Corretta gestione del paziente con diabete tipo 2 ad alto rischio cardiovascolare

MILANO
9 OTTOBRE 2019

SGLT2 inibitori
effetti collaterali e terapie concomitanti: come comportarsi?

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Il Prof. Gian Paolo Fadini dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- AstraZeneca
- Boehringer
- Lilly
- MSD
- Mundipharma
- Novartis
- Novonordisk
- Sanofi

Safety

Efficacy

Common AEs during SGLT2i therapy

Genital tract infections (GTI)

Real World

410 patients	2,2% GTI	Hong et al. Diabetes Metab J 2019
189 patients	2,6% GTI	Thewjitcharoen et al. Diabetol Metab Syndr. 2017
70 patients	2,8% GTI	Sosale et al. Diabetes Ther 2016
527 patients	9,5% GTI	Woo et al. DOM 2018
100 patients	4,0% GTI	Sosale et al. J Assoc Physicians India. 2016
8505 patients	2,2% infections	Yokote et al. Expert Opin Pharmacother. 2016

RCTs meta-analysis

22753 patients	5,8% GTI	Zaccardi et al. DOM 2016

Hypoglycemia

Real World

410 patients	6,3% Hypo	Hong et al. Diabetes Metab J 2019
189 patients	7,9% Hypo	Thewjitcharoen et al. Diabetol Metab Syndr. 2017
527 patients	0,9% severe Hypo	Woo et al. DOM 2018
8505 patients	0,7% Hypo	Yokote et al. Expert Opin Pharmacother. 2016

RCTs meta-analysis

22753 patients	19% any Hypo	Zaccardi et al. DOM 2016

Endocrine (2018) 59:690–693
DOI 10.1007/s12020-017-1301-x

RESEARCH LETTER

Lower urinary tract symptoms (LUTS) in males with type 2 diabetes recently treated with SGLT2 inhibitors—overlooked and overwhelming? A retrospective case series

Nino Cristiano Chilelli[1] · Giuseppe Bax[1] · Giulio Bonaldo[2] · Eugenio Ragazzi[3] · Massimo Iafrate[2] · Filiberto Zattoni[2] · Federico Bellavere[4] · Annunziata Lapolla[1]

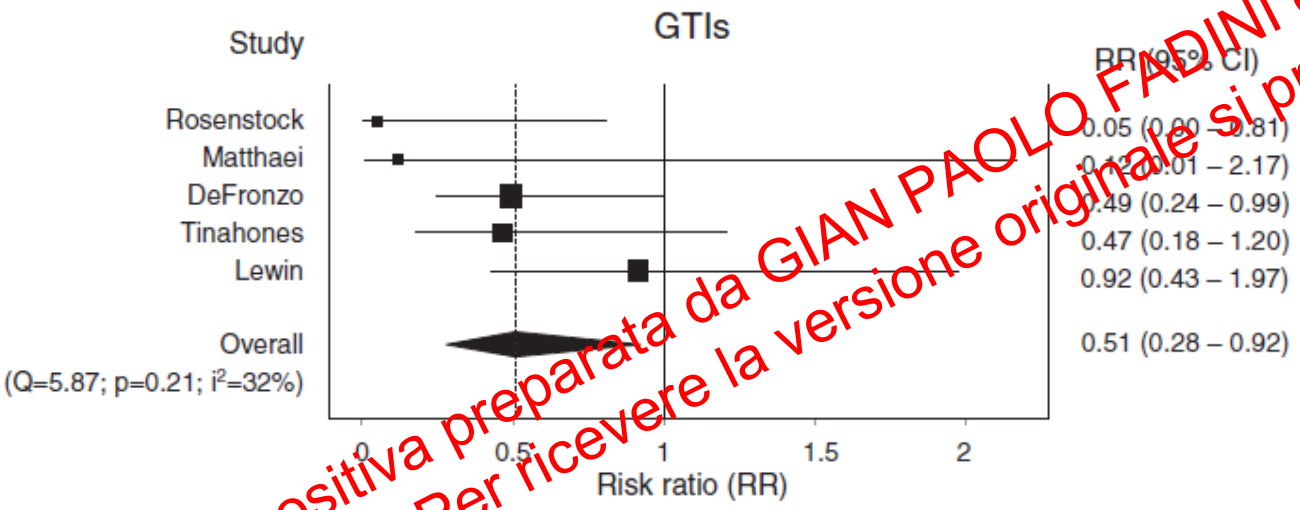
	Patients with autonomic neuropathy ($n = 16$)	Patients without autonomic neuropathy ($n = 34$)
LUTS (new-onset cases in brackets)		
IPSS	7.3 ± 4.7	10.3 ± 4.5*
Incomplete voiding (%)	37.5 (6.3)	41.2 (0)
Increased frequency of urination/ pollakiuria (%)	56.3 (43.8)	85.3% (73.6)*
Hesitancy (%)	12.5 (0)	17.6 (0)
Increased urgency of urination (%)	43.8 (0)	58.8 (5.9)
Poor stream (%)	25.0 (0)	26.5 (0)
Painful urination (%)	0 (0)	5.9 (0)
Nocturia (%)	68.8 (25.0)	85.3 (50.0)

