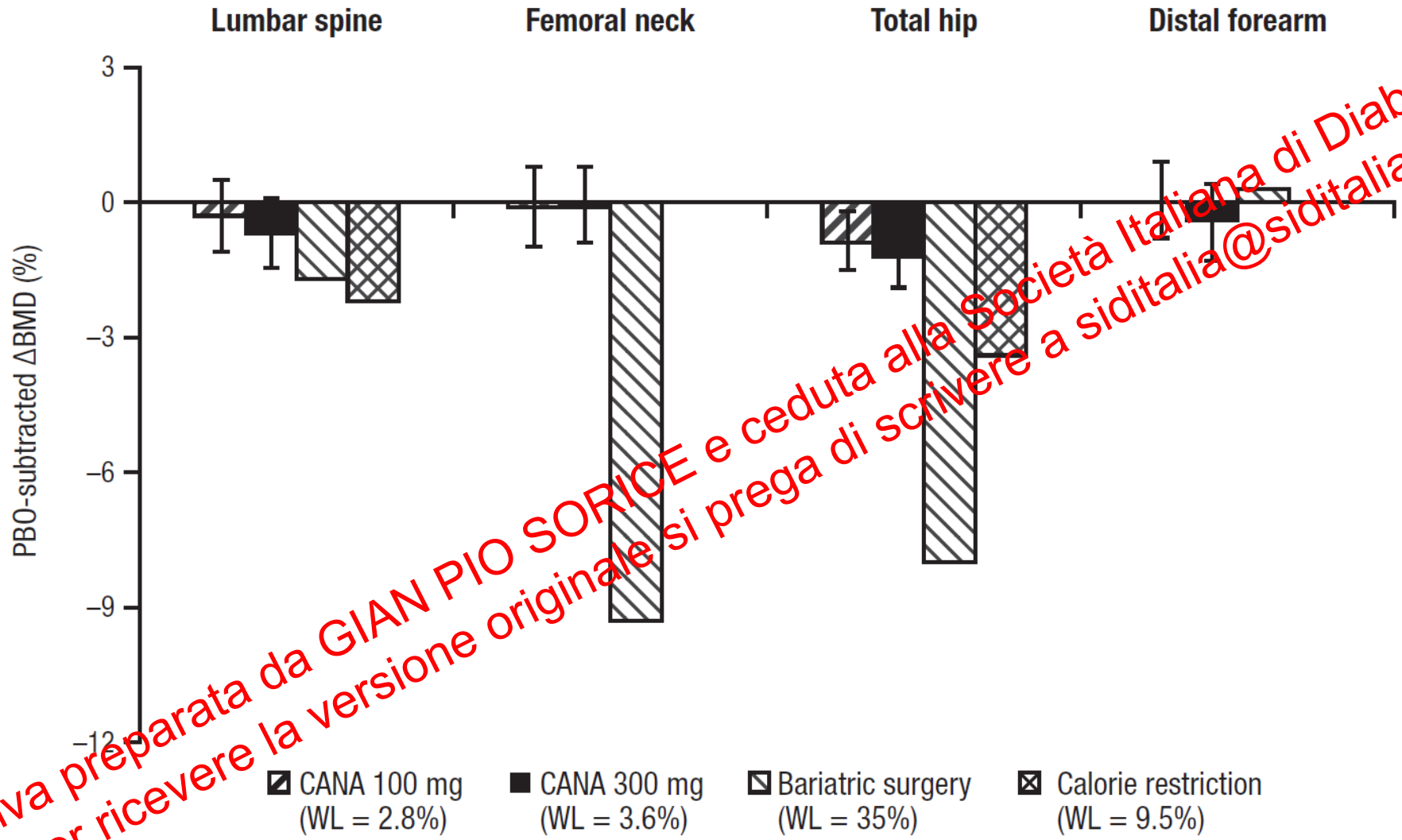


Figure 5. Changes in BMD associated with canagliflozin (study in older patients) and weight-loss interventions[36,44,45]. BMD, bone mineral density; PBO, placebo; CANA, canagliflozin; WL, weight loss.

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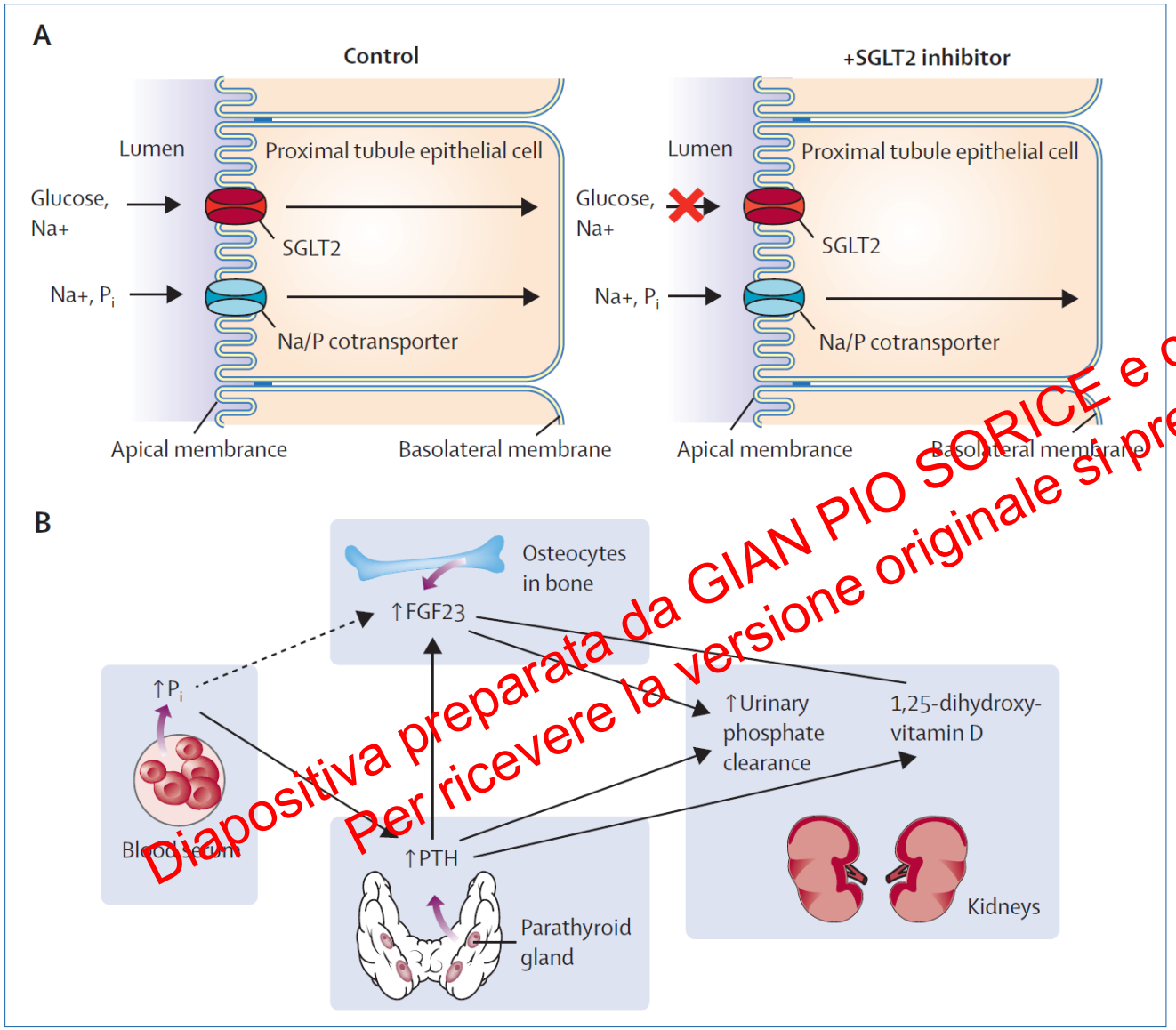


SGLT2 inhibitors cause excretion of glucose in the urine which

Leads to increased phosphate concentration in the blood serum.

