IMPATTO DEGLI INIBITORI DI SGLT-2 NEI PAZIENTI CON DIABETE MELLITO TIPO 2

EFFETTI MENO FREQUENTI DEI FARMACI INIBITORI DI SGLT2

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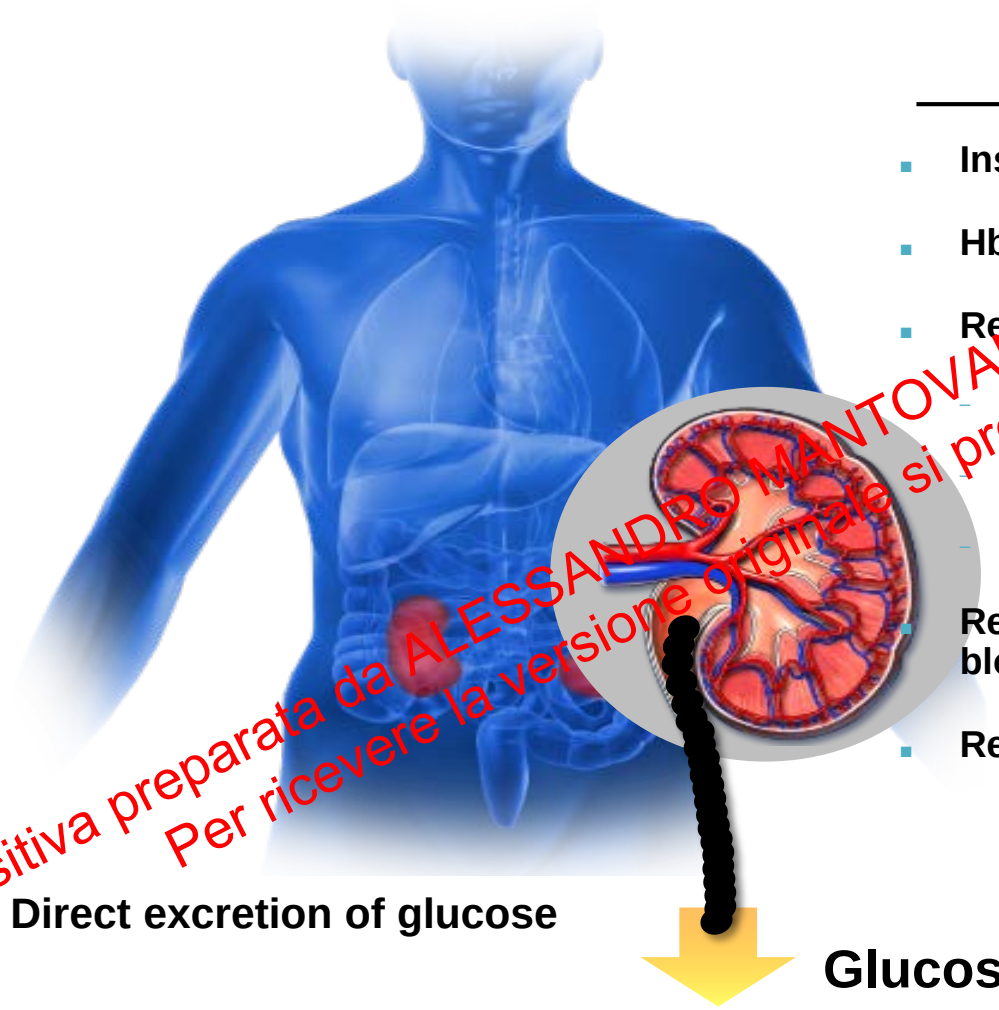
Il dr. Alessandro Mantovani dichiara di **NON** aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

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.).

Potential Effects of SGLT2 Inhibition



Direct excretion of glucose

Glucosuria

Potential benefits

- Insulin-independent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure
- Reduction in uric acid

Potential risks

- Hypoglycaemia
- Renal function
- Diuretic effect
  - Hypovoalaemia
  - Hypotension
  - Dehydration
  - Alterations of electrolytes
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events

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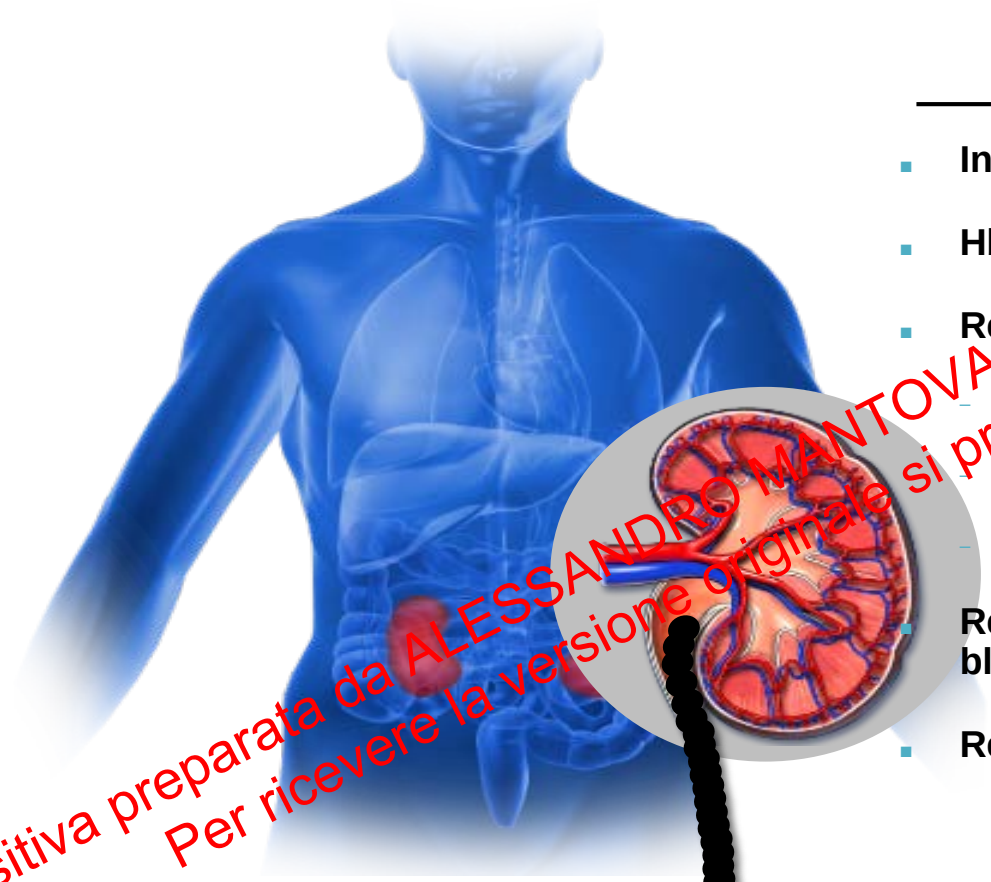

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Domanda n.1

Quale tipo di paziente potrebbe incorrere con maggior probabilità ad infezione delle vie genitourinarie durante il trattamento con SGLT2i?

a)Uomo senza storia di infezioni genitali

b)Donna senza storia di infezioni urinarie

c) Donna con infezioni genitali ricorrenti

d) Nessuno dei precedenti

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EMPA-REG OUTCOME – Adverse events

7,020 T2DM patients randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time 3.1 years).

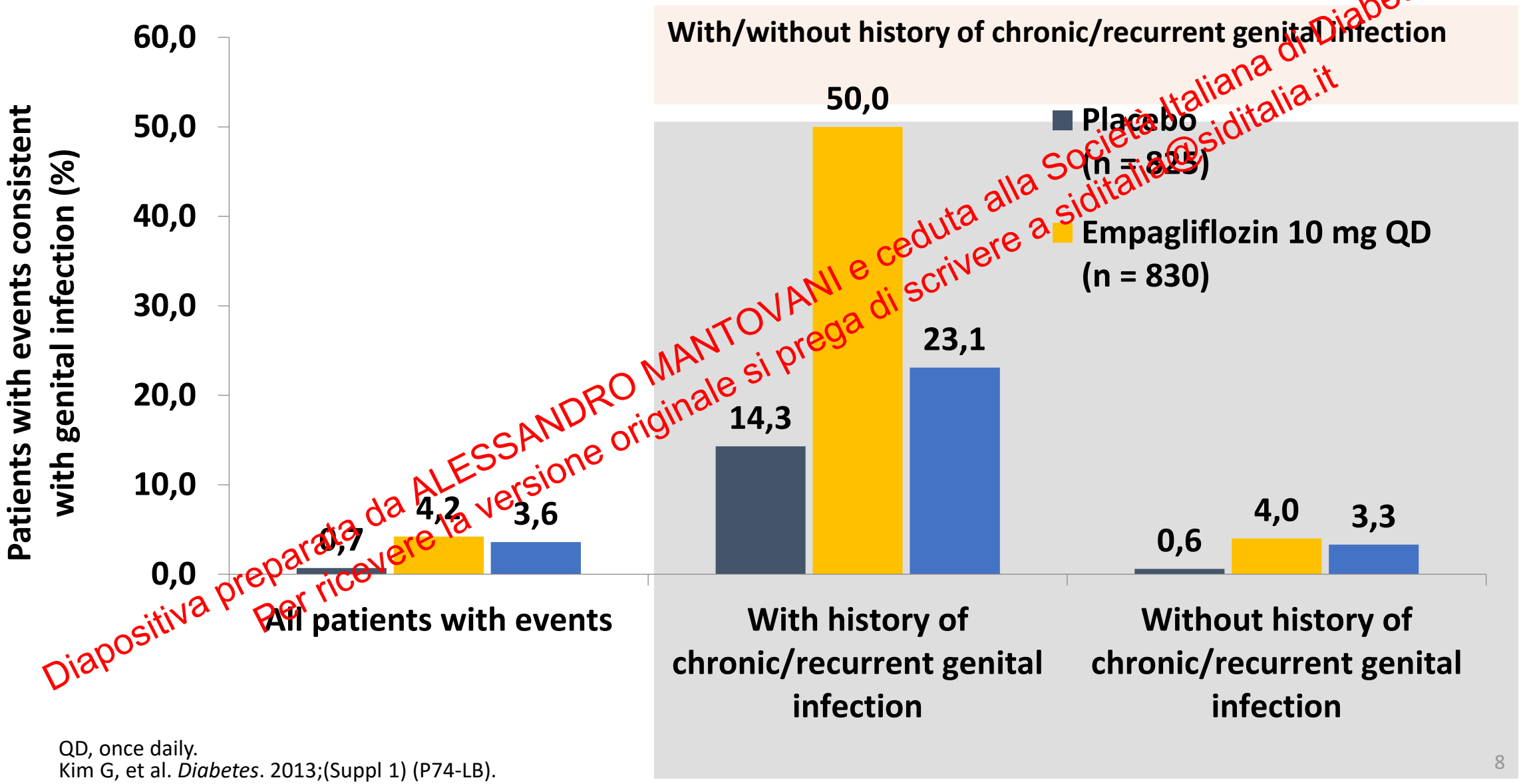
Table 2. Adverse Events.*

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)	1303 (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 (9.9)	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 (2.6)	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)

* Data are for patients who had one or more event and who had received at least one dose of a study drug. All events occurred within 7 days after the last receipt of the study drug.
† P<0.001 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.01 for the comparison with placebo.

Zinman B et al. N Engl J Med 2015;373:2117-28.

Phase III pooled safety and tolerability analysis events consistent with genital infection



Pooled data from 4 pivotal Phase III trials

QD, once daily.

Kim G, et al. *Diabetes*. 2013;(Suppl 1) (P74-LB).

EMPA-REG OUTCOME – Complicated urinary tract infections

7,020 T2DM patients randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time 3.1 years).

Section R. Complicated urinary tract infections

Table S13. Breakdown of complicated urinary tract infections by MedDRA preferred term

	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
	no. (%) with one or more event			
Complicated urinary tract infection	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Urinary tract infection	16 (0.7)	13 (0.6)	16 (0.7)	29 (0.6)
Urosepsis	3 (0.1)	6 (0.3)	11 (0.5)	17 (0.4)
Pyelonephritis	4 (0.2)	3 (0.1)	10 (0.4)	13 (0.3)
Pyelonephritis chronic	10 (0.4)	4 (0.2)	6 (0.3)	10 (0.2)
Pyelonephritis acute	6 (0.3)	7 (0.3)	1 (<0.1)	8 (0.2)
Cystitis	2 (0.1)	0	0	0
Kidney infection	2 (0.1)	1 (<0.1)	3 (0.1)	4 (0.1)
Urinary tract infection fungal	0	0	3 (0.1)	3 (0.1)
Cystitis bacterial	1 (<0.1)	0	0	0
Escherichia urinary tract infection	1 (<0.1)	0	0	0
Urinary tract infection pseudomonal	0	0	1 (<0.1)	1 (<0.1)
Cystitis glandularis	0	0	1 (<0.1)	1 (<0.1)
Cystitis hemorrhagic	1 (<0.1)	0	0	0
Nephritis	0	1 (<0.1)	0	1 (<0.1)

Data are from patients treated with ≥1 dose of study drug based on events that occurred on treatment or ≤7 days after the last intake of study medication. Complicated urinary tract infection defined as pyelonephritis, urosepsis or serious adverse event consistent with urinary tract infection. There were no significant differences ($p<0.05$) between pooled empagliflozin and placebo.

Zinman B et al. N Engl J Med 2015;373:2117-28.

CANVAS Program – Adverse effects

10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

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	52.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion‖	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	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

Neal B et al. N Engl J Med 2017;377:644-657.

Dapagliflozin - A pooled analysis of safety data from phase IIb/III clinical trials

Data were pooled from 13 placebo-controlled trials of up to 24 weeks' duration (dapagliflozin, n = 2360; placebo, n = 2295).

TABLE 2 Summary of AEs of special interest (13-, 21- and 30-study pools)

	Placebo-controlled 13-study pool[a]	
	Placebo group (N = 2295; 957.9 patient-years)	Dapagliflozin 10 mg group (N = 2360; 997.6 patient-years)
UTI, n (%)	81 (3.5)	110 (4.7)
Most common UTI AEs (>1 patient in either treatment group), n (%)		
UTI	61 (2.7)	91 (3.9)
Cystitis	15 (0.7)	16 (0.7)
Prostatitis	3 (0.1)	0
Genital infection, n (%)	14 (0.6)	130 (5.5)
Most common genital infection AEs (>1 patient in either treatment group), n (%)		
Vulvovaginal mycotic infection	7 (0.3)	34 (1.4)
Balanitis	0	29 (1.2)
Vaginal infection	1 (<0.1)	18 (0.8)
Genital infection fungal	2 (0.1)	12 (0.5)
Genital infection	1 (<0.1)	11 (0.5)
Vulvovaginal candidiasis	1 (<0.1)	8 (0.3)
Balanitis candida	0	6 (0.3)
Vulvovaginitis	0	5 (0.2)
Genital candidiasis	0	3 (0.1)
Vulvitis	0	2 (0.1)

Jabbour S et al. Diabetes Obes Metab 2018; 20: 620-628

Effects of SGLT2 inhibitors on safety otucomes

A systematic review and meta-analyses including data from 6 regulatory submissions (37,525 participants) and 57 published trials (33,385 participants), which provided data for 7 different SGLT2 inhibitors.