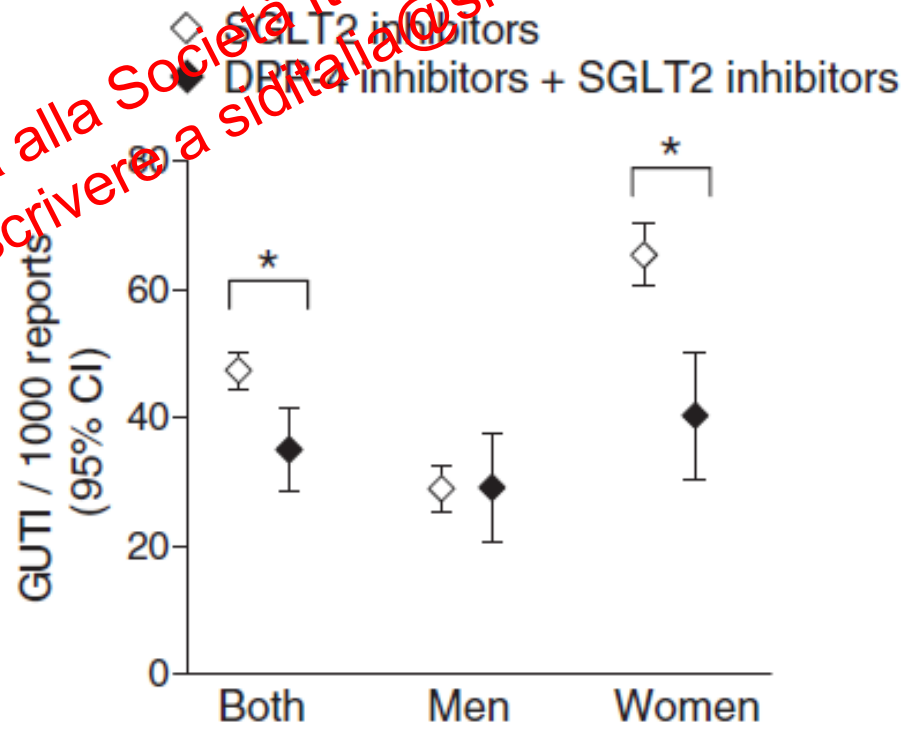
DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

WILEY

Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors

Gian Paolo Fadini MD[1] | Benedetta Maria Bonora MD[1] | Sarangdhar Mayur PhD[2] | Mauro Rigato MD[1] | Angelo Avogaro MD[1]