Leads to sustained release of parathyroid hormone which controls calcium level in blood.

increases fibroblast growth factor 23 which is associated with bone disease.

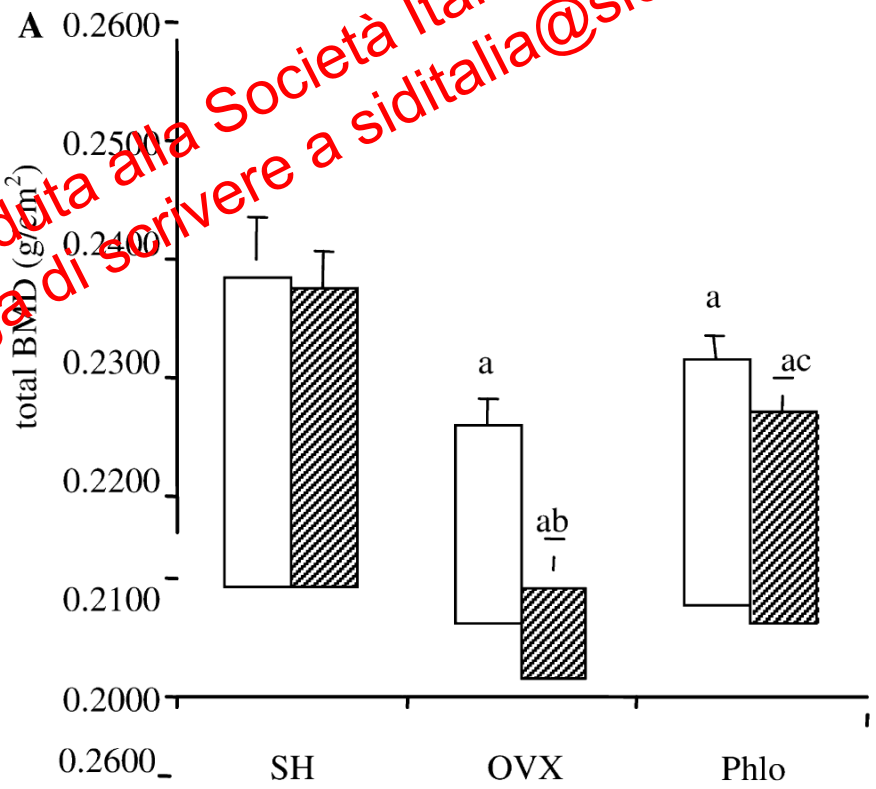
Increases urinary phosphate & and lowers 1,25- dihydroxyvitamin D.

Increased bone fracture risk

Prevention of Bone Loss by Phloridzin, an Apple Polyphenol, in Ovariectomized Rats under Inflammation Conditions

The present work was thus carried out to provide further data on the phytochemicals implicated in the protective effect of fruits. We focused on the effect of phloridzin (phloretin-2′-glucose, Phlo), a flavonoid exclusively found in apple, which is used as a staple in the Western diet, on a model of inflammation/ovariectomy-induced bone loss in rats.

Consumption of this polyphenol was associated with a decrease of bone resorption, as indicated by a lower urinary DPD excretion in OVX rats with or without inflammation, compared to the values in OVX controls. This effect allowed prevention of osteopenia at the diaphysis level in OVX rats (Fig. 3). The same pattern was observed on each femoral compartment in inflammatory conditions. In this case, mechanical properties were even improved (higher femoral load failure in $Phlo_{inf}$ than OVX_{inf} rats, Fig. 4).



Calcif Tissue Int (2005) xx:1–9
DOI: 10.1007/s00223-005-0060-5

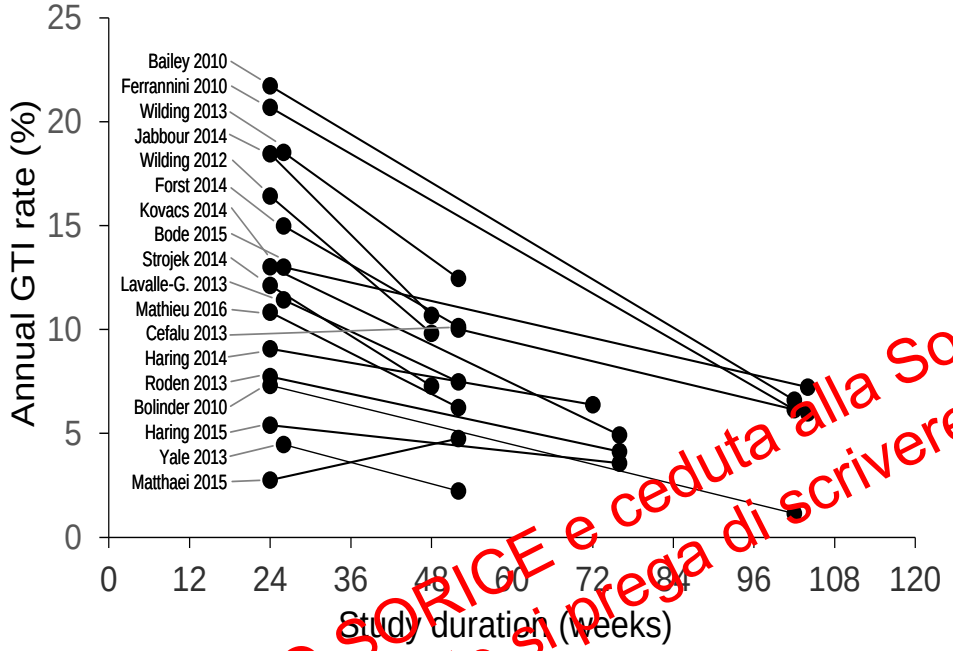
Infezioni tratto urinario

Infezioni genitali (micosi)

By inducing glycosuria, sodium glucose cotransporter-2 inhibitors (SGLT2i) reduce glycaemia, blood pressure and body weight. As a result, they improve cardiovascular outcomes in people with type 2 diabetes (T2D), but such benefit need to be weighed against their safety profile. The most common adverse events (AEs) during therapy with SGLT2i are genitourinary tract infections (GUTI), which are generally attributed to the predisposing effect of glycosuria. In randomized controlled trials (RCTs), where AEs are adjudicated using standardized procedures, SGLT2i mostly increase the risk of genital tract infections (GTI), but not that of urinary tract infections (UTI). In clinical practice, the risk of GUTI may be a barrier preventing patients from receiving or continuing a potentially life-saving therapy.