	Drugs with data	SGLT2 inhibitors (n/N)	Control (n/N)	Relative risk (95% CI)	I^2 (%)
Data from regulatory submissions					
Urinary tract infection	6	1419/19835	690/10847	1·15 (1·06–1·26)	0
Genital infection	6	1243/19835	143/10847	4·75 (4·00–5·63)	59%*
Cancer	6	253/25071	112/12454	1·07 (0·85–1·34)	0
Bone fracture	5	301/19120	161/10383	0·99 (0·82–1·21)	29%
Volume depletion	6	505/19835	159/10847	1·53 (1·27–1·83)	40%
Thromboembolism	3	26/13375	6/6976	1·54 (0·63–3·79)	0
Hypoglycaemia	6	2283/18147	1308/9364	1·00 (0·94–1·07)	67%*
Acidosis	1	1/1630	0/311	0·57 (0·02–14·10)	NA
Kidney disease	4	145/20973	661/11709	1·21 (0·91–1·62)	10%
Data from scientific reports					
Urinary tract infection	6	1852/17096	872/8965	1·02 (0·95–1·10)	45%*
Genital infection	6	1419/19702	279/10694	2·88 (2·48–3·34)	79%*
Cancer	3	13/1865	14/1890	0·72 (0·34–1·54)	0
Bone fracture	4	254/8469	142/4914	0·96 (0·78–1·18)	21%
Volume depletion	4	438/14402	184/7782	1·16 (0·98–1·38)	0
Thromboembolism	1	30/4687	20/2333	0·75 (0·42–1·31)	0
Hypoglycaemia	7	3203/19260	2093/10289	0·95 (0·91–1·00)	89%*
Acidosis	1	4/4687	1/2333	1·99 (0·22–17·80)	NA
Kidney disease	2	292/7075	171/3955	0·83 (0·69–1·00)	6%

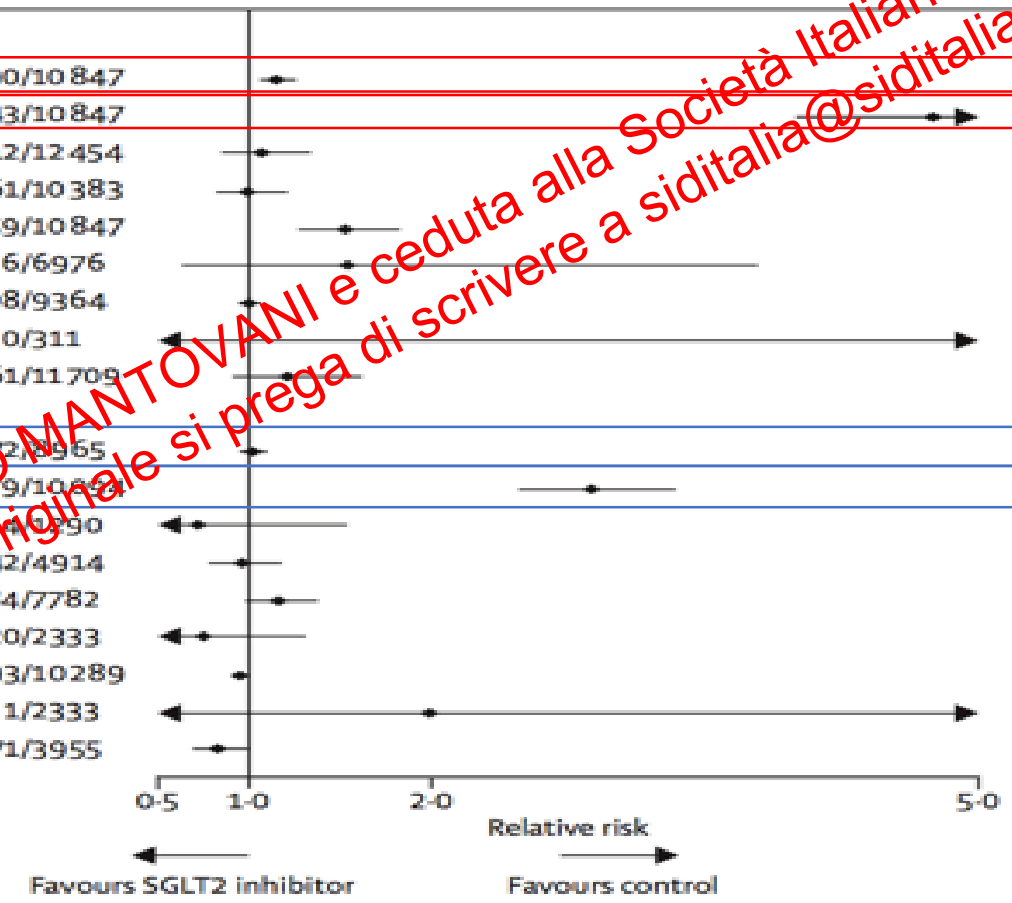


***Figure 3*: Effects of SGLT2 inhibitors on safety outcomes, overall and for each drug, based on data from regulatory submissions and scientific reports**
Summary effects for all drugs obtained from fixed-effects meta-analysis. NA=not applicable. SGLT2=sodium-glucose cotransporter-2. *p heterogeneity <0·05.

Wu JH et al. Lancet Diabetes Endocrinol 2016;4:411-9.

A global analysis of international spontaneous reporting systems

Eudravigilance, WHO-Vigibase (as of Feb 25, 2017) and the FDA Adverse Event Reporting System (FAERS, from 2004 to 2016 second quarter) were queried to extract AEs recording SGLT2-Is as suspect.

Raschi E et al. Nutrition, Metabolism & Cardiovascular Diseases 2017; 27:1098-1107

KEY MESSAGE

- **The most common side effect of SGLT2 inhibitors is an increased incidence of genital mycotic infections (mainly balanitis and vulvovaginitis).**

- **Some, but not all, studies showed that these drugs are also associated with a small increase in the risk of urinary tract infections (UTIs).**

- **Generally, the events are mild to moderate in severity and do not necessitate discontinuation of the drug.**

- **Infections of the upper urinary tract, such as pyelonephritis, and urosepsis are extremely rare complications.**

KEY MESSAGE

- **Genital mycotic infections can be treated with a single dose of an oral antifungal drug (e.g. fluconazole) or several days' application of an antifungal cream (e.g. miconazole, clotrimazole).**

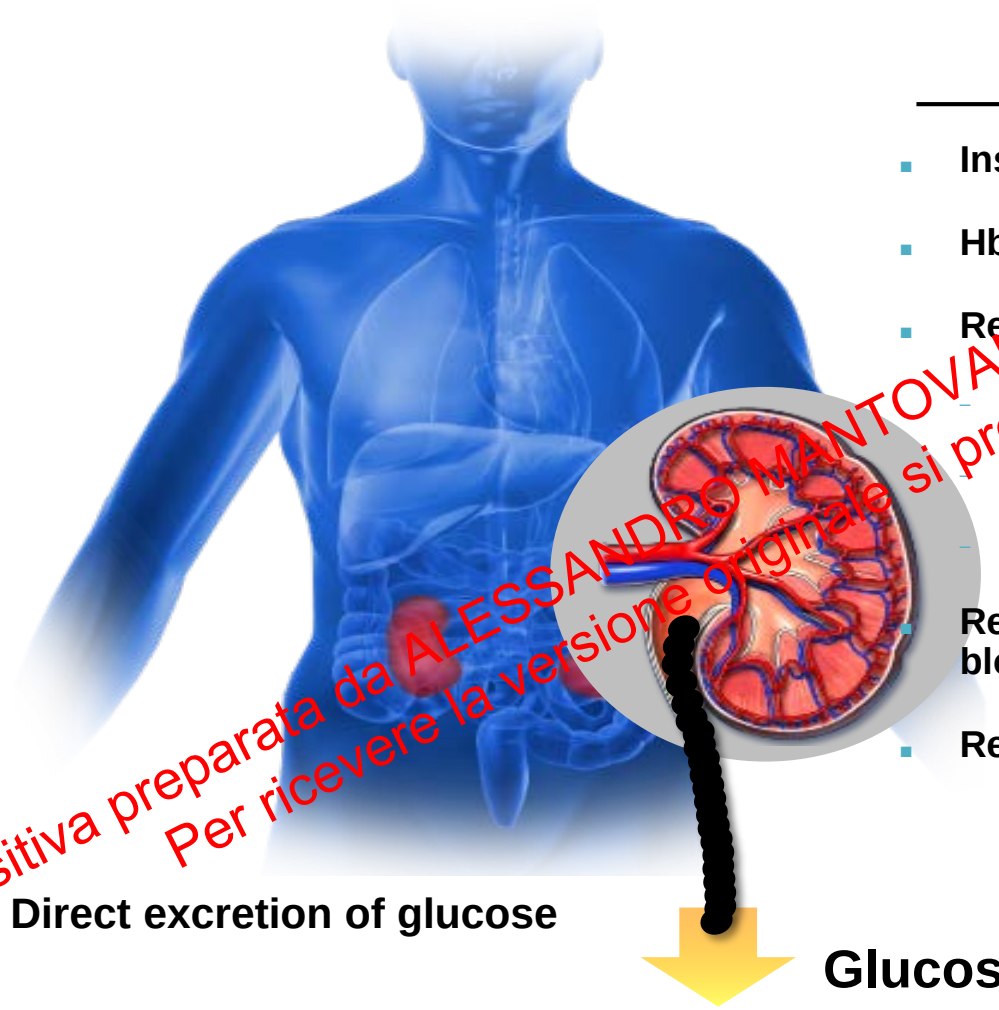
- **Uncomplicated UTIs can usually be managed with routine therapy.**

- **There are no data to support surveillance urinalyses or urine cultures in diabetic individuals taking SGLT2 inhibitors.**

- **SGLT2 inhibitors should be avoided in individuals with prior history of complicated UTIs such as pyelonephritis or urosepsis, those with an indwelling urinary catheter and those with recurrent genital mycotic infections.**

- **Men with prostatic hypertrophy and women with urinary incontinence will find this drug class challenging to use, and this is likely to have a negative impact on quality of life.**

Potential Effects of SGLT2 Inhibition



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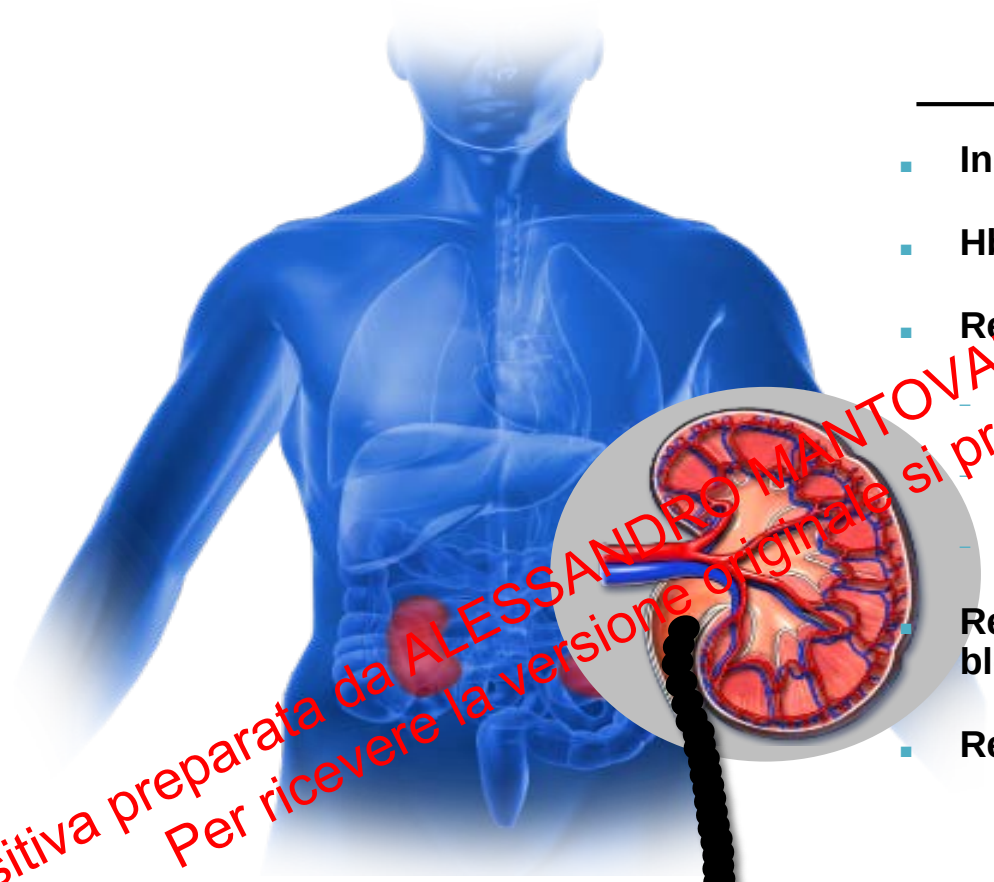

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Phase I–III pooled safety analysis* - Events consistent with volume depletion†

n, (%)	Placebo (n = 3522)	Empagliflozin 10 mg QD (n = 3630)	Empagliflozin 25 mg QD (n = 4602)
Events consistent with volume depletion	49 (1.4)	52 (1.4)	67 (1.5)
Hypotension	28 (0.8)	22 (0.6)	25 (0.5)
Orthostatic hypotension	6 (0.2)	8 (0.2)	11 (0.2)
Blood pressure decrease	1 (< 0.1)	0 (0.0)	2 (< 0.1)
Hypovolemia	2 (< 0.1)	0 (0.0)	1 (< 0.1)
Dehydration	4 (0.1)	9 (0.2)	8 (0.2)
Syncope	11 (0.3)	16 (0.4)	22 (0.5)
Events consistent with volume depletion leading to discontinuation	4 (0.1)	1 (< 0.1)	4 (0.1)
Events consistent with volume depletion, serious AEs	12 (0.3)	9 (0.2)	11 (0.2)

Pooled data from 21 Phase I–III trials

*Data were pooled from 3 Phase I trials, 5 dose-finding Phase II trials and 13 Phase IIb/III trials (including extension trials) that investigated empagliflozin.

†Investigator-defined based on 8 prospectively defined preferred terms: blood pressure (BP) decreased, BP ambulatory decreased, BP systolic decreased, dehydration, hypotension, orthostatic hypotension, hypovolemia and syncope.

Toto R, et al. *J Am Soc Nephrol.* 2013;24:711A (SA-PO373).

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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)

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† P<0.001 for the comparison with placebo.
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Zinman B et al. N Engl J Med 2015;373:2117-28.

CANVAS Program – Adverse events

RCT enrolling 10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

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	31.5	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
Serious thromboembolic events	1.7	1.7	0.63
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	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	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 300 mg has a higher renal excretion of glucose when compared to empagliflozin 25 mg (~113 g/day *vs.* 77 g/day, respectively)

Neal B et al. N Engl J Med 2017;377:644-657.

Dapagliflozin - A pooled analysis of safety data from phase IIb/III clinical trials

Data were pooled from 13 placebo-controlled trials of up to 24 weeks' duration (dapagliflozin, n = 2360; placebo, n = 2295).

TABLE 2 Summary of AEs of special interest (13-, 21- and 30-study pools)

	Placebo-controlled 13-study pool[a]	
	Placebo group (N = 2295; 957.9 patient-years)	Dapagliflozin 10 mg group (N = 2360; 997.6 patient-years)
Volume depletion AEs[c], n (%)	17 (0.7)	27 (1.1)
Most common volume depletion AEs (>1 patient in either treatment group), n (%)		
Hypotension	5 (0.2)	15 (0.6)
Syncope	3 (0.1)	6 (0.3)
Orthostatic hypotension	6 (0.3)	2 (0.1)
Dehydration	0	2 (0.1)

Jabbour S et al. Diabetes Obes Metab 2018; 20: 620-628

KEY MESSAGE

- SGLT2 inhibitors lower BP by inducing osmotic diuresis.

- This effect is beneficial in individuals with uncontrolled hypertension but can lead to postural dizziness, orthostatic hypotension and dehydration, especially in elderly individuals with kidney disease or those taking loop diuretics.

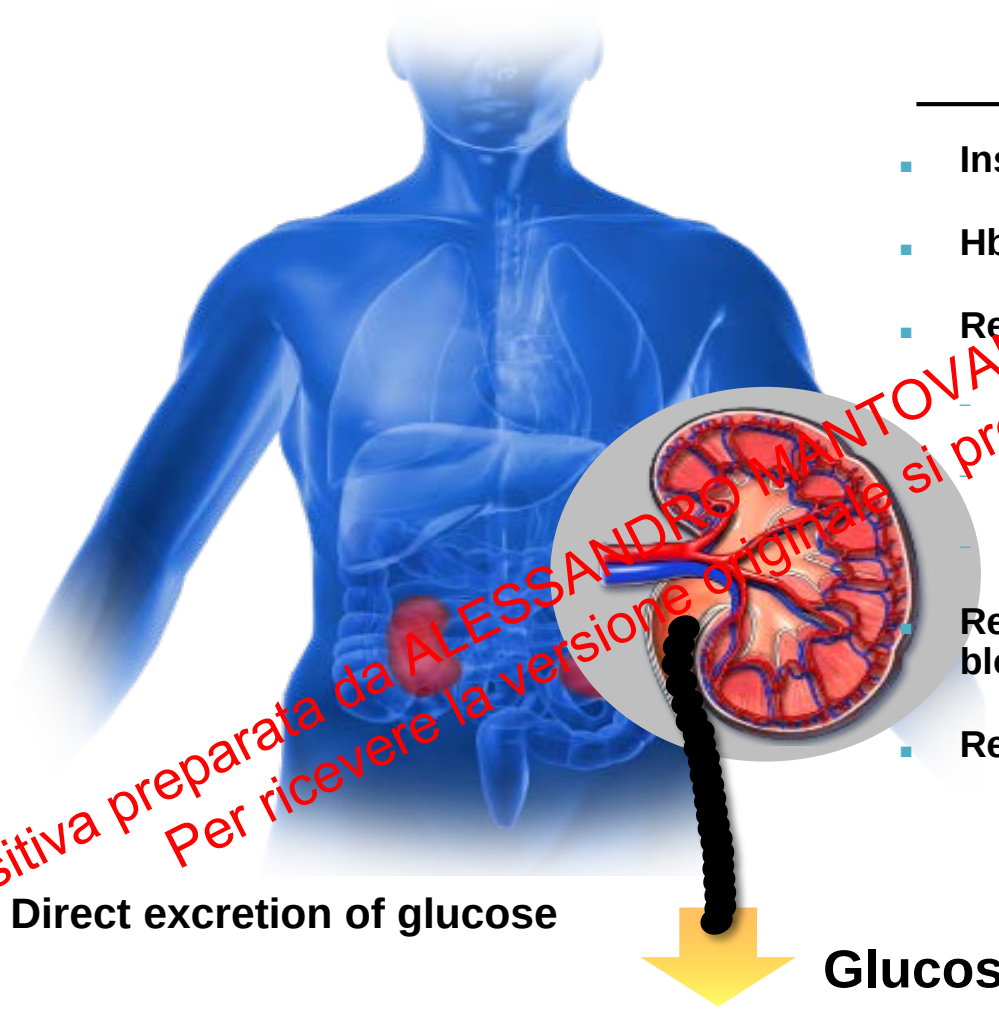
- In the EMPA-REG OUTCOME trial, adverse events consistent with volume depletion were rare and occurred at similar frequency in the empagliflozin and placebo groups (5.1% vs 4.9%, respectively).