Dehydration / hypovolemia

4.5 Interazioni con altri medicinali ed altre forme d'interazione

Interazioni farmacodinamiche

Diuretici

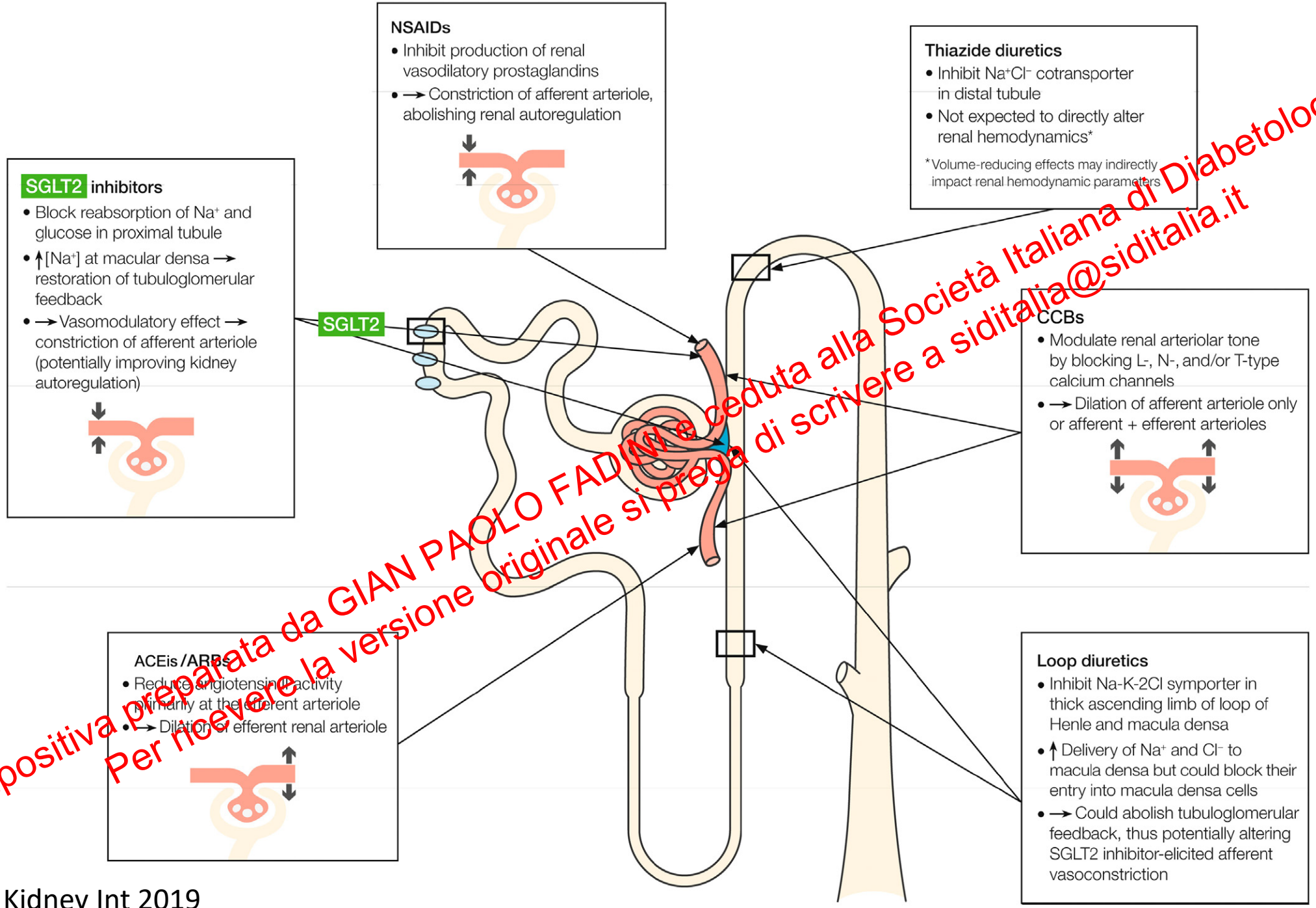
Empagliflozin può aumentare l'effetto diuretico dei diuretici tiazidici e dei diuretici dell'ansa e può aumentare quindi il rischio di disidratazione e di ipotensione (vedere paragrafo 4.4).

Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
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

Do we really understand the renal effects of all these drugs in type 2 diabetes (T2D) patients?

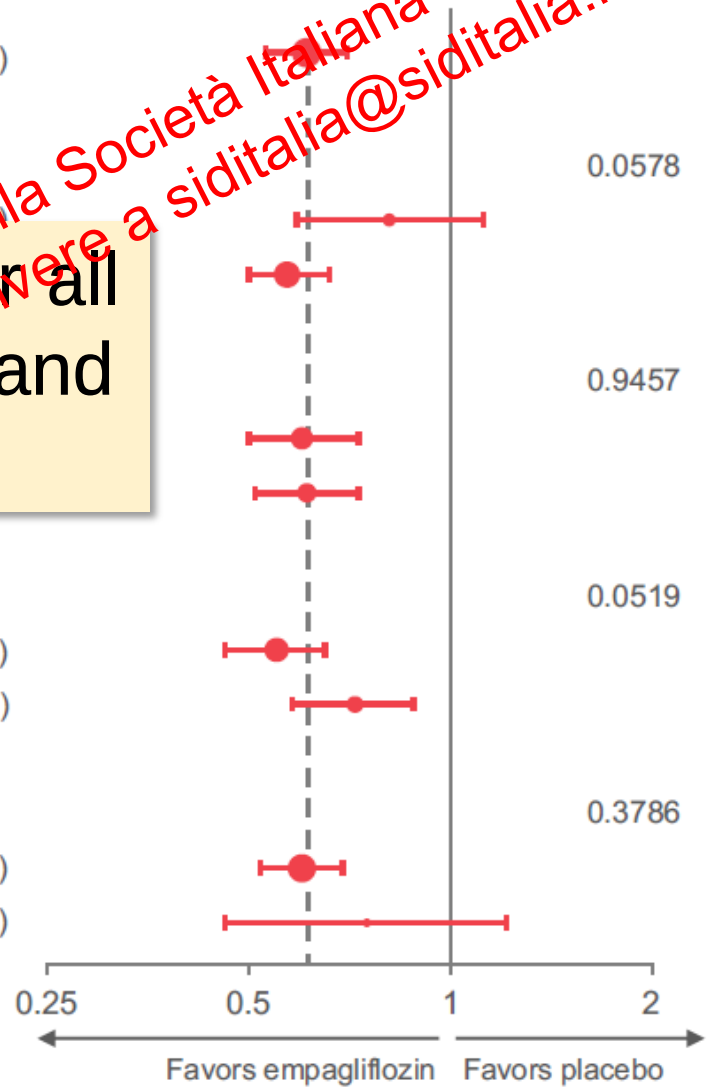
Van Baar et al. Kidney Int 2019



Mayer et al. Kidney Int 2019

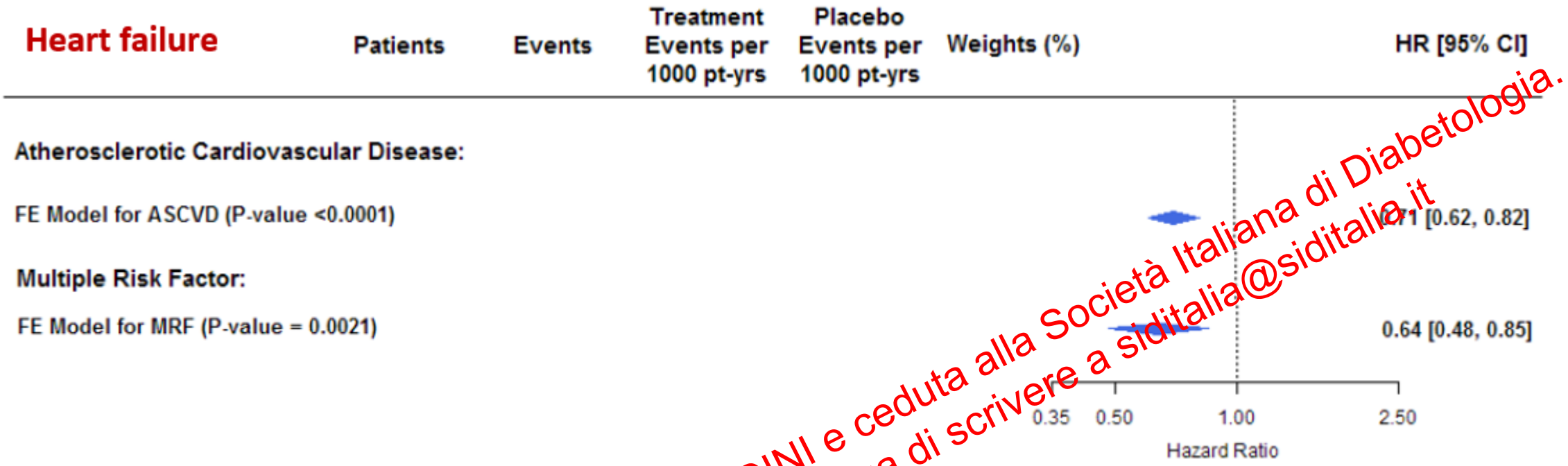
Incident or worsening nephropathy by background medication use at baseline

	Empagliflozin	Placebo	Hazard ratio	Hazard ratio	Interaction
	n with event/*N* analyzed (%)		(95% CI)	(95% CI)	*P* value
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)		
Use of ACEis/ARBs					0.0578
No	95/792 (12.0)	58/413 (14.0)	0.81 (0.59, 1.12)		
Yes	430/33				