Diabetes Obes Metab, 2018 Mar

Most GTI events occur in the first weeks after SGLT2i initiation and thus change in HbA1c at study end is unlikely to determine GTI risk



Diabetes Obes Metab, 2018 Mar

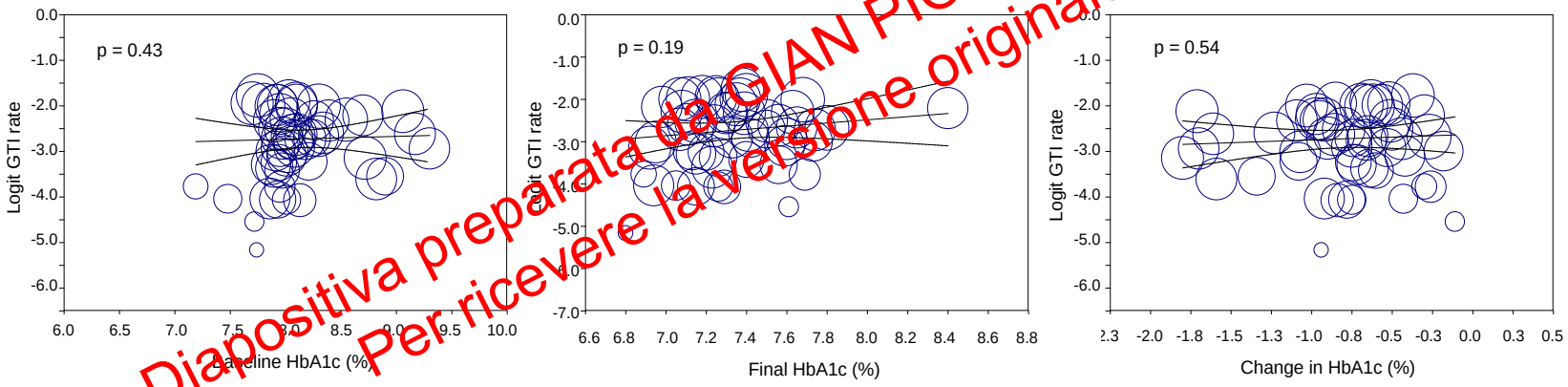


Figure S3. New meta-regression analysis of Li et al.

The degree of hyperglycaemia, represented by HbA1c, is not the major determinant of SGLT2i-associated GTI.

Diabetes Obes Metab . 2017 Mar;19(3):348-355

Infezioni tratto urinario

Infezioni genitali (micosi)

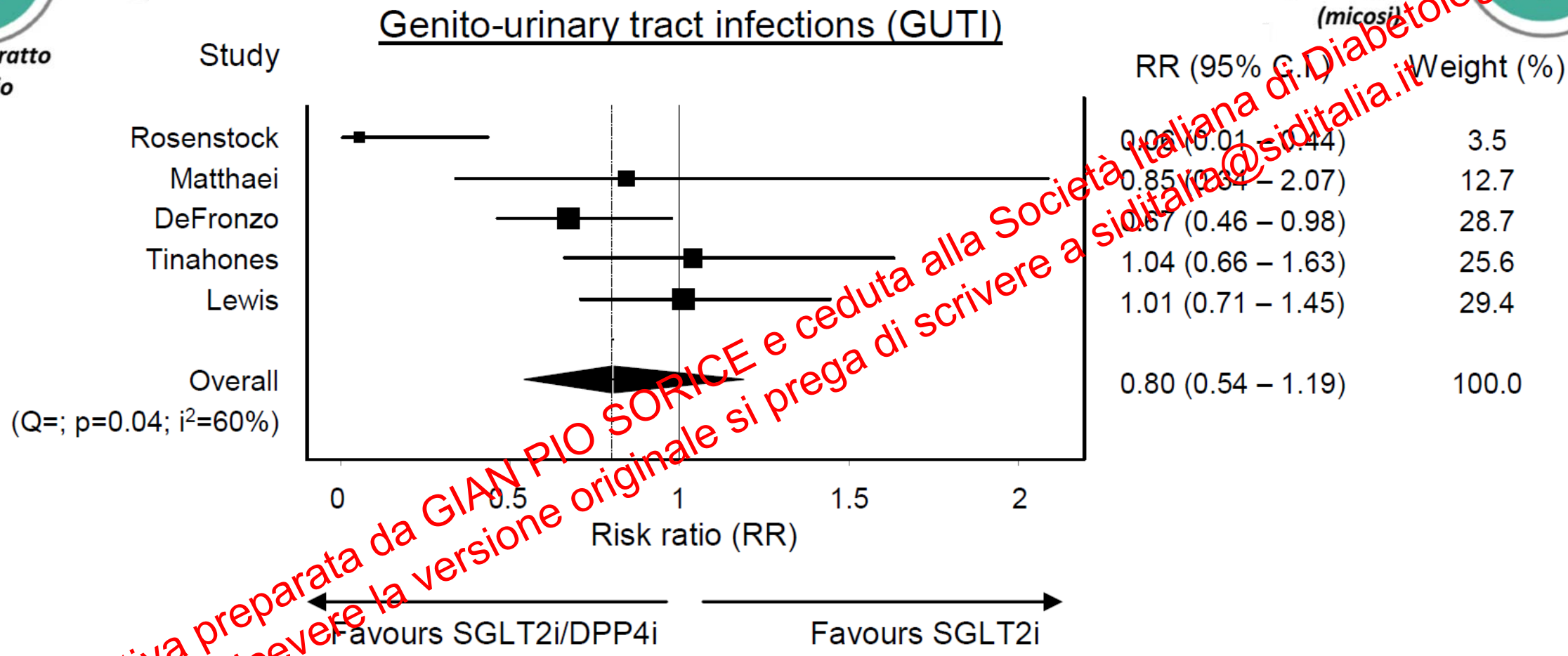


Figure 1. Meta-analysis forest plots.