- In contrast, in CANVAS Program, volume depletion was more common in the canagliflozin vs placebo group (26.0 vs. 18.5 events per 1000 person-years; p=0.009)

- The diuretic effect exerted by SGLT2 inhibitors means it is important to assess volume status and BP before initiating treatment.
- In hypovolaemic or hypotensive individuals, the SGLT2 inhibitor should be delayed until the fluid status and BP are corrected.
- If an individual is euvolaemic but verging towards hypotension, SGLT2 inhibitors should be initiated cautiously and close monitoring is advised.
- Euvolaemic, normotensive individuals on thiazide therapy can continue with the thiazide as this diuretic does not further reduce BP beyond the reduction achieved with SGLT2 inhibitors.
- In contrast, in individuals receiving more potent loop diuretics, reducing the dose by 50% should be considered, with close follow-up.

years; p=0.009)

Potential Effects of SGLT2 Inhibition



Direct excretion of glucose

Glucosuria

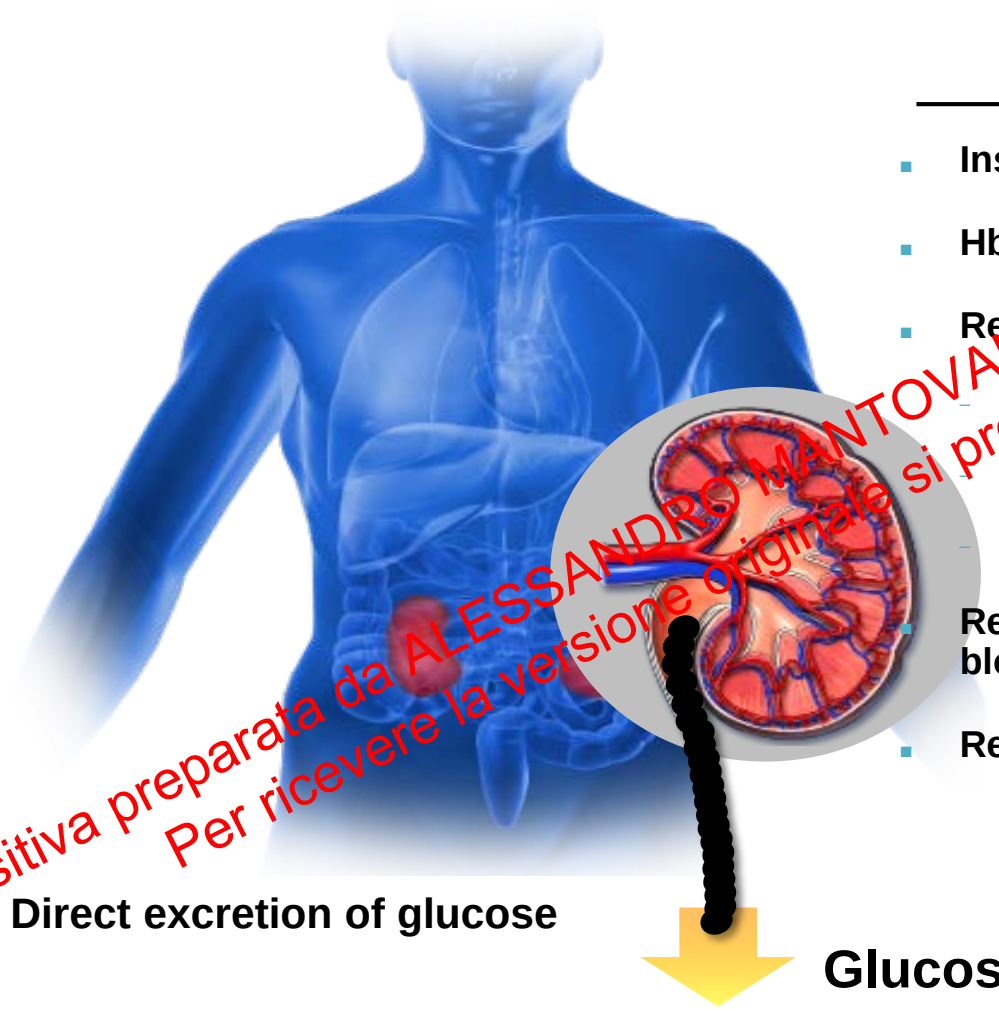
Potential benefits

- Insulin-independent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure
- Reduction in uric acid

Potential risks

- Hypoglycaemia
- Renal function
- Diuretic effect
  - Hypovoalaemia
  - Hypotension
  - Dehydration
  - Alterations of electrolytes
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events

Potential Effects of SGLT2 Inhibition



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Domanda n.2

Il trattamento con SGLT2 inhibitors non modifica in alcun modo gli elettroliti sierici

a) Vero

b) Falso

Domanda n.2

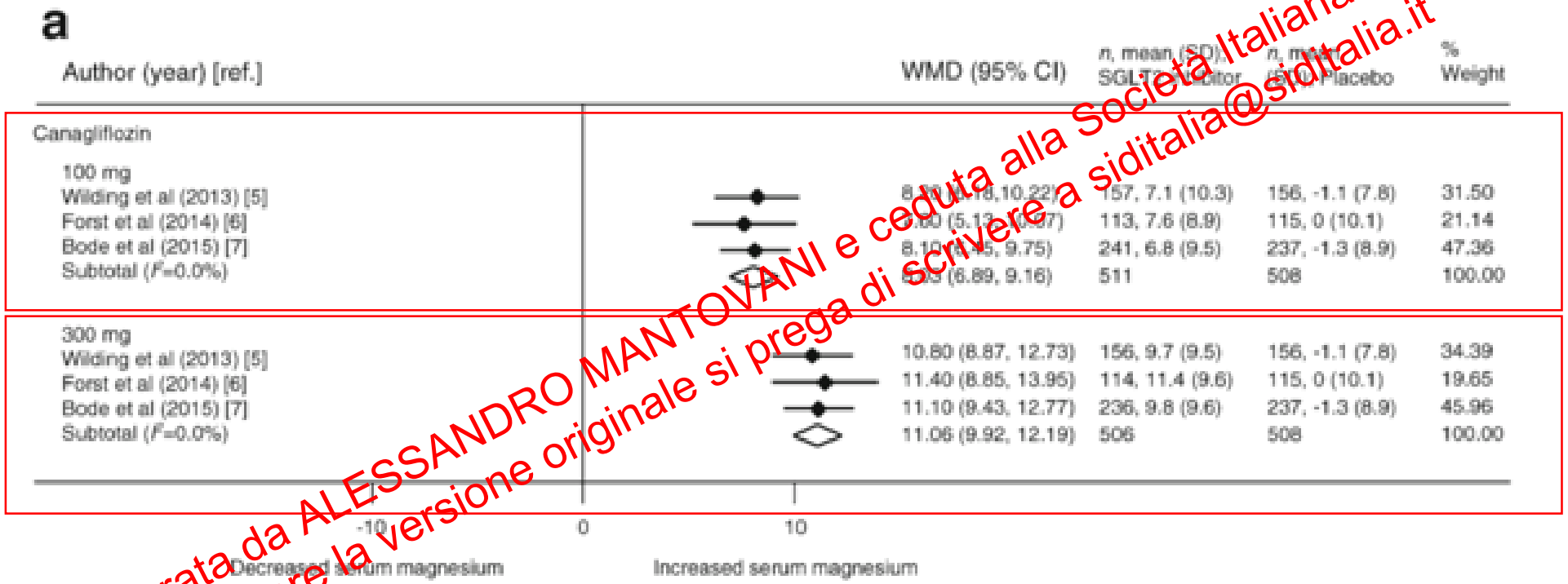
Il trattamento con SGLT2 inhibitors non modifica in alcun modo gli elettroliti sierici

a) Vero

b) Falso

Magnesium

A meta-analysis of 18 RCTs that reported changes in serum electrolyte levels, for a total of 15,309 patients and 4 SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ipragliflozin)



Weighted mean differences (WMD) for changes in serum magnesium level for SGLT2 inhibitors vs placebo, stratified by dose. A WMD (95% CI) for canagliflozin calculated as mean percentage change from baseline.

Tang H et al. Diabetologia 2016;59:2546–2551

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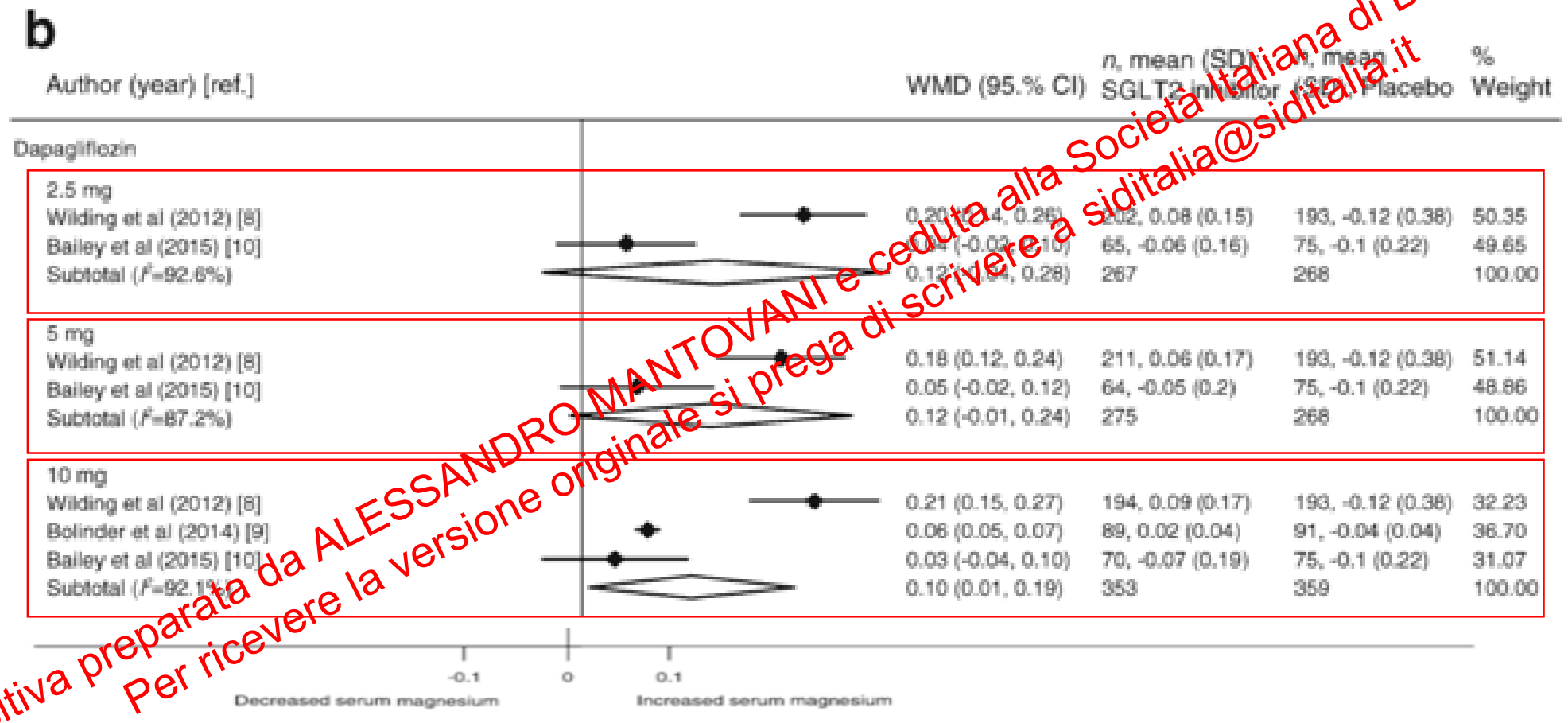
A meta-analysis of 18 RCTs that reported changes in serum electrolyte levels, for a total of 15,309 patients and 4 SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ipragliflozin)



Weighted mean differences (WMD) for changes in serum magnesium level for SGLT2 inhibitors vs placebo, stratified by dose. A WMD (95% CI) for dapagliflozin was calculated as mean change from baseline in mmol/l.

Tang H et al. Diabetologia 2016;59:2546–2551

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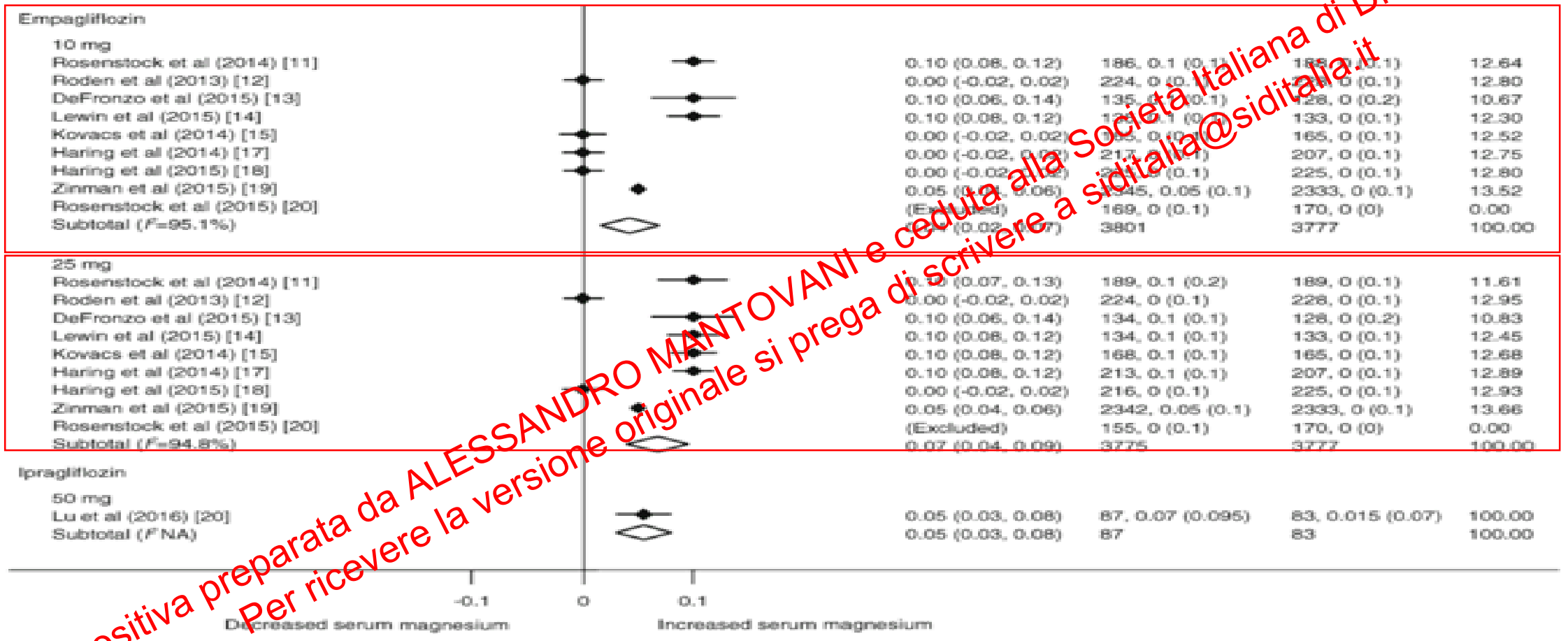
A meta-analysis of 18 RCTs that reported changes in serum electrolyte levels, for a total of 15,309 patients and 4 SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ipragliflozin)



Weighted mean differences (WMD) for changes in serum magnesium level for SGLT2 inhibitors vs placebo, stratified by dose. A WMD (95% CI) for empagliflozin was calculated as mean change from baseline in mmol/l.