Use of any diuretic					0.9457
No	256/2				
Yes	269/1				
Use of CCBs					0.0519
No	296/2818 (10.5)	241/1387 (17.4)	0.55 (0.46, 0.65)		
Yes	229/1306 (17.5)	147/ 674 (21.8)	0.72 (0.58, 0.88)		
Use of NSAIDs					0.3786
No	482/3796 (12.7)	360/1890 (19.0)	0.60 (0.52, 0.69)		
Yes	43/328 (13.1)	28/171 (16.4)	0.75 (0.46, 1.21)		



Quite similar results for all other renal endpoints and eGFR slopes

Mayer et al. Kidney Int 2019



Data from CVOTs indicate that CV protection by SGLT2i may extend to primary prevention (at least for HF)

↓

The number of patients receiving SGLT2i worldwide is expected to increase substantially

↓

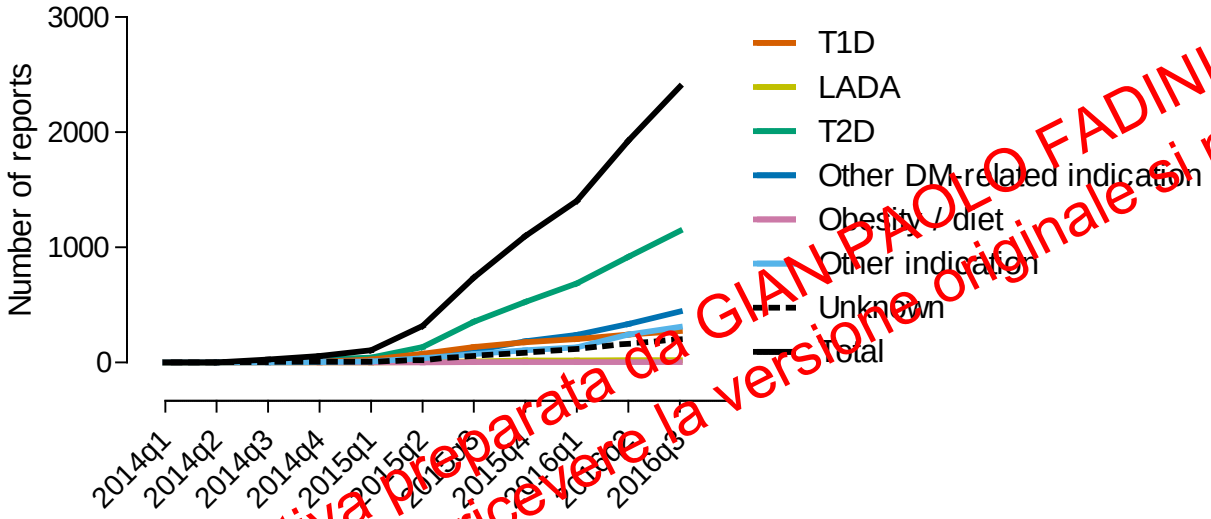
More attention should be payed to rare but severe AEs