Diabetes Obes Metab, 2018 Mar

Infezioni tratto urinario

Infezioni genitali (micosi)

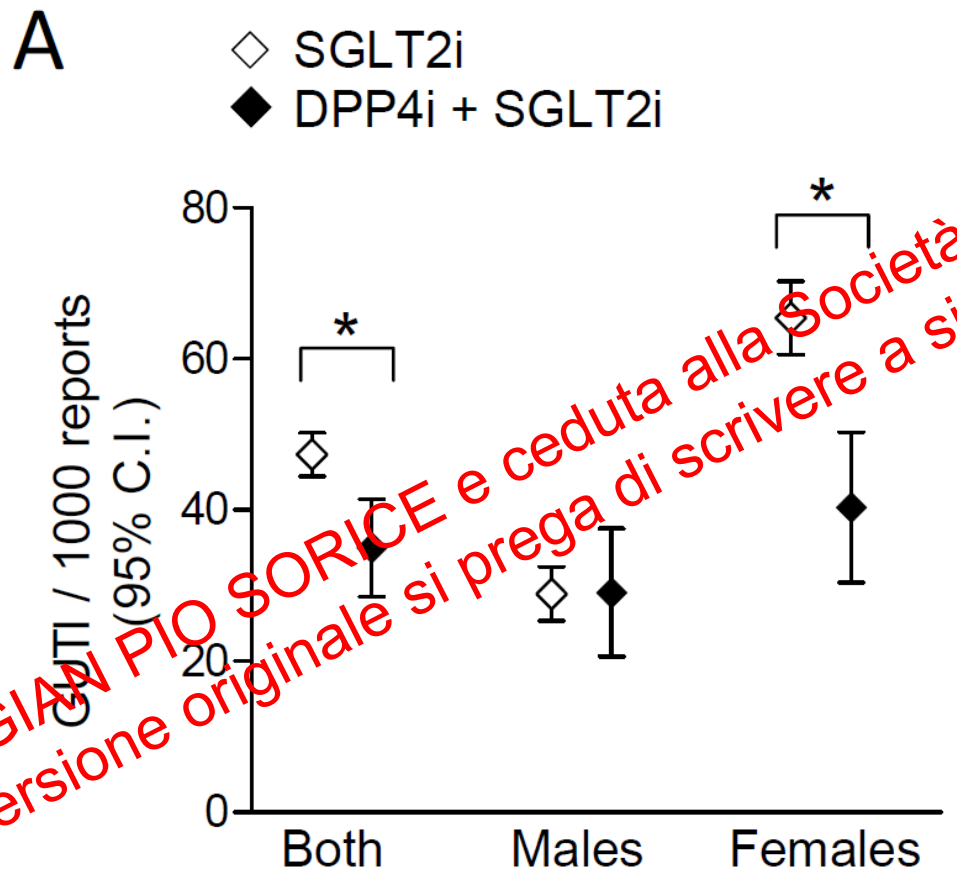


Figure 2. Frequencies of genitourinary tract infections in the FDA adverse events reporting system. Rates of genitourinary tract infections (GUTI) per 1000 reports (bars indicate the 95% confidence intervals) are shown in males, females and both for the association between SGLT2i and DPP4i (A) or SU (B) versus SGLT2i alone. *p<0.05 using the chi square test.

Diabetes Obes Metab, 2018 Mar

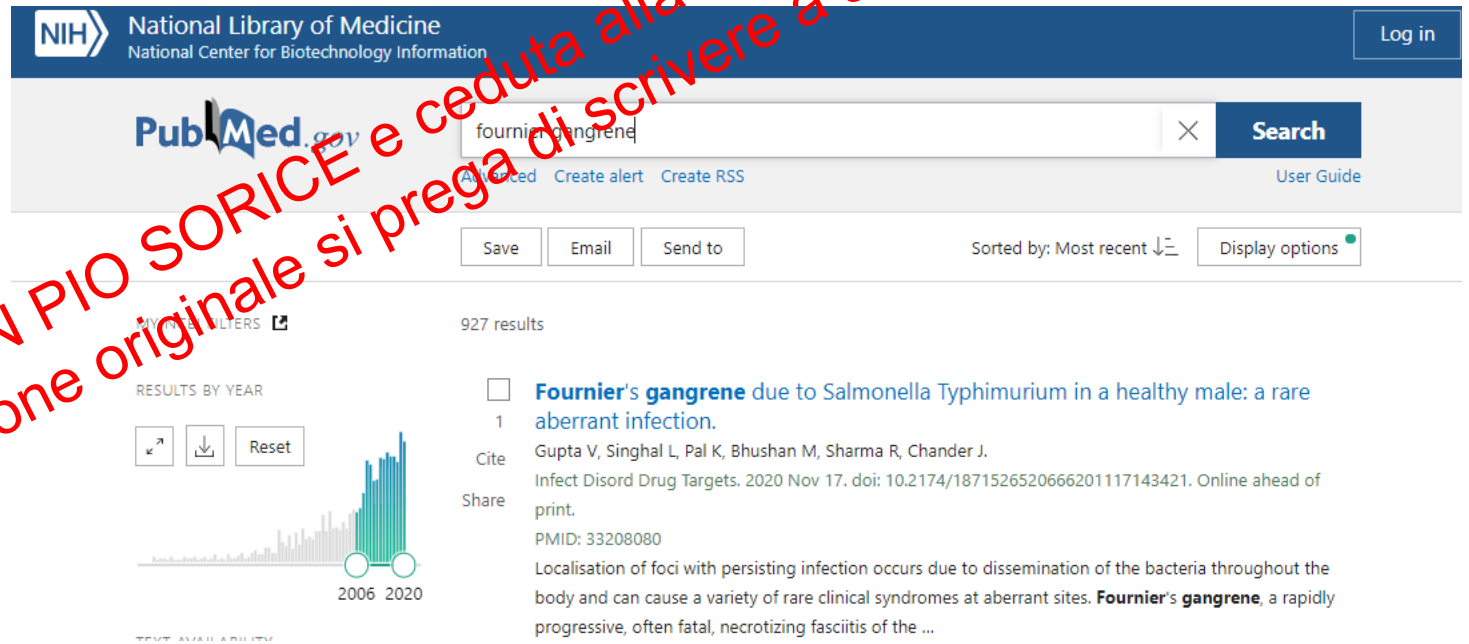
Infezioni tratto urinario

Infezioni genitali (micosi)

The putative mechanisms whereby DPP4i may moderate SGLT2i-associated G(U)TI risk deserve some comments. By far the most straightforward explanation is that the DPP4i/SGLT2i **combination reduced glycaemia and glycosuria more than SGLT2i alone**, thereby resulting in protection from GTI. Unfortunately, no data is available to confirm this hypothesis and there are some arguments against it.

Diabetes Obes Metab, 2018 Mar

Fournier's gangrene (FG) is a synergistic necrotizing fasciitis of the perineal, genital, and perianal region that leads to thrombosis of the small subcutaneous vessels and results in the development of gangrene of the overlying skin.



Eke N. Fournier's gangrene: a review of 1726 cases. Br. J. Surg. 2000; 87: 718–28

Co-existing disorders as predisposing factors for Fournier's gangrene

Co-existing Disorders	n (%)
Diabetes mellitus	16 (46)
Cardiac disorders	11 (31)
Chronic obstructive pulmonary disease	7 (20)
Obesity	7 (20)
Malignancy	4 (11)
Renal failure	2 (6)
Pemfigus vulgaris	1 (3)
Other	3 (9)

Mortality rates of patients with risk factors

Patient Characteristics	Mortality % (n)
Diabetes mellitus (DM)	50 (8/16)
Older than 55	46 (12/26)
Female	55 (6/11)
Sepsis	78 (7/9)
Late admission	45 (10/22)
Overall mortality	40 (14/35)

Predisposing factors for FG include **diabetes mellitus, cardiac disorders, chronic obstructive pulmonary disease, alcoholism, and cortisone treatment**. Although the relationship between FG and DM has not been established, neuroangiopathy and immunosuppression associated with DM could play an important role. Presence of DM has been reported as 39%–64% in the published literature. Similarly, DM was found to be a factor in 45.7% of the patients in our study

World J Surg (2006) 30: 1750–1754

Lower limb amputation

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
		number of patients (percent)		
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (4.8)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event‖‖	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes N Engl J Med 2015;373:2117-28.

Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

This article was published on November 10, 2018, at NEJM.org.

Lower limb amputation

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	0.93
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.[illegible]	0.009
Hypoglycemia	30.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	5.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

N Engl J Med 2017;377:644-57.

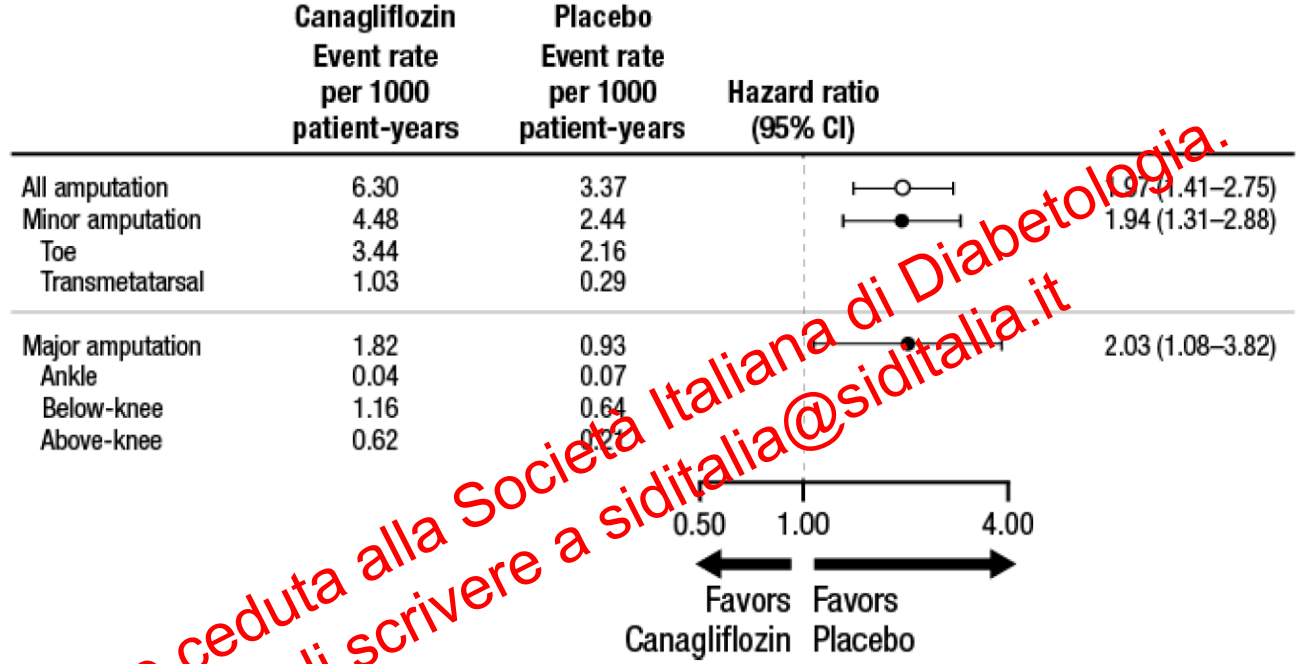


Table 1. CANVAS Amputations

	Placebo N=1,441	Canagliflozin 100 mg N=1,445	Canagliflozin 300 mg N=1,441	Canagliflozin (pooled) N=2,886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations*	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard ratio (95% CI)	—	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

* Some patients had more than one amputation.

Table 2. CANVAS-R Amputations

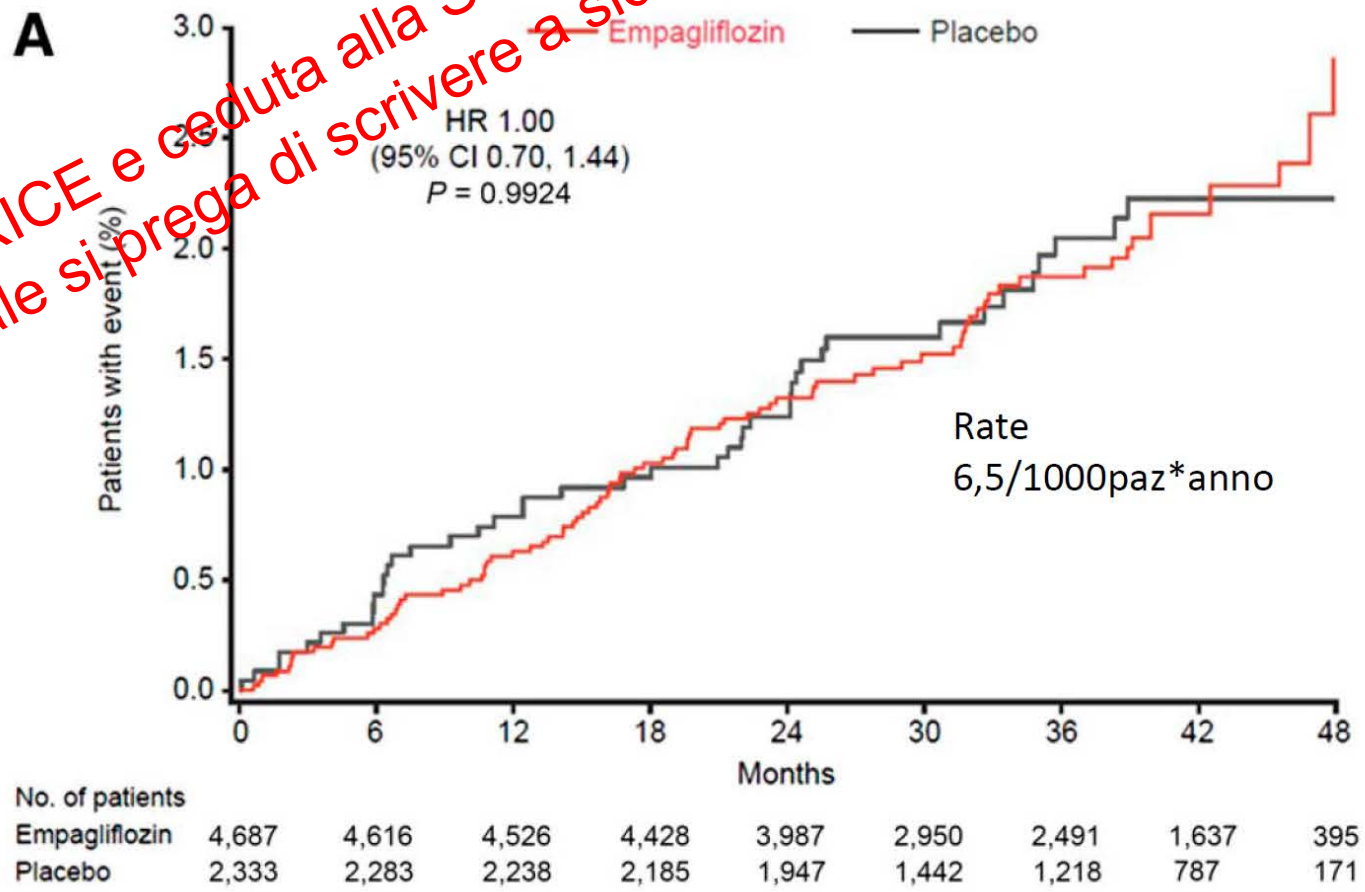
	Placebo N=2,903	Canagliflozin 100 mg (with up-titration to 300 mg) N=2,904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations*	36	59
Amputation incidence rate (per 1,000 patient-years)	4.2	7.5
Hazard ratio (95% CI)	—	1.80 (1.10, 2.93)

* Some patients had more than one amputation.

Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial

Diabetes Care 2018;41:e4–e5 | https://doi.org/10.2337/dc17-1551

Silvio E. Inzucchi,[1] Hristo Iliev,[2] Egon Pfarr,[2] and Bernard Zinman[3]



Dapagliflozin in patients with type 2 diabetes mellitus: A pooled analysis of safety data from phase IIb/III clinical trials

Serge Jabbour MD[1] | Jochen Seufert MD, PhD, FRCPE[2] | Andre Scheen MD, PhD[3] | Clifford J. Bailey PhD[4] | Cathrina Karup MD[5] | Anna M. Langkilde MD, PhD[6]

Amputation	Placebo/comparator-controlled 30-study pool	
	Control (N = 4629; 4177 patient-years)	Dapagliflozin total (N = 9195; 8059 patient-years)
Patients with lower-limb amputation, n (%)	7 (0.2)	8 (0.1)

Received: 3 May 2018 | Revised: 1 June 2018 | Accepted: 12 June 2018
DOI: 10.1111/dom.13424

WILEY

ORIGINAL ARTICLE

Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D)

Patrick B. Ryan PhD[1] | John B. Buse MD[2] | Martijn J. Schuemie PhD[1] | Frank DeFalco BA[3] | Zhong Yuan MD, PhD[1] | Paul E. Stang PhD[1] | Jesse A. Berlin ScD[4] | Norman Rosenthal MD[3]

SCOPO DELLO STUDIO

Valutare in pazienti affetti da DMT2 e nuovi utilizzatori di canagliflozin, il rischio di:

- Ospedalizzazioni per Scompenso Cardiaco (HHF)
- Amputazioni al di sotto del ginocchio (BKLA)

Sono stati considerati due tempi primari per la valutazione del rischio:

- **ON TREATMENT:** per valutare il rischio DURANTE l'uso del farmaco
- **INTENT TO TREAT:** per valutare «overall» il rischio una volta che il trattamento è stato iniziato ed eventualmente anche sospeso

Eseguite sotto-analisi in pazienti con o senza anamnesi di malattia CV nota

Confronto: canagliflozin con altri iSGLT2 e altri anti-diabetici non iSGLT2

Ryan et al., Diabetes Obes Metab. 2018;1–13

TABLE 4 Risk of BKLE amputation in the overall population for selected comparisons during on-treatment and intent-to-treat time-at-risk periods[a]

Comparison	Source	Exposure (n/PY) Target	Exposure (n/PY) Comparator	On-treatment Outcomes Target	On-treatment Outcomes Comparator	On-treatment HR (95% CI)	On-treatment P	On-treatment Calibrated P	Intent-to-treat Outcomes Target	Intent-to-treat Outcomes Comparator	Intent-to-treat HR (95% CI)	Intent-to-treat P	Intent-to-treat Calibrated P
Canagliflozin vs all non-SGLT2i	CCAE	60 073/29 965	217 583/125 189	24	190	0.56 (0.32-0.92)	.03	.06	144	467	1.01 (0.80-1.28)	.90	.95
	MDCD	5998/1775	38 172/16 482	10	61	1.35 (0.46-3.41)	.56	.46	30	236	1.05 (0.62-1.73)	.84	.71
	MDCR	9206/4707	42 744/30 668	9	57	1.16 (0.48-2.66)	.73	.62	26	138	0.88 (0.53-1.47)	.65	.77
	Optum	36 055/16 676	146 868/84 306	17	173	0.67 (0.35-1.18)	.19	.31	85	437	1.08 (0.78-1.36)	.82	.71
	Meta-analysis	111 332/53 125	445 367/256 646	60	481	0.75 (0.40-1.41) I^2 = 0.18	.25	.30	295	1308	1.01 (0.93-1.10) I^2 = 0.00	.71	.51
Canagliflozin vs select non-SGLT2i	CCAE	64 795/32 238	158 992/76 081	34	86	1.08 (0.65-1.75)	.76	.68	171	382	0.96 (0.77-1.21)	.75	.78
	MDCD	6727/1993	21 355/7401	10	15	3.11 (0.87-11.70)	.06	.08	34	109	1.21 (0.73-1.97)	.45	.43
	MDCR	10 217/5222	35 398/20 471	11	37	0.60 (0.19-1.64)	.36	.42	34	142	0.78 (0.48-1.24)	.31	.33
	Optum	39 142/18 081	104 231/45 912	23	71	1.30 (0.64-2.53)	.46	.42	110	363	1.10 (0.84-1.44)	.49	.46
	Meta-analysis	120 881/57 536	319 976/149 866	78	209	1.17 (0.55-2.47) I^2 = 0.21	.56	.43	349	996	1.01 (0.81-1.25) I^2 = 0.00	.93	.86
Canagliflozin vs other SGLT2i	CCAE	43 411/20 312	70 519/31 520	19	34	0.88 (0.38-2.01)	.77	.73	102	135	1.13 (0.81-1.57)	.46	.50
	MDCD	1424/403	1425/419	3	1	2.00 (0.19-43.01)	.62	.52	8	7	1.25 (0.33-5.05)	.75	.70
	MDCR	4395/2000	5041/2123	6	5	1.73 (0.28-13.34)	.58	.55	15	15	1.38 (0.58-3.39)	.47	.56
	Optum	20 324/8652	21 184/7603	12	15	1.40 (0.49-4.28)	.54	.54	46	52	1.06 (0.67-1.68)	.82	.85
	Meta-analysis	69 554/31 369	98 169/41 666	40	53	1.14 (0.67-1.93) I^2 = 0.00	.48	.53	171	209	1.13 (0.99-1.29) I^2 = 0.00	.06	.06
Other SGLT2i vs all non-SGLT2i	CCAE	54 424/24 642	175 560/96 683	23	143	0.59 (0.32-1.04)	.08	.14	87	327	0.78 (0.57-1.04)	.09	.15
	MDCD	0878/405	25 995/10 106	0	28	0.36 (NA-5.96)	—	—	5	111	0.99 (0.33-2.39)	.98	.96
	MDCR	4336/1837	31 228/21 522	4	37	1.65 (0.37-5.26)	.46	.39	13	85	1.56 (0.72-3.12)	.23	.17
	Optum	27 588/7076	118 027/64 041	12	115	1.02 (0.49-1.98)	.95	.77	45	306	1.31 (0.88-1.89)	.17	.13
	Meta-analysis	78 248/33 556	324 755/182 247	39	295	0.84 (0.27-2.55) I^2 = 0.23	.57	.68	150	829	I^2 = 0.51		

Abbreviations: BKLE, below-knee lower extremity; CI, confidence interval; HR, hazard ratio; CCAE, Truven MarketScan Commercial Claims and Encounters; MDCD, Truven MarketScan Multi-state Medicaid; MDCR, Truven MarketScan Medicare Supplemental Beneficiaries; NA, not available; PY, patient-years; SGLT2i, sodium glucose co-transporter 2 inhibitors.