Tang H et al. Diabetologia 2016;59:2546–2551

Calcium, phosphate, potassium and sodium

A meta-analysis of 18 RCTs that reported changes in serum electrolyte levels, for a total of 15,309 patients and 4 SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ipragliflozin)

Table 1 Meta-analysis of WMD in changes in serum calcium, phosphate, potassium and sodium levels for each SGLT2 inhibitor vs placebo, stratified by dose

SGLT2 inhibitor	Serum calcium level				Serum phosphate level				Serum potassium level				Serum sodium level			
	n	*N*[c]	WMD (95% CI)	Het-I^2% (95% CI)	*n*	*N*[c]	WMD (95% CI)	Het-I^2% (95% CI)	*n*	*N*[c]	WMD (95% CI)	Het-I^2% (95% CI)	*n*	*N*[c]	WMD (95% CI)	Het-I^2% (95% CI)
Canagliflozin[a]																
100 mg	–	–	–	–	2	541	1.60 (−6.33, 9.54)	90.3	3	1019	0.15 (−0.88, 1.17)	0 (0, 90)	2	541	−0.22 (−0.61, 0.17)	34.3
300 mg	–	–	–	–	2	541	2.56 (−3.32, 8.44)	88.2	3	1014	0.61 (−1.45, 2.27)	72 (5, 92)	2	541	−0.36 (−0.68, −0.05)	0
Dapagliflozin[b]																
2.5 mg	2	535	0.03 (−0.02, 0.08)	63	2	535	0.01 (−0.02, 0.04)	0	2	535	−0.02 (−0.20, 0.15)	69.5	2	535	0.05 (−0.68, 0.77)	21.8
5 mg	2	543	0.00 (−0.03, 0.03)	20.9	2	543	0.04 (0.01, 0.08)	0	2	543	−0.08 (−0.17, 0.01)	2.1	2	543	0.49 (−0.11, 1.08)	0
10 mg	3	712	0.00 (−0.03, 0.03)	46.6 (0, 84)	3	712	0.05 (0.02, 0.09)	43.3 (0, 83)	3	712	−0.04 (−0.20, 0.13)	64.6	2	532	0.37 (−0.31, 1.06)	0
Empagliflozin[b]																
10 mg	9	7578	0.00 (−0.01, 0.01)	0 (0, 65)	9	7578	0.02 (−0.01, 0.05)	93 (89, 96)	9	7578	0.01 (−0.02, 0.04)	65.2 (29, 83)	9	7578	0.19 (−0.03, 0.49)	77 (56, 88)
25 mg	9	7552	0.00 (−0.01, 0.01)	0 (0, 65)	9	7552	0.02 (−0.01, 0.05)	93 (89, 96)	9	7552	−0.00 (−0.04, 0.04)	76.7 (56, 88)	9	7552	0.31 (0.04, 0.58)	86.1 (75, 92)
Ipragliflozin[b]																
50 mg	1	170	−0.01 (−0.04, 0.02)	–	1	170	0.13 (−0.02, 0.28)	–	1	170	0.02 (−0.08, 0.12)	–	1	170	0.00 (−0.62, 0.62)	–

[a] Mean percentage change from baseline

[b] Mean change from baseline (mmol/l)

[c] Safety analysis set

–, data not available; *n*, number of trials; *N*, number of patients; Het, heterogeneity

Tang H et al. Diabetologia 2016;59:2546–2551

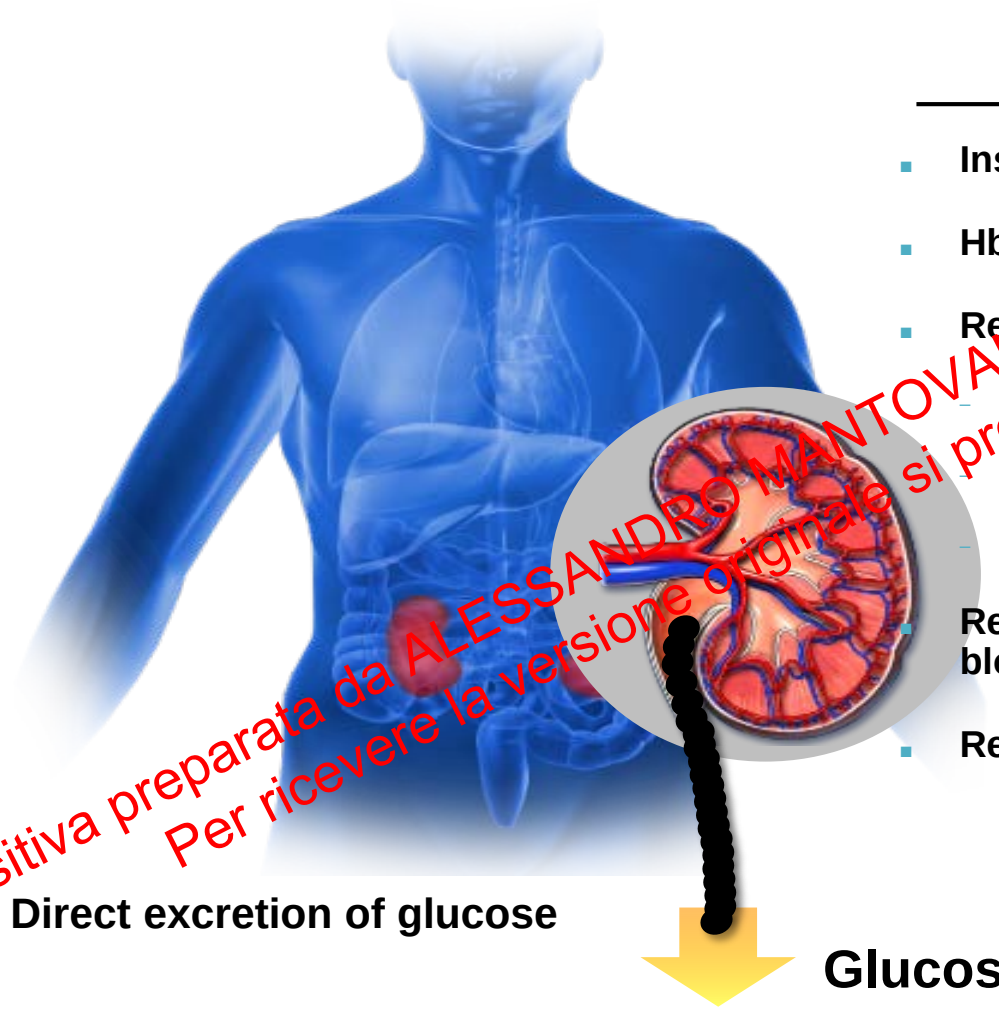
KEY MESSAGE

- An increase in serum **magnesium** levels by 0.1–0.2 mEq/L in patients without chronic kidney disease, receiving SGLT-2 inhibitors (i.e., canagliflozin, empagliflozin, dapagliflozin, and ipragliflozin) was reported in different studies.

- Significant changes in serum **sodium** and **potassium** concentration have not been observed in all studies with SGLT2 inhibitors.

- A small increase in serum **phosphate** levels following SGLT2 inhibitor administration has been reported in some clinical trials.

Potential Effects of SGLT2 Inhibition



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- Diuretic effect
  - Hypovoalaemia
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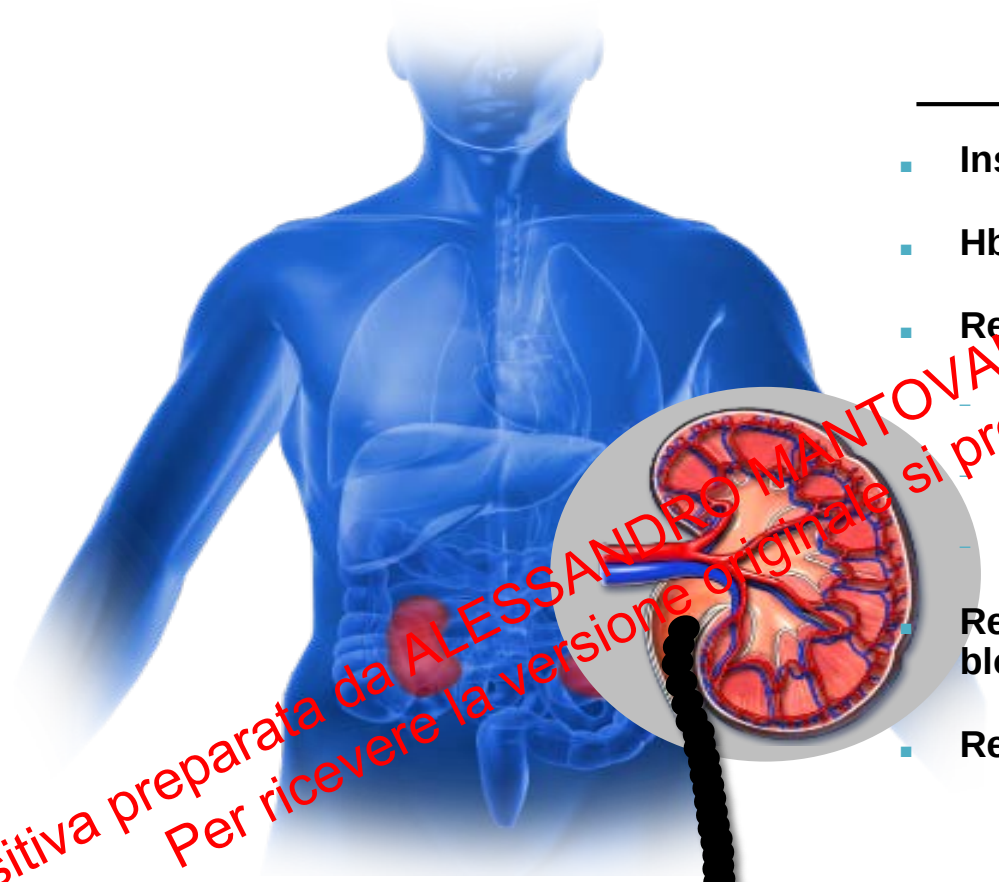
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events

Potential Effects of SGLT2 Inhibition



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- Rare or unexpected events

Domanda n.3

Il trattamento con SGLT2 inhibitors può provocare occasionalmente fratture ossee

a) Vero

b) Falso

c) Dai dati disponibili questo sembra vero solo per il canagliflozin

Domanda n.3

Il trattamento con SGLT2 inhibitors può provocare occasionalmente fratture ossee

a) Vero

b) Falso

c) Dai dati disponibili questo sembra vero solo per il canagliflozin

EMPA-REG OUTCOME – Adverse events

7,020 T2DM patients randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time 3.1 years).

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 (27.8)	656 (28.0)	647 (27.6)	1303 (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 (9.9)	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 (2.6)	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)

* Data are for patients who had one or more event and who had received at least one dose of a study drug. All events occurred within 7 days after the last receipt of the study drug.
† P<0.001 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.01 for the comparison with placebo.

Zinman B et al. N Engl J Med 2015;373:2117-28.

CANVAS Program – Bone Fractures

10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

Table S9. Effects of canagliflozin versus placebo on fracture in CANVAS, CANVAS-R, and the CANVAS Program

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value*
Low-trauma fracture (primary outcome)				
CANVAS	17.98	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

Analysis of fractures included all events at any time point in all patients who were randomized and received ≥1 dose of study drug.

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

Neal B et al. N Engl J Med 2017;377:644-657.

CANVAS Program – Adverse events

RCT enrolling 10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

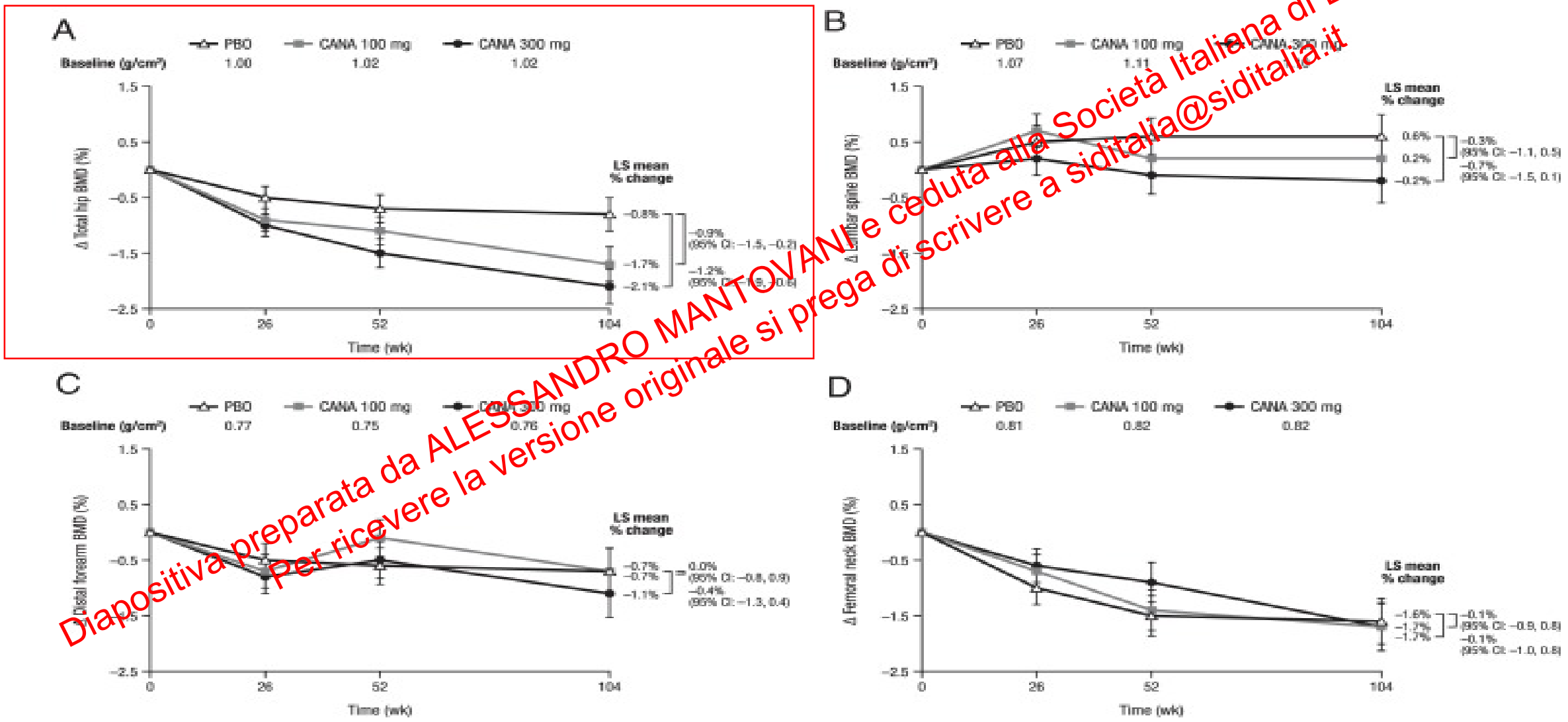
Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	[illegible]
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	[illegible]	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	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

Neal B et al. N Engl J Med 2017;377:644-657.

Bone Mineral Density in Patients With Type 2 Diabetes Treated With Canagliflozin

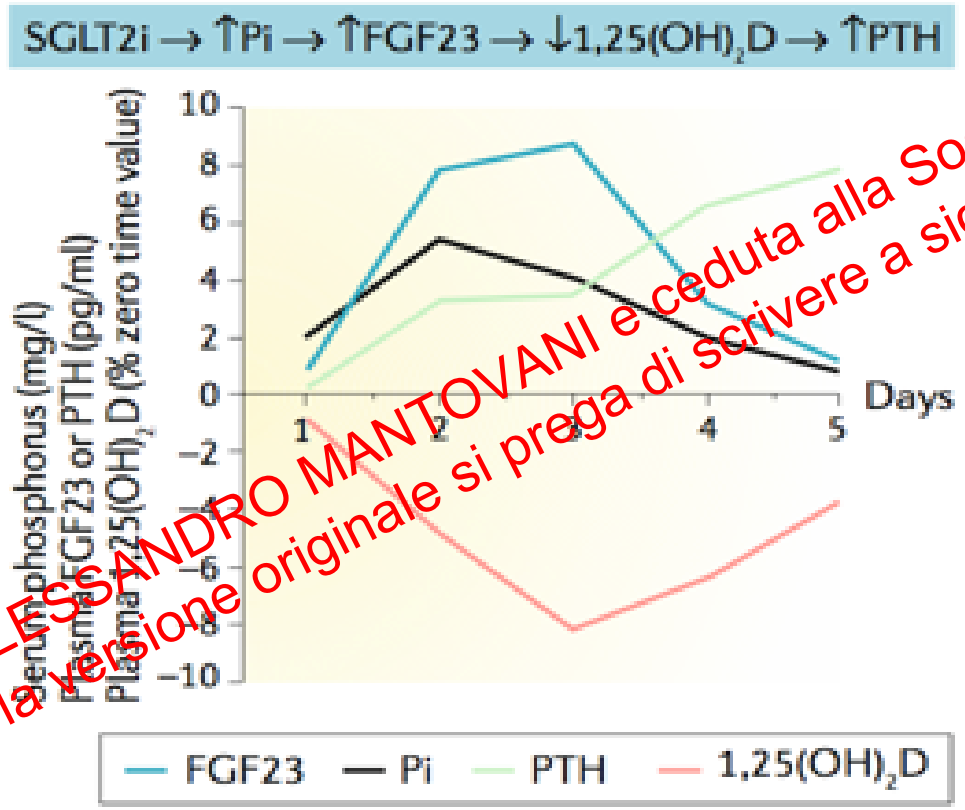
716 T2DM patients (55–80 years) randomly assigned to receive canagliflozin 100 or 300 mg or placebo; BMD was assessed using dual-energy x-ray absorptiometry at weeks 26, 52, and 104.



Bilezikian JP et al. J Clin Endocrinol Metab 2016;101:44–51.

Pharmacodynamic responses to canagliflozin treatment

A randomized crossover trial of 25 healthy volunteers: individuals were randomly assigned to treatment groups (placebo or canagliflozin [300 mg/day]) for 5 days and were subsequently crossed over to the other treatment.



In healthy volunteers, canagliflozin treatment induced only a transient increase in serum phosphorus, followed by induction of FGF23 and PTH, which together function to restore serum phosphorus to normal levels.
Whereas FGF23 and 1,25(OH) D also returned to baseline levels, PTH levels remained elevated at the end of the 5-day study.

Blau JE et al. Nature Review Nephrology 2018, in press.

Effects of SGLT2 inhibitors on safety otucomes

A systematic review and meta-analyses including data from 6 regulatory submissions (37,525 participants) and 57 published trials (33,385 participants), which provided data for 7 different SGLT2 inhibitors.

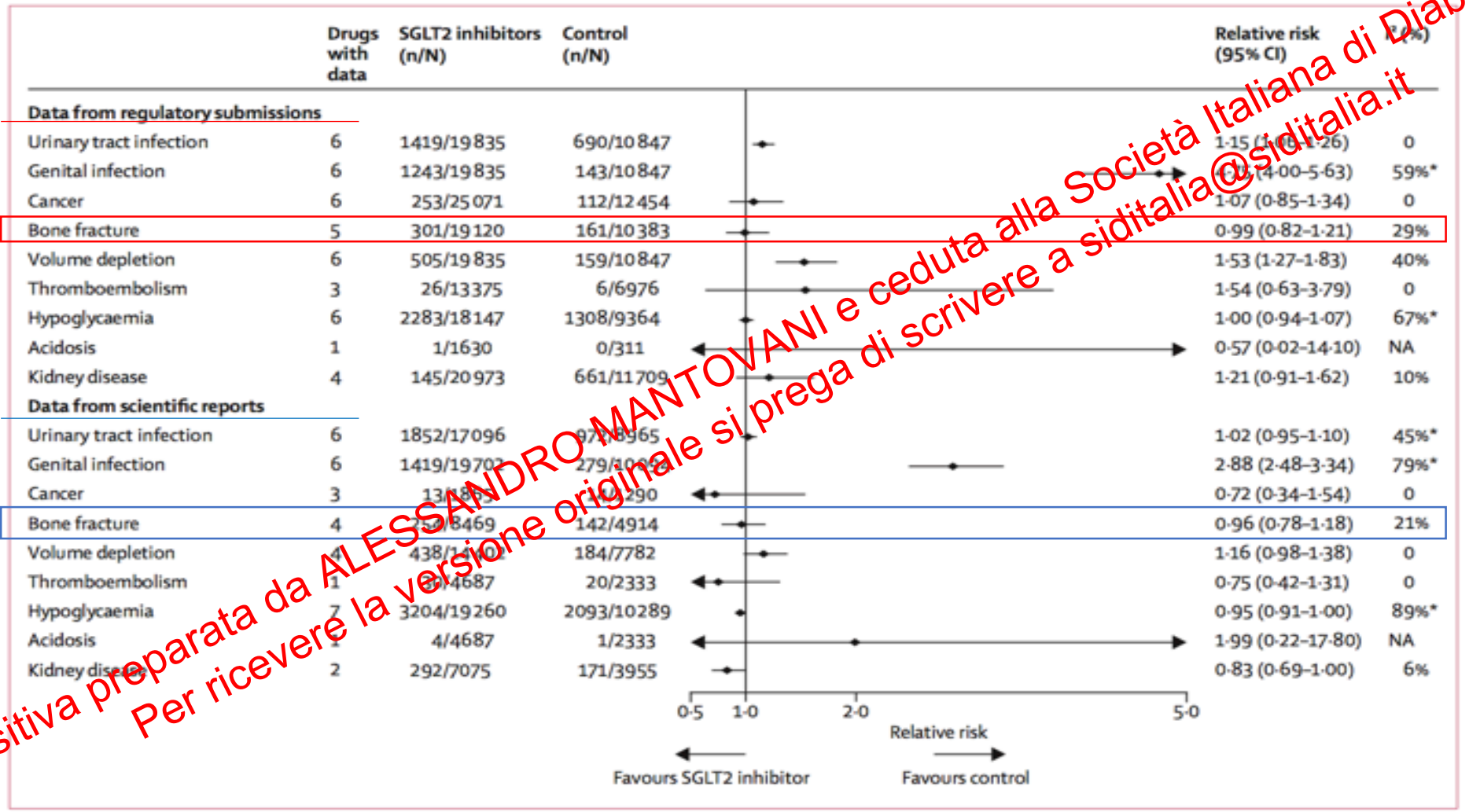


***Figure 3*: Effects of SGLT2 inhibitors on safety outcomes, overall and for each drug, based on data from regulatory submissions and scientific reports**
Summary effects for all drugs obtained from fixed-effects meta-analysis. NA=not applicable. SGLT2=sodium-glucose cotransporter-2. *p heterogeneity <0·05.

Wu JH et al. Lancet Diabetes Endocrinol 2016;4:411-9.

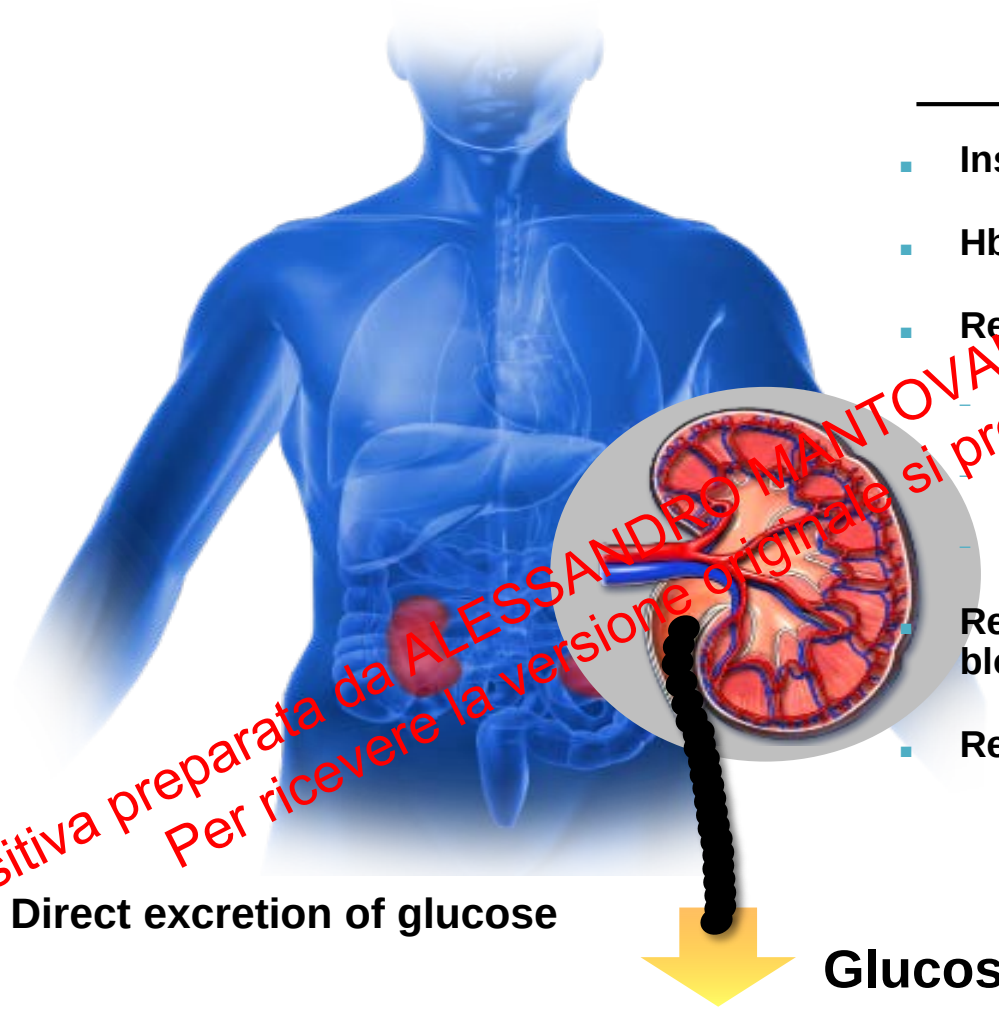
KEY MESSAGE

- **Canagliflozin may also increase the risk of bone fractures. In the CANVAS Program the rate of all fractures was higher with canagliflozin vs placebo (15.4 vs 11.9 participants with fracture per 1000 person-years; HR 1.26 [95% CI 1.04, 1.52]).**

- **In the EMPA-REG OUTCOME study, the proportion of participants who developed fractures was low in both the pooled empagliflozin group and the placebo group (3.8% and 3.9%, respectively).**

- **A meta-analysis of trials evaluating combined safety outcomes of canagliflozin, dapagliflozin and empagliflozin did not support a harmful effect of SGLT2 inhibitors on bone.**

Potential Effects of SGLT2 Inhibition



Direct excretion of glucose

Glucosuria

Potential benefits

- Insulin-independent
- HbA1c lowering
- Reduction in:
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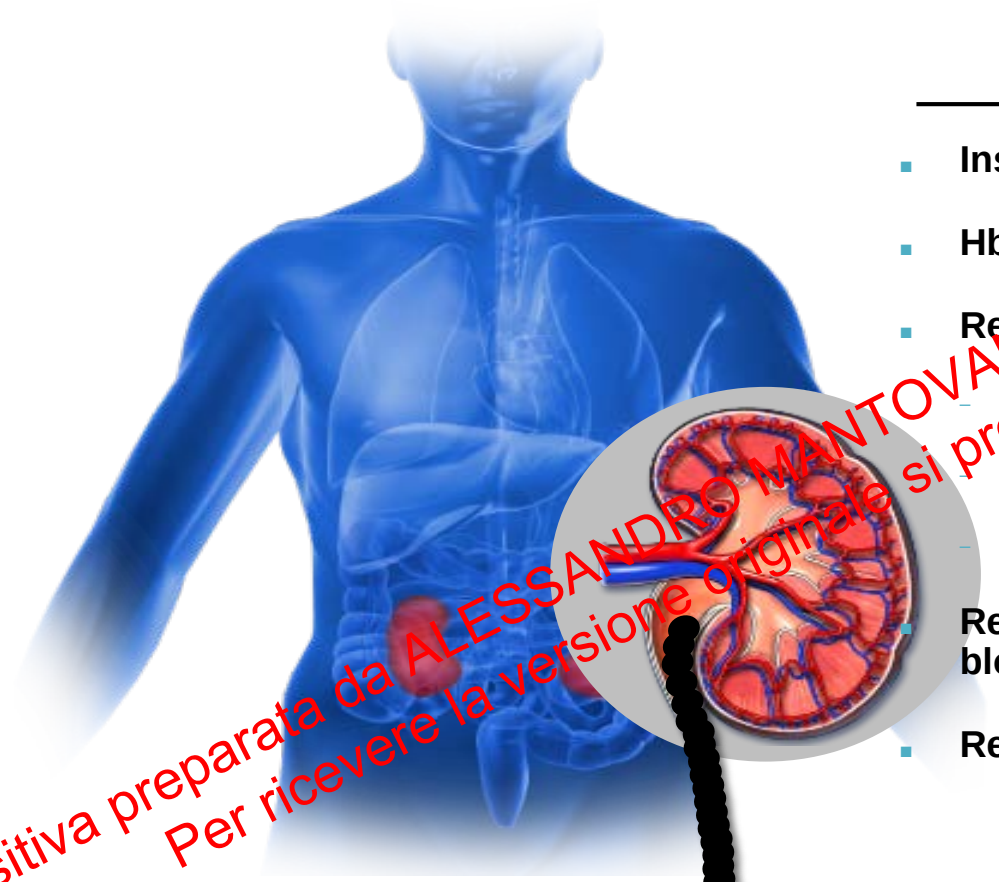
  - Weight
- Reduction in blood pressure
- Reduction in uric acid

Potential risks

- Hypoglycaemia
- Renal function
- Diuretic effect
  - Hypovoalaemia
  - Hypotension
  - Dehydration
  - Alterations of electrolytes
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events

Potential Effects of SGLT2 Inhibition



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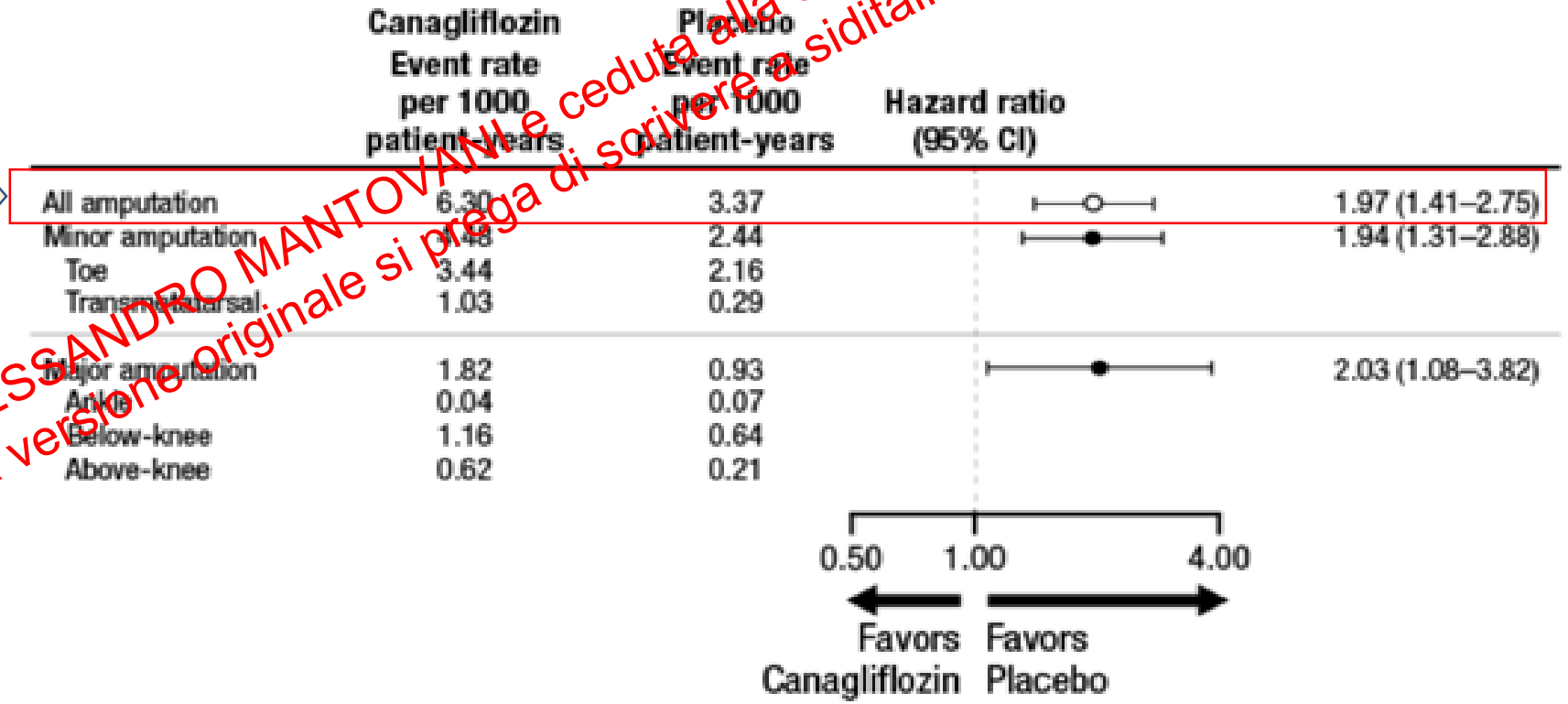
CANVAS Program – Lower limb amputations

10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

- **71% of the affected participants having their highest amputation at the level of the toe or metatarsal.**
- **The increased risk of amputation began to emerge after 6 to 12 months of exposure.**

Figure S5. Highest-level atraumatic lower-limb amputations experienced by participants in the CANVAS Program



Neal B et al. N Engl J Med 2017;377:644-657.

CANVAS Program – Lower limb amputations

10,142 participants with type 2 diabetes randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188 weeks.