Possibili meccanismi – fattori di rischio/predisponenti

- Ipovolemia
- Ridotta perfusione, in pazienti con alterata risposta arteriolare, può facilitare la necrosi
- Effetto diretto sulla funzione vascolare
- Aumentata viscosità
- L'improvvisa sospensione dei farmaci potrebbe portare modifiche emodinamiche con spasmo ed ischemia distale

QNOW

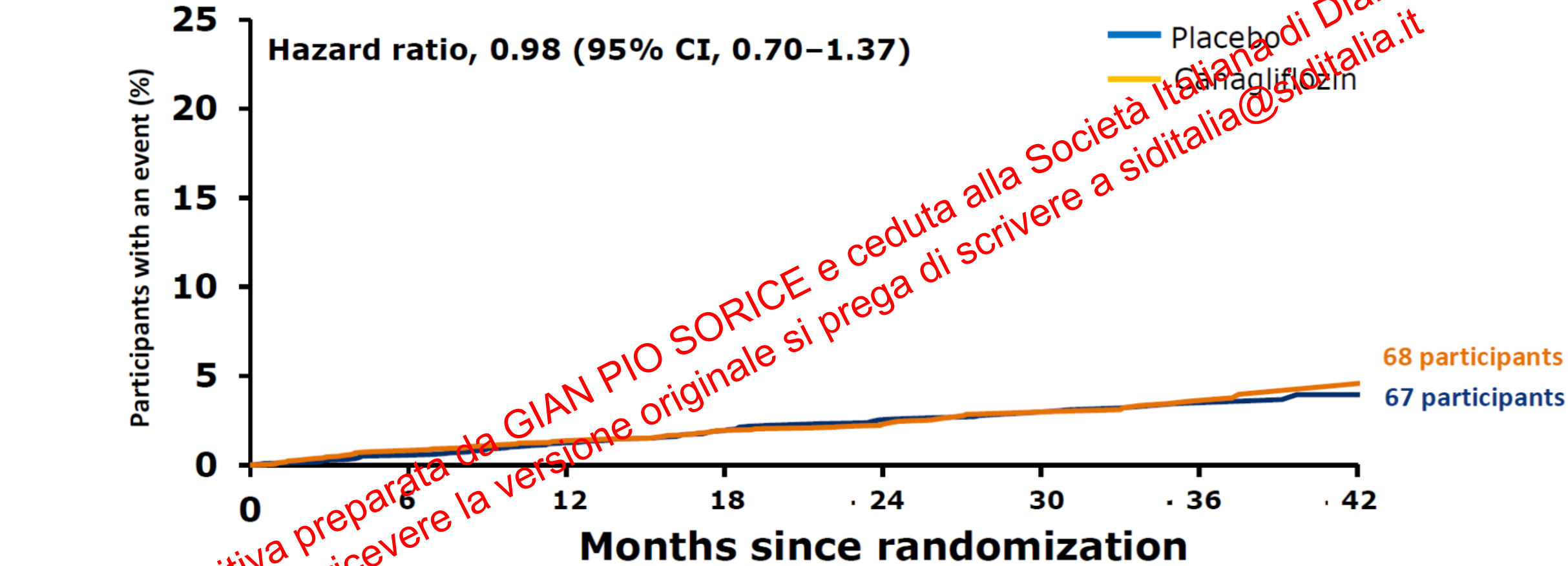
Lo studio CREDENCE ha confermato la tendenza dello studio CANVAS in merito alle fratture?

SI, SEPPUR IN MODO NON SIGNIFICATIVO

NO

NON SO

Fratture ossee



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

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Safety‡						NA
Any adverse event						NA
Any serious adverse event						NA
Serious adverse event related to trial drug						NA
Amputation						NA
Fracture						NA
Cancer						
Renal-cell carcinoma						NA
Breast cancer§						NA
Bladder cancer						NA
Acute pancreatitis						NA
Hyperkalemia¶						NA
Acute kidney injury						NA
Diabetic ketoacidosis‖						NA

The similar rates of amputation and fracture that we observed with canagliflozin and placebo are reassuring and consistent with trials of other SGLT2 inhibitors[6,7,20] but differ from the CANVAS Program findings.[5] Whether the increased risk of lower-limb amputation in the CANVAS Program was due to differing trial populations or protocols or to chance remains unclear. The overall safety profile in our trial is otherwise consistent with the known adverse effects associated with canagliflozin.

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

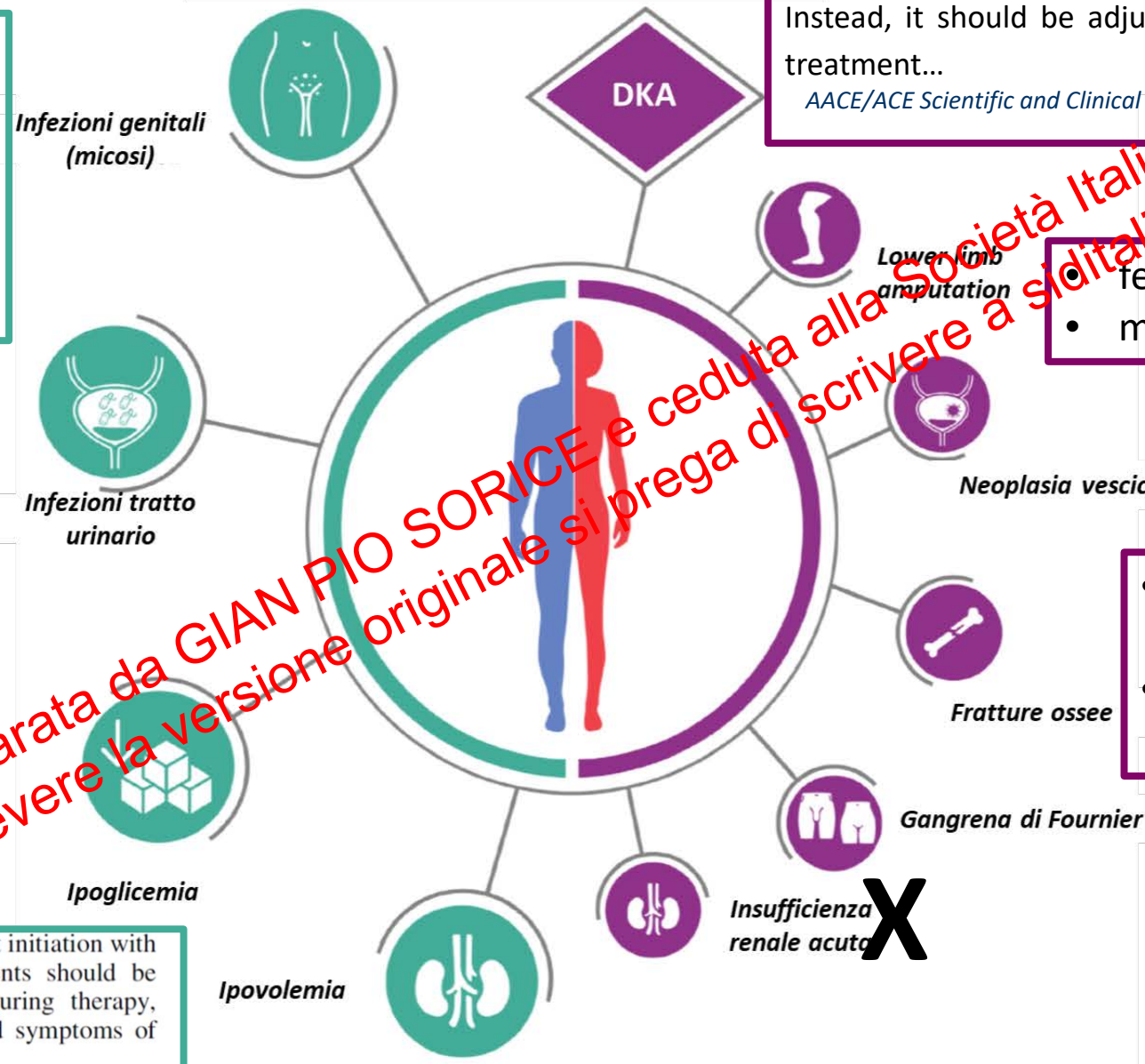
This article was published on April 14, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1811744