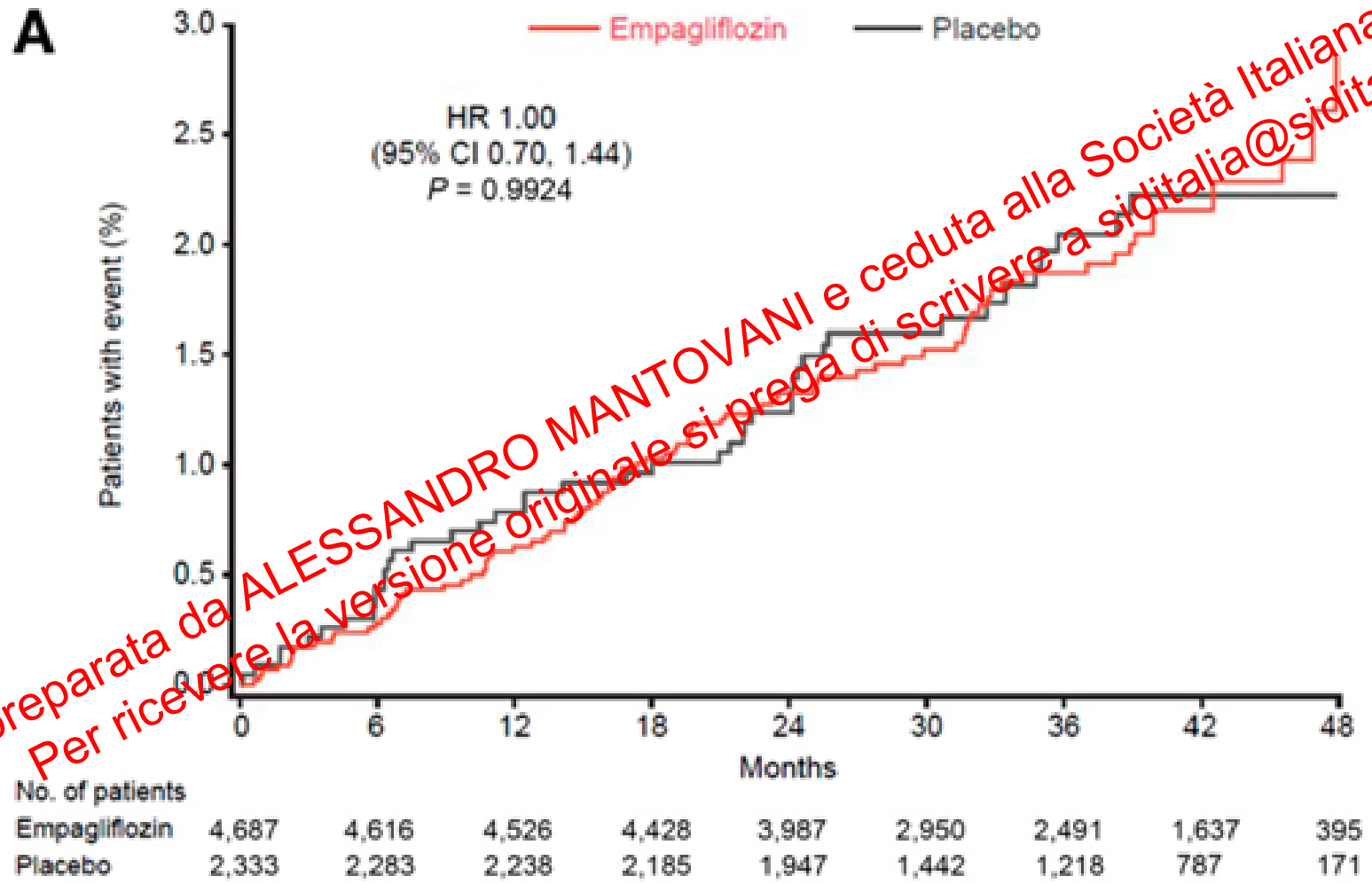
Table S8. Effects of canagliflozin versus placebo on atraumatic lower limb amputation in key subgroups in the CANVAS Program

	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 B et al. N Engl J Med 2017;377:644-657.

EMPA-REG OUTCOME – Lower limb amputation

7,020 T2DM patients randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time 3.1 years).



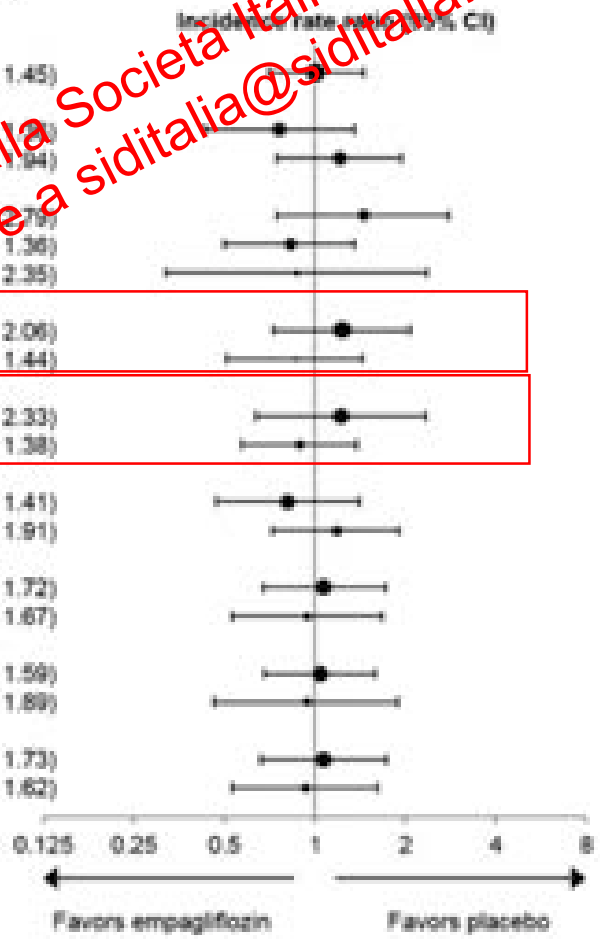
Inzucchi SE et al. Diabetes Care 2018;41: e4-e5

EMPA-REG OUTCOME – Lower limb amputation

7,020 T2DM patients randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily (median observation time 3.1 years).

B

	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*	
All patients	88/4,687 (1.9)	6.5	43/2,333 (1.8)	6.5	1.01 (0.70, 1.45)
HbA_{1c}					
<8.0%	30/2,339 (1.3)	4.5	19/1,156 (1.6)	5.8	0.76 (0.43, 1.34)
≥8.0%	58/2,346 (2.5)	8.6	24/1,177 (2.0)	7.1	1.21 (0.73, 1.94)
Smoking status					
Never smoked	35/1,925 (1.8)	6.3	12/957 (1.3)	4.4	1.45 (0.75, 2.79)
Ex-smoker	42/2,135 (2.0)	6.8	25/1,074 (2.3)	8.2	0.83 (0.50, 1.36)
Smoker	11/627 (1.8)	6.3	6/302 (2.0)	7.3	0.86 (0.32, 2.35)
History of diabetic foot					
No	50/4,424 (1.1)	3.9	20/2,188 (0.9)	3.2	1.23 (0.73, 2.06)
Yes	38/263 (14.4)	57.1	23/145 (15.9)	66.6	0.86 (0.51, 1.44)
History of peripheral artery occlusive disease					
No	32/3,669 (0.9)	3.0	13/1,841 (0.7)	2.4	1.22 (0.64, 2.33)
Yes	56/1,018 (5.5)	22.5	30/492 (6.1)	22.9	0.89 (0.57, 1.38)
History of diabetic neuropathy					
No	33/3,217 (1.0)	3.5	20/1,606 (1.2)	4.3	0.81 (0.47, 1.41)
Yes	55/1,470 (3.7)	15.6	23/727 (3.2)	11.8	1.18 (0.72, 1.91)
History of diabetic retinopathy					
No	51/3,664 (1.4)	5.2	25/1,810 (1.4)	4.8	1.07 (0.67, 1.72)
Yes	33/1,023 (3.2)	11.7	18/523 (3.4)	12.4	0.94 (0.53, 1.67)
History of diabetic nephropathy					
No	66/3,783 (1.7)	6.0	31/1,866 (1.7)	5.8	1.04 (0.68, 1.59)
Yes	22/904 (2.4)	8.7	12/467 (2.6)	9.3	0.94 (0.46, 1.89)
eGFR (ml/min/1.73 m²)					
≥60	52/3,473 (1.5)	5.2	24/1,726 (1.4)	4.9	1.07 (0.66, 1.73)
<60	36/1,212 (3.0)	10.4	19/607 (3.1)	11.2	0.93 (0.53, 1.62)



Inzucchi SE et al. Diabetes Care 2018;41: e4-e5

SGLT2 inhibitors and amputations in different studies

Table 1 | **Risk of lower limb amputation with SGLT2 inhibitors in different studies**

SGLT2 inhibitor	Study	Comparator	Events	Results (95% CI)	Refs
RCTs					
Meta-analysis (all three inhibitors)	14 RCTs	Placebo or active AHA	221 (1.8%) versus 96 (1.3%)	OR 1.40 (0.81–2.41)[a]	1
Canagliflozin 100–300 mg	CANVAS	Placebo	6.3 versus 3.4 per 1,000 pt-yrs	HR 1.97 (1.41–2.75)	2
Canagliflozin 100–300 mg	Phase III–IV RCTs	Placebo or active AHA	0.5 versus 2.2 per 1,000 pt-yrs	RR 0.23 (0.06–0.89)	9
Empagliflozin 10–25 mg	EMPA-REG OUTCOME	Placebo	88 (1.9%) versus 49 (1.8%)	IRR 1.05 (0.70–1.44)	4
Empagliflozin 10–25 mg	14 RCTs	Placebo or active AHA	46 (1.1%) versus 94 (1.1%)	IRR 1.00 (NA)	6
Dapagliflozin 10 mg	30 RCTs	Placebo or active AHA	8 (0.1%) versus 7 (0.1%)	IRR 1.04 (NA)	7
Observational studies					
Canagliflozin	US retrospective cohort study	Active AHA	99 versus 87 (1.18 versus 1.12 per 1,000 pt-yrs)	HR 0.98 (0.68–1.41)	9
Canagliflozin (58.1%), empagliflozin (26.4%) and dapagliflozin (15.5%)	US Department of Defense Military Health System	Active AHA	1.7 versus 0.9 per 1,000 pt-yrs	HR 1.99 (1.12–3.51)	8
Pharmacovigilance reports					
All three inhibitors[b]	FAERS	Active AHA	55	PRR 3.56 (2.73–4.65)[c], $P<0.0001$	10
All three inhibitors[d]	FAERS	Active AHA	32	PRR 1.01 (0.71–1.43)[e], $P=0.972$	10
All three inhibitors	WHO VigiBase	Active AHA	92	PRR 5.95 (4.61–7.67)[f]	3

AHA, anti-hyperglycaemic agent; HR, hazard ratio; IRR, incidence rate ratio; NA, not available; OR, odds ratio; PRR, proportional reporting ratio; pt-yrs, patient-years; RCTs, randomized controlled trials; RR, relative risk; SGLT2, sodium–glucose cotransporter 2. [a]Canagliflozin (132 events), OR 1.89 (95% CI 1.37–2.60) and empagliflozin (89 events), OR 1.02 (95% CI 0.71–1.48). [b]No indication filter. [c]Canagliflozin (50 events), PRR 5.33 (95% CI 4.04–7.04), $P<0.0001$; empagliflozin (5 events), PRR 2.37 (95% CI 0.99–5.70), $P=0.054$; dapagliflozin (1 event), PRR 0.25 (95% CI 0.03–1.76), $P=0.163$. [d]Only diabetes indication. [e]Canagliflozin (31 events), PRR 1.59 (95% CI 1.12–2.30), $P=0.009$; empagliflozin (2 events), PRR 0.47 (95% CI 0.11–1.86), $P=0.277$; 0 events with dapagliflozin. [f]Canagliflozin (67 events), PRR 7.09 (95% CI 5.25–9.57); empagliflozin (14 events), PRR 4.96 (95% CI 2.89–8.50); dapagliflozin (11 events), PRR 1.79 (95% CI 0.98–3.26).

EASEL cohort

No indication filter

Only diabetes indication

Scheen AJ. Nat Rev Endocrinol 2018;14:326-328.

OBSERVE 4D: A real-world meta-analysis of 4 observational databases

Data from 4 large US administrative databases enrolling 142,800 new users of canagliflozin, 110,897 new users of other SGLT2i, and 460,885 new users of non-SGLT2i. Follow-up: 6 months.

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)	.92	.85
	MDCD	5998/1775	38 172/16 482	10	61	1.35 (0.46-3.41)	.56	.46	21	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	128	0.88 (0.51-1.47)	.65	.77
	Optum	36 055/16 676	146 868/84 306	17	173	0.67 (0.35-1.18)	.19	.31	95	467	1.03 (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	.78	171	382	0.96 (0.77-1.21)	.75	.78
	MDCD	6727/1993	21 355/7401	10	15	3.11 (0.87-10.70)	.07	.08	34	109	1.21 (0.73-1.97)	.45	.43
	MDCR	10 217/5222	35 398/20 471	11	37	0.60 (0.29-1.64)	.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 (0.64-2.65)	.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 (0.75-2.47) 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	3	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	13	1.40 (0.49-4.28)	.54	.54	46	52	1.06 (0.67-1.68)	.82	.85
	Meta-analysis	69 554/31 369	98 169/41 658	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	54 824/24 642	179 500/96 683	23	143	0.59 (0.32-1.04)	.08	.14	87	327	0.78 (0.57-1.04)	.09	.15
	MDCD	1978/405	25 995/10 106	0	28	0.36 (NA-5.96)	—	—	5	111	0.99 (0.33-2.39)	.98	.96
	MDCR	4336/1937	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	19 588/7076	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.

[a] Time-to-first-post-index-event analysis using variable-ratio propensity score matching.

Rayan PB et al. Diabetes Obes Metab. 2018 Jun 25. doi: 10.1111/dom.13424. [Epub ahead of print]

- In the CANVAS Program, the increased risk of amputation began to emerge after 6 to 12 months of exposure and the incidence rates for amputation were 6.3 and 3.4 participants per 1000 patient-years with canagliflozin and placebo, respectively, over a median follow-up period of 126 weeks, and the HR (95% CI) was 1.97 (1.41-2.75).

- Compared with the CANVAS Program, OBSERVE 4D had a lower event rate (1-5 events per 1000 person-years, on-treatment and in the overall population) and a shorter follow-up time (median, 60-100 days on-treatment).

- Thus, OBSERVE 4D had limited statistical power to detect differences in the 6 to 12-month period, the time at which amputation risk began to emerge in the CANVAS Program, particularly in patients with established cardiovascular disease.

- It is also possible that differences in the risk of BKLE amputation could be attributable to the composition of the patient population, as patients who opt to participate in clinical trials may not always reflect the general population.

- **In the CANVAS Program, the increased risk of amputation began to emerge after 6 to 12 months of exposure and the incidence rates for amputation were 6.3 and 3.4 participants per 1000 patient-years with canagliflozin and placebo, respectively, over a median follow-up period of 126 weeks, and the HR (95% CI) was 1.97 (1.41-2.75)**
- **The comparative safety results for amputation are not so concordant and warrant further scrutiny.**
- **It is also possible that differences in the risk of BKLE amputation could be attributable to the composition of the patient population, as patients who opt to participate in clinical trials may not always reflect the general population.**

KEY MESSAGE

- **A more detailed approach that considers individual clinical profiles and risk factors potentially involved in this severe complication would help to further unravel the cause for the suspected increased risk of lower limb amputation with SGLT2 inhibitors and identify good candidates for such a pharmacological approach.**

- **The possible adverse event of lower limb amputation should not offset the cardiovascular and renal protection offered by SGLT2 inhibitors in patients with T2DM at high cardiovascular risk.**

KEY MESSAGE

- With the exception of CANVAS with canagliflozin and a meta-analysis of 14 RCTs
- [illegible]
- [illegible]
- T2DM at high cardiovascular risk.

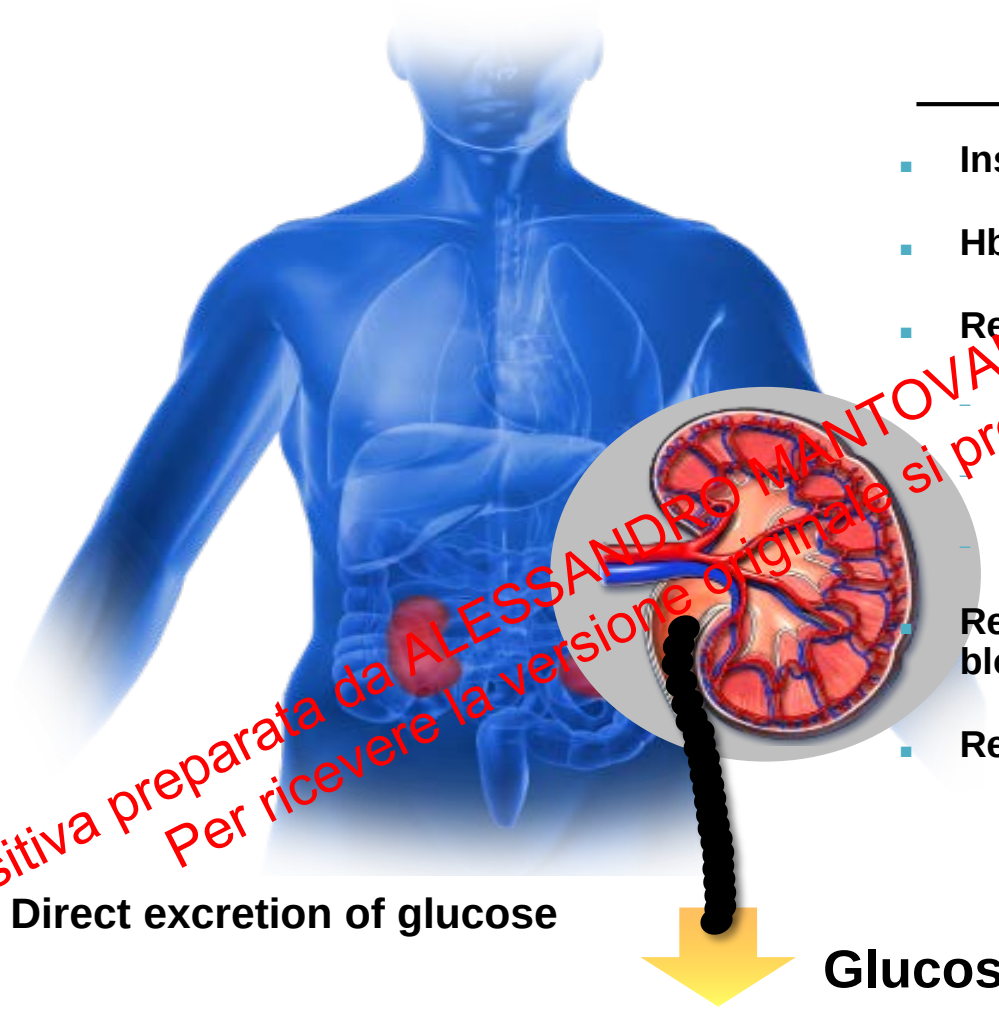
For instance, in CANVAS, the number needed to harm for peripheral amputation is ~330 per year, compared with a number needed to treat to avoid a major cardiovascular event (including death) of ~200 per year. The ultimate goal is to exploit the cardiovascular and renal benefit of SGLT2 inhibitors, while avoiding adverse effects (Nat Rev Endocrinol 2018;14:326-328).

KEY MESSAGE

- With the exception of CANVAS with canagliflozin and a meta-analysis of 4 RCTs

Even though amputations were not seen in the EMPA-REG OUTCOME trial, it is not unreasonable to avoid the entire class in those at the highest amputation risk until more safety data are accumulated.

Potential Effects of SGLT2 Inhibition



Direct excretion of glucose

Glucosuria

Potential benefits

- Insulin-independent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure
- Reduction in uric acid

Potential risks

- Hypoglycaemia
- Renal function
- Diuretic effect
  - Hypovoalaemia
  - Hypotension
  - Dehydration
  - Alterations of electrolytes
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events

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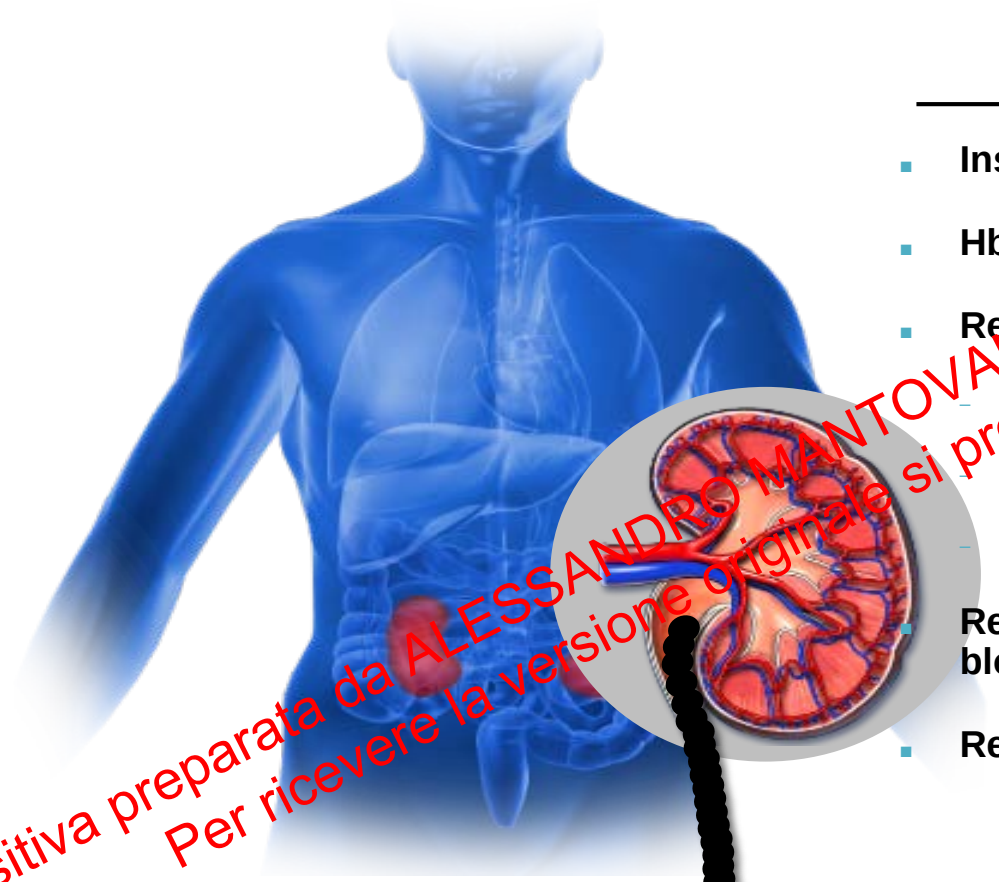

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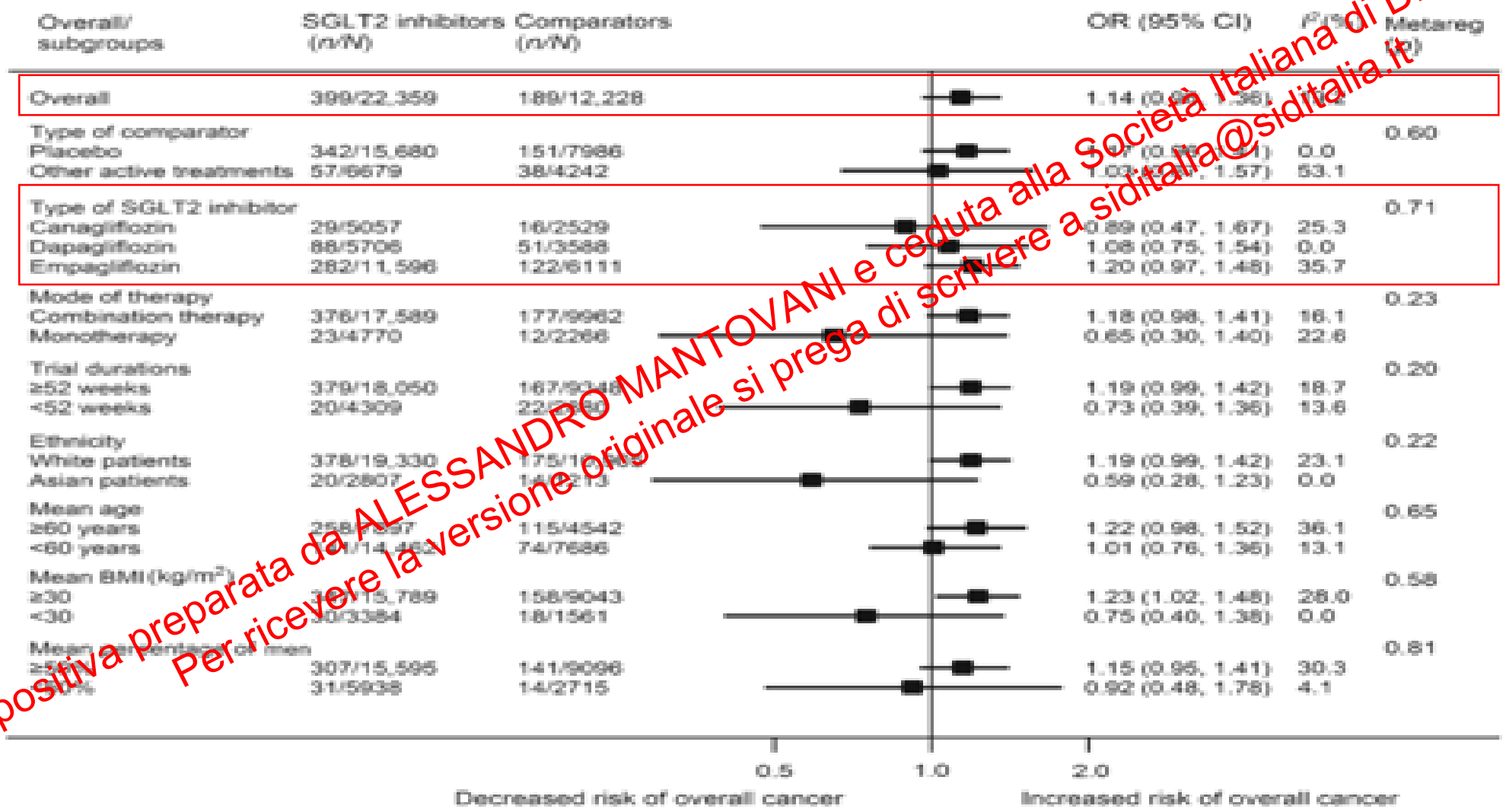
CANCER

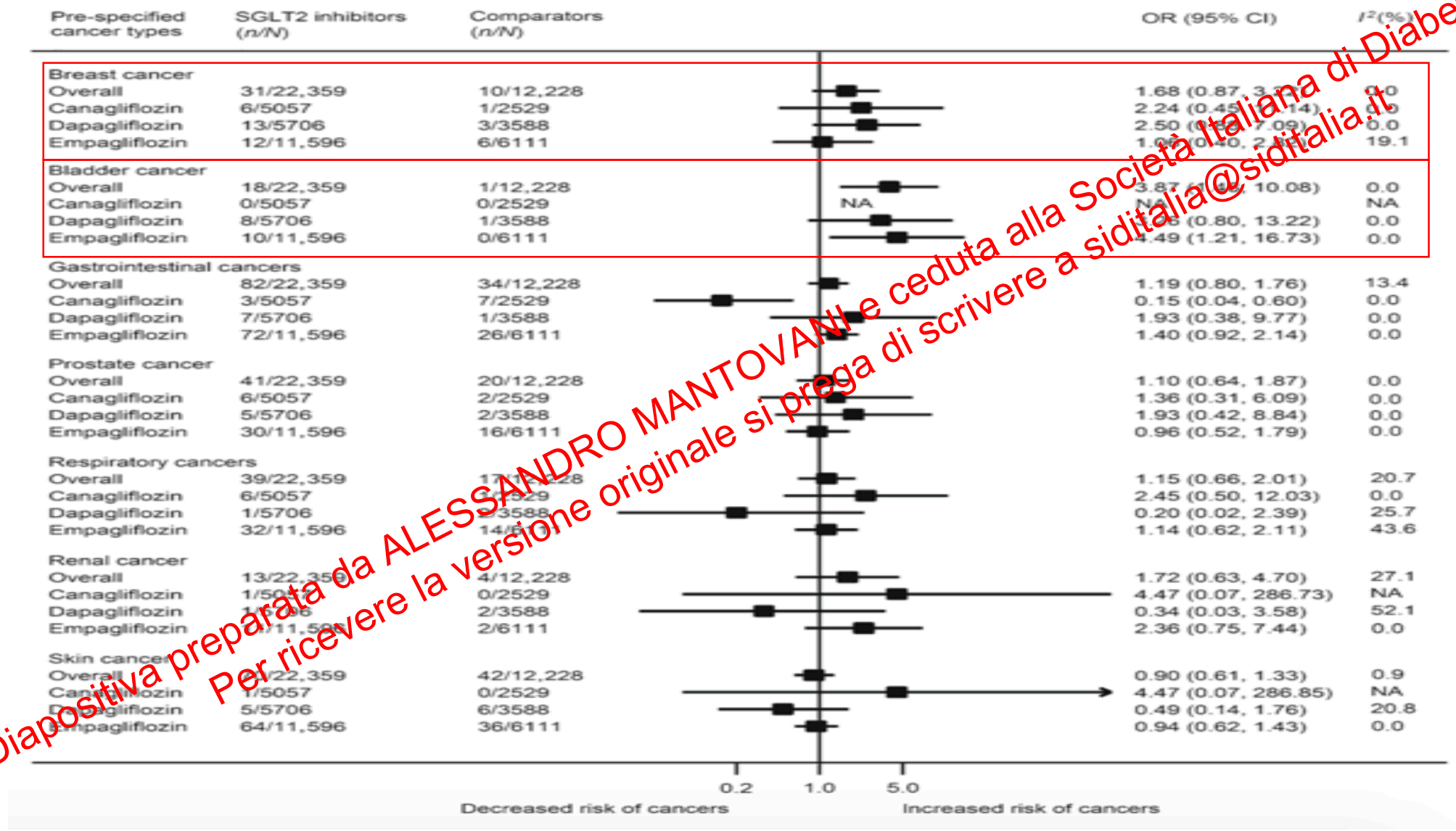
Meta-analysis of the effects of SGLT2 inhibitors on the risk of overall cancer

580 incidences of cancer among 34,569 individuals were identified from 46 independent RCTs with a mean trial duration of 61 weeks



Tang H *et al.* Diabetologia 2017; 60: 1862–1872

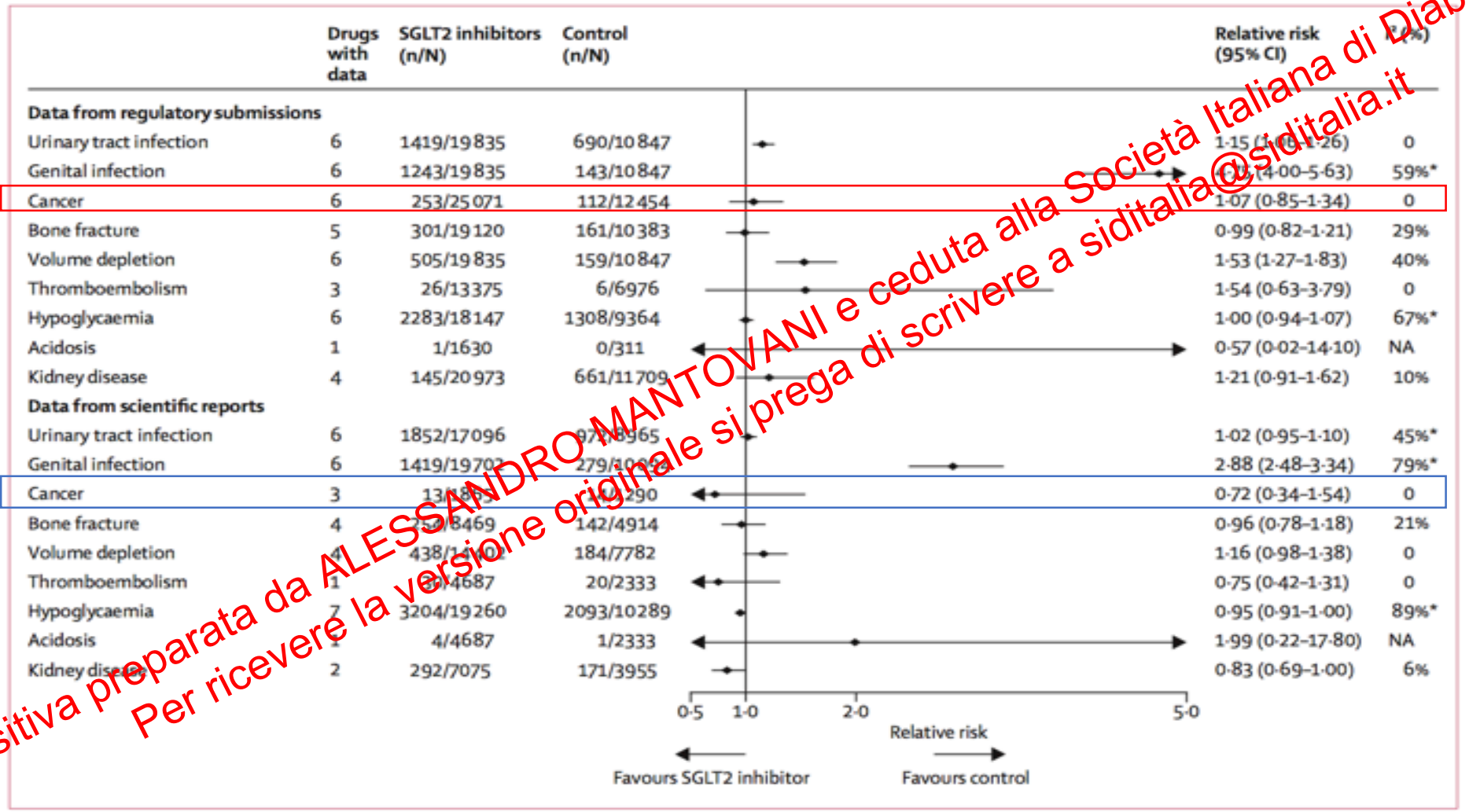
Meta-analysis of the effects of SGLT2 inhibitors on the risk of pre-specified cancer types



Tang H *et al.* Diabetologia 2017; 60: 1862–1872

Effects of SGLT2 inhibitors on safety otucomes

A systematic review and meta-analyses including data from 6 regulatory submissions (37,525 participants) and 57 published trials (33,385 participants), which provided data for 7 different SGLT2 inhibitors.