- educazione terapeutica (…)
- monitoraggio periodico
- idratazione
- associazione con DPP-IVi

Patients taking SGLT2-i should be educated to avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets. Insulin dose should not automatically be reduced when SGLT2i are begun. Instead, it should be adjusted based on the individual response to treatment…

AACE/ACE Scientific and Clinical Review: Association of SGLT2 Inhibitors and DKA, 2015



- fenotipizzazione
- monitoraggio periodico

- opportuna titolazione della terapia antipertensiva
- attenzione ai fattori di rischio per cadute

opportuna titolazione della restante terapia ipoglicemizzante

Before treatment initiation with SGLT2 inhibitors, volume status of patients should be assessed and corrected as appropriate. During therapy, patients should be monitored for signs and symptoms of hypotension and treated as appropriate.

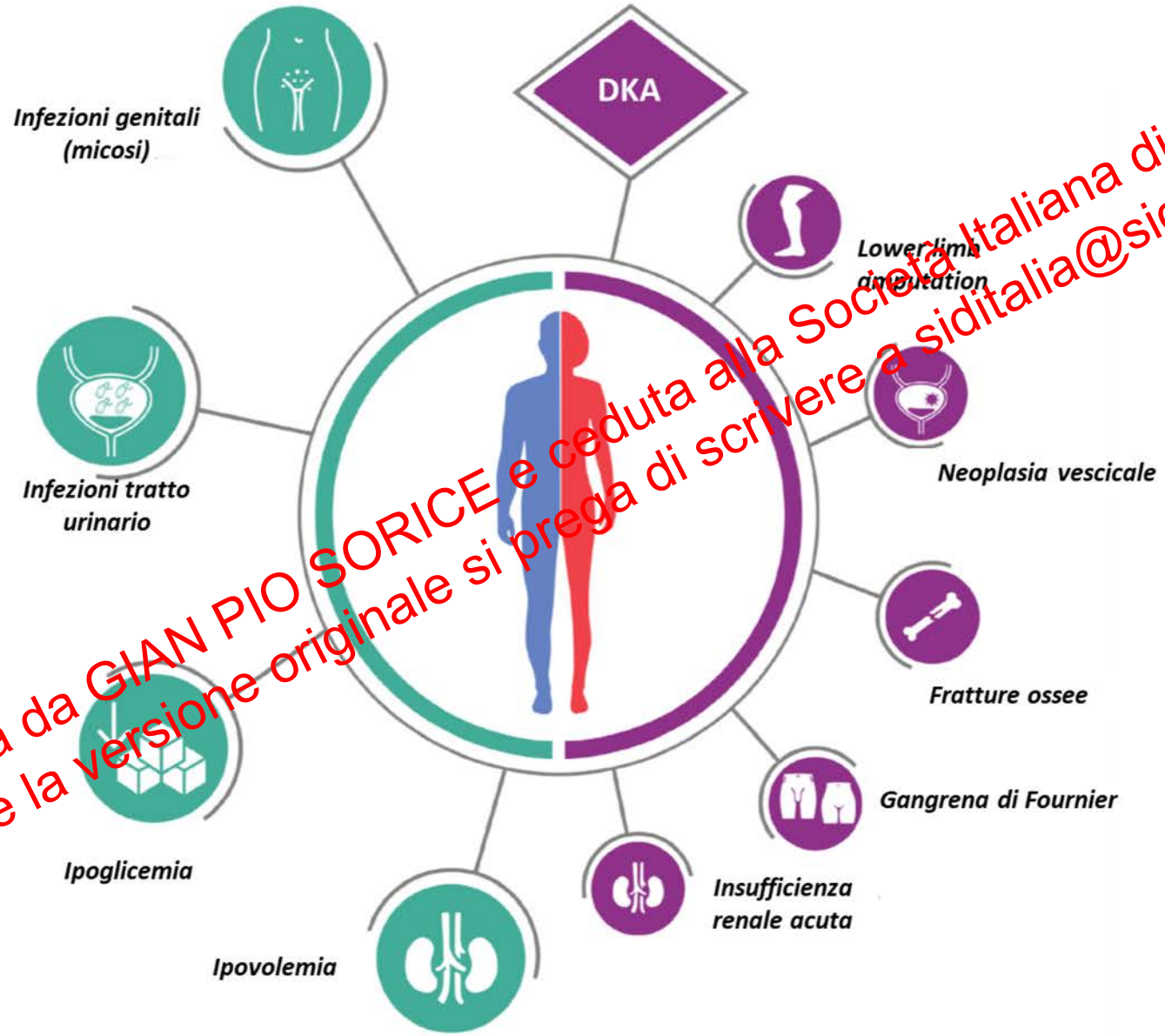
QNOW

È EVIDENTE CHE I NOTI *SIDE EFFECTS* NON POSSONO, IN MODO ASSOLUTO, LIMITARE L'UTILIZZO DI FARMACI AD ELEVATO IMPATTO BENEFICO SU ASPETTATIVA DI VITA, RIDUZIONE DI MORTE CV, MIGLIORAMENTO DEGLI ENDPOINT RENALI, RIDUZIONE DELLE IPOGLICEMIE, RIDUZIONE DEL FABBISOGNO INSULINICO, CALO PONDERALE?

SI

NO

NON SO



SID
Società Italiana di Diabetologia
fondata nel 1964

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

Gian Pio Sarice

SGLT2 INIBITORI

e progressione della **malattia renale** nel **diabete tipo 2**