	Drugs with data	SGLT2 inhibitors (n/N)	Control (n/N)	Relative risk (95% CI)	P (%)
Data from regulatory submissions					
Urinary tract infection	6	1419/19835	690/10847	1·15 (1·01–1·26)	0
Genital infection	6	1243/19835	143/10847	4·02 (4·00–5·63)	59%*
Cancer	6	253/25071	112/12454	1·07 (0·85–1·34)	0
Bone fracture	5	301/19120	161/10383	0·99 (0·82–1·21)	29%
Volume depletion	6	505/19835	159/10847	1·53 (1·27–1·83)	40%
Thromboembolism	3	26/13375	6/6976	1·54 (0·63–3·79)	0
Hypoglycaemia	6	2283/18147	1308/9364	1·00 (0·94–1·07)	67%*
Acidosis	1	1/1630	0/311	0·57 (0·02–14·10)	NA
Kidney disease	4	145/20973	661/11709	1·21 (0·91–1·62)	10%
Data from scientific reports					
Urinary tract infection	6	1852/17096	977/8965	1·02 (0·95–1·10)	45%*
Genital infection	6	1419/19702	279/10092	2·88 (2·48–3·34)	79%*
Cancer	3	134/8795	140/8290	0·72 (0·34–1·54)	0
Bone fracture	4	252/8469	142/4914	0·96 (0·78–1·18)	21%
Volume depletion	4	438/14402	184/7782	1·16 (0·98–1·38)	0
Thromboembolism	1	34/4687	20/2333	0·75 (0·42–1·31)	0
Hypoglycaemia	7	3204/19260	2093/10289	0·95 (0·91–1·00)	89%*
Acidosis	1	4/4687	1/2333	1·99 (0·22–17·80)	NA
Kidney disease	2	292/7075	171/3955	0·83 (0·69–1·00)	6%

***Figure 3*: Effects of SGLT2 inhibitors on safety outcomes, overall and for each drug, based on data from regulatory submissions and scientific reports**
Summary effects for all drugs obtained from fixed-effects meta-analysis. NA=not applicable. SGLT2=sodium-glucose cotransporter-2. *p heterogeneity <0·05.

Wu JH et al. Lancet Diabetes Endocrinol 2016;4:411-9.

KEY MESSAGE

- **Overall, the available data do not point to a causative role of SGLT2 inhibitors on malignancy risk, although more studies with longer duration are needed in order to determine the effect of SGLT2 inhibitors on cancer risk.**

- **However, these drugs should be used with caution (or better avoided) in patients with known hematuria or history of bladder cancer.**

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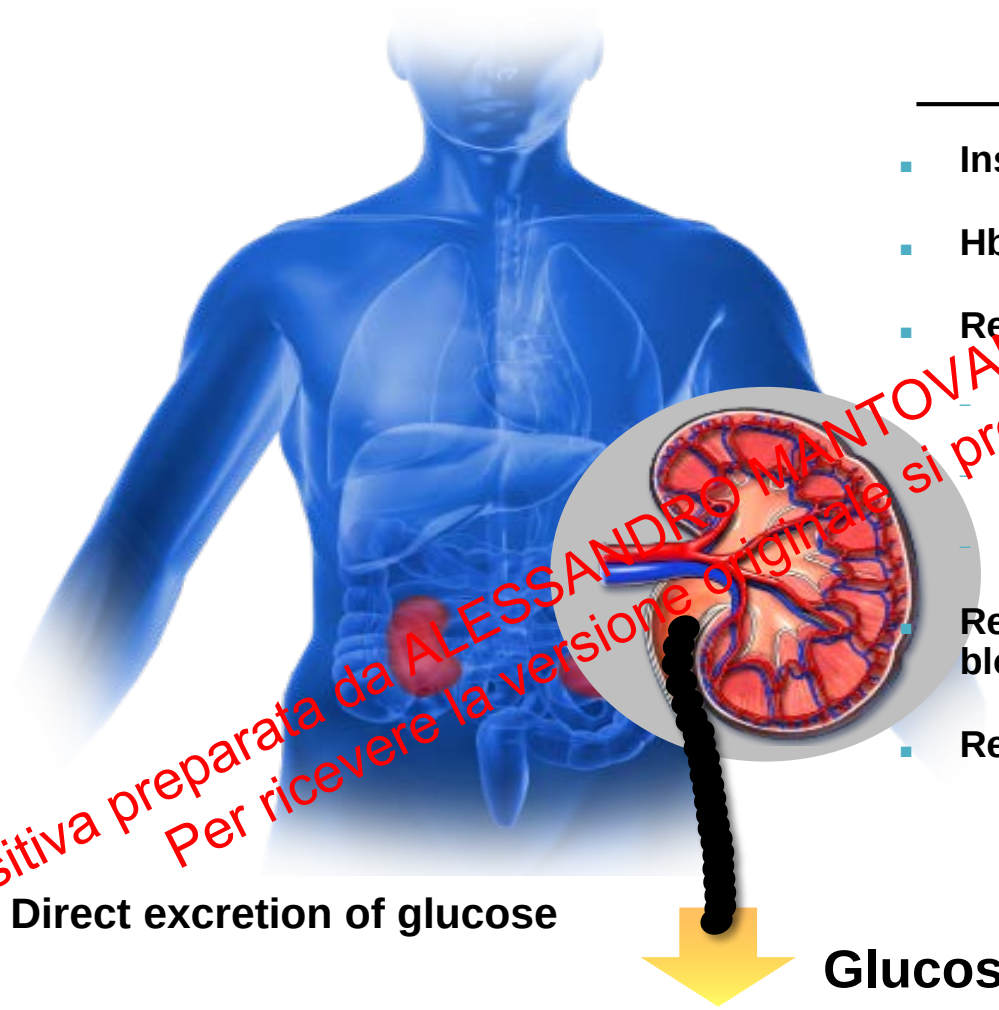

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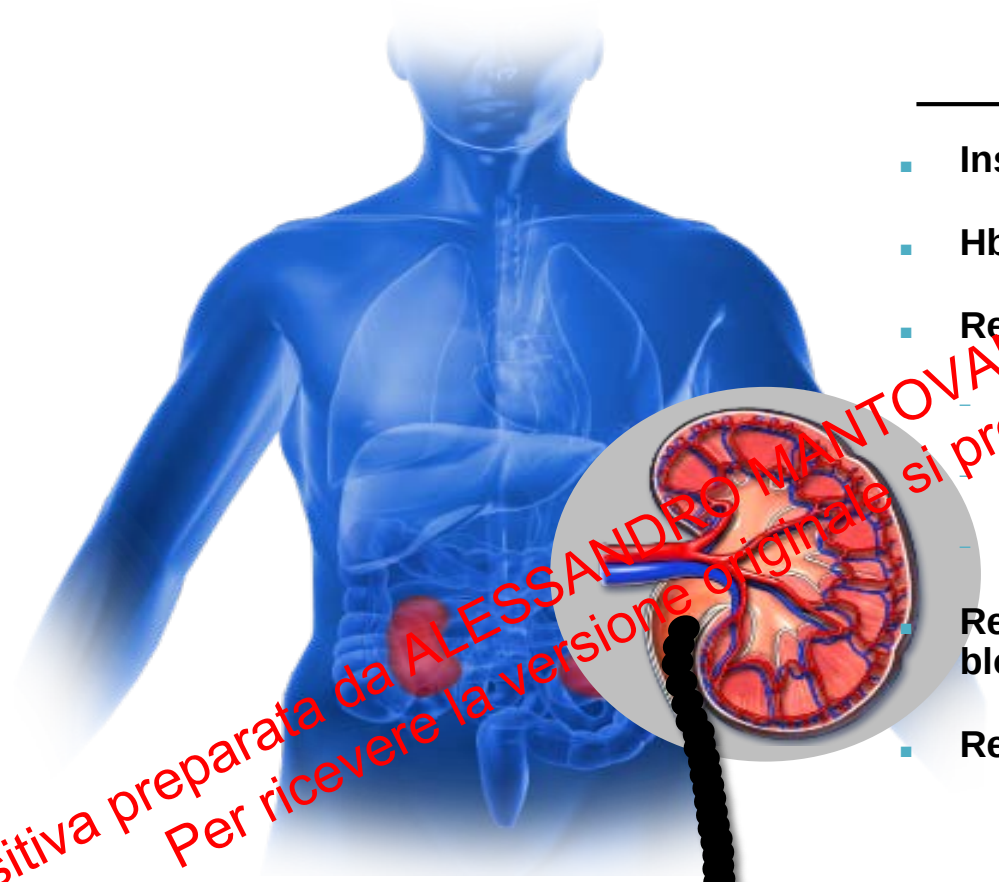

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Domanda n.6

Il trattamento con SGLT2 inhibitors può causare talvolta reazioni cutanee inaspettate?

a) Vero

b) Falso

Domanda n.6

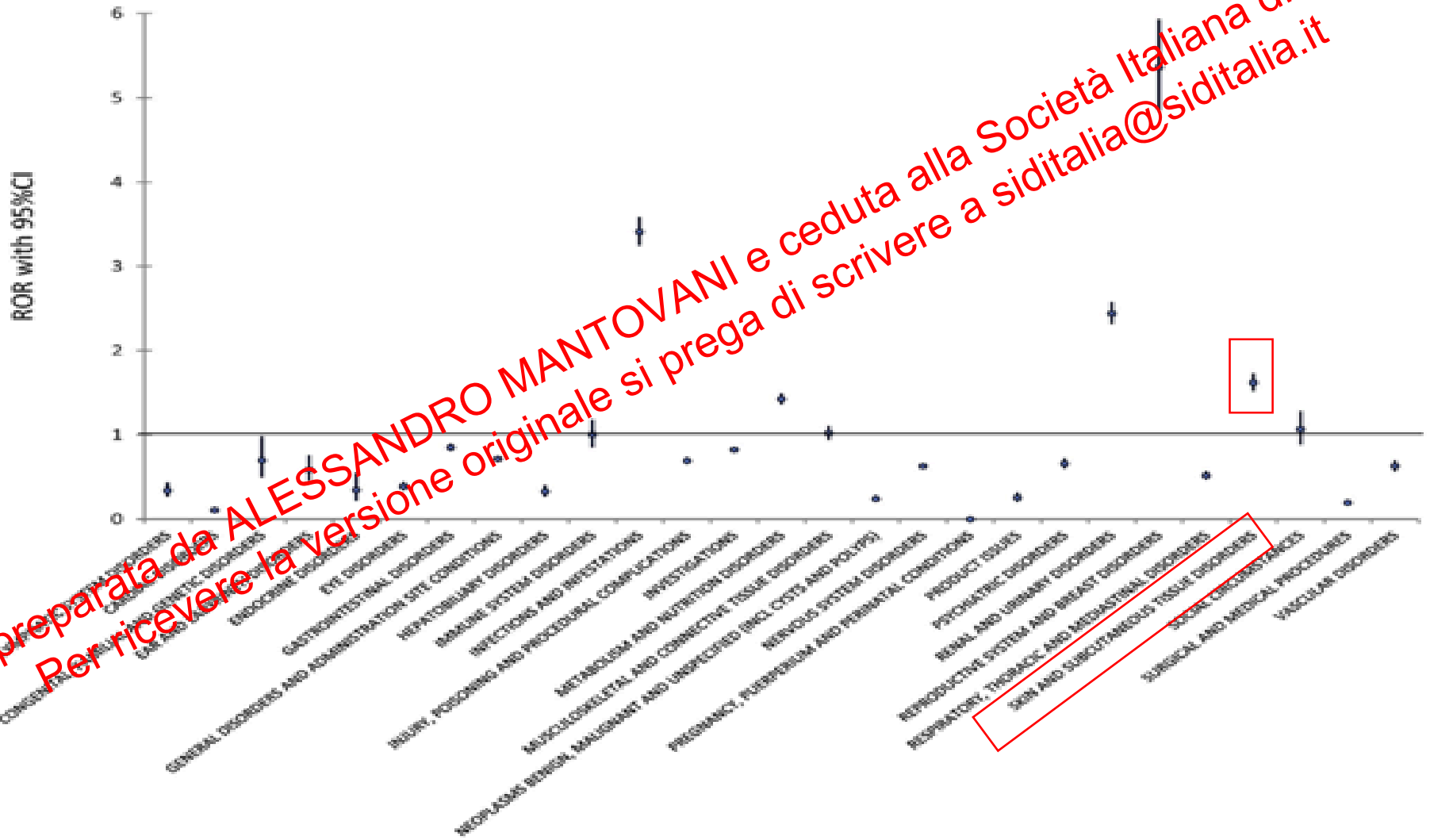
Il trattamento con SGLT2 inhibitors può causare talvolta reazioni cutanee inaspettate?

a) Vero

b) Falso

A global analysis of international spontaneous reporting systems

Eudravigilance, WHO-Vigibase (as of Feb 25, 2017) and the FDA Adverse Event Reporting System (FAERS, from 2004 to 2016 second quarter) were queried to extract AEs recording SGLT2-Is as suspect.



Raschi E et al. Nutrition, Metabolism & Cardiovascular Diseases 2017; 27:1098-1107

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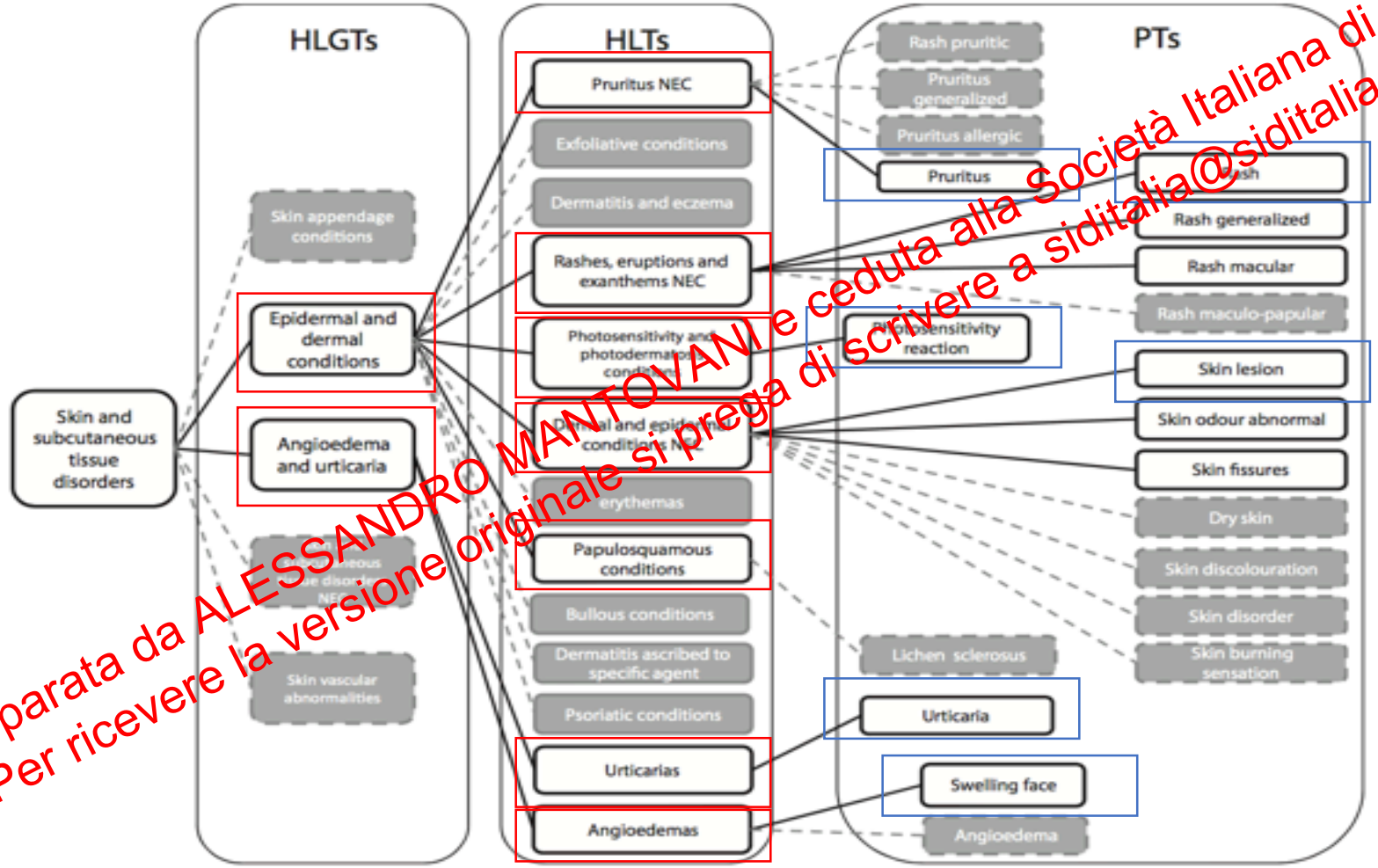

Figure 2 Disproportionality across MedDRA hierarchy for "Skin and subcutaneous tissue disorders", considering the entire class of SGLT2-Is in FAERS. See methods for details. Dotted lines indicate non-statistically significant disproportionality. HLGTs: high-level group terms; HLTs: high-level terms; PT: preferred terms.

Raschi E et al. Nutrition, Metabolism & Cardiovascular Diseases 2017; 27:1098-1107

KEY MESSAGE

- **SGLT2 inhibitor administration has been occasionally associated with skin reactions.**

- **Skin and subcutaneous disorders mostly appear within 2 weeks of SGLT2 inhibitor administration and include serious generalized rash, drug eruption, urticaria, erythema, and eczema.**

- **The incidence of skin reactions is higher when ipragliflozin was administered possibly because ipragliflozin and its metabolites are more readily found in the skin as animal studies have suggested.**

CONCLUSIONS

- **SGLT2 inhibitors should be considered reasonable second-line treatment options for individuals at risk of cardiovascular events or those with underlying nephropathy, if good glycaemic control has not been achieved with metformin monotherapy.**

- **Possible side effects include urinary frequency and orthostasis. Additional potential adverse effects include genitourinary tract infections, euglycaemic DKA, AKI, lower-extremity amputations and fractures—the latter two to date being associated solely with canagliflozin.**

- **Individuals at risk for such complications should be monitored closely and treatment should be discontinued or at least reconsidered if they occur.**