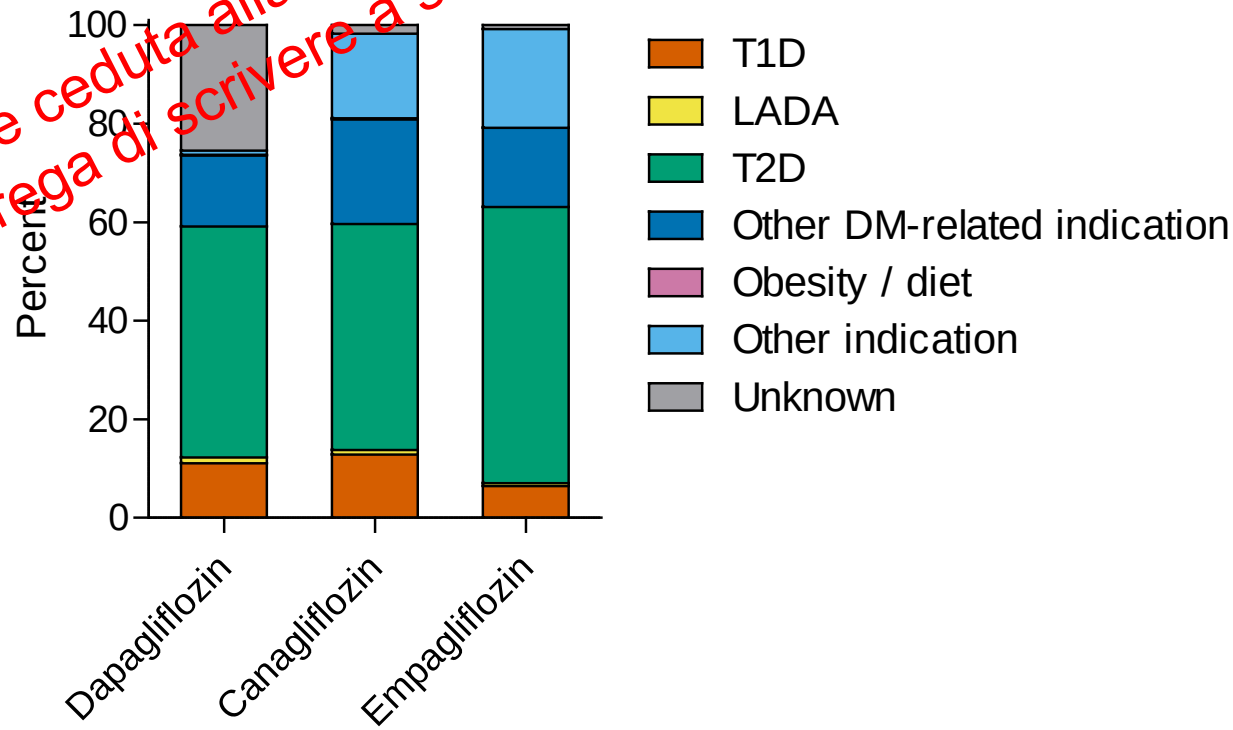
Uncommon but severe AEs during SGLT2i therapy

- **Diabetic ketoacidosis**
- **Lower limb amputations**
- **Fournier's gangrene**
- **Fractures**

DKA during SGLT2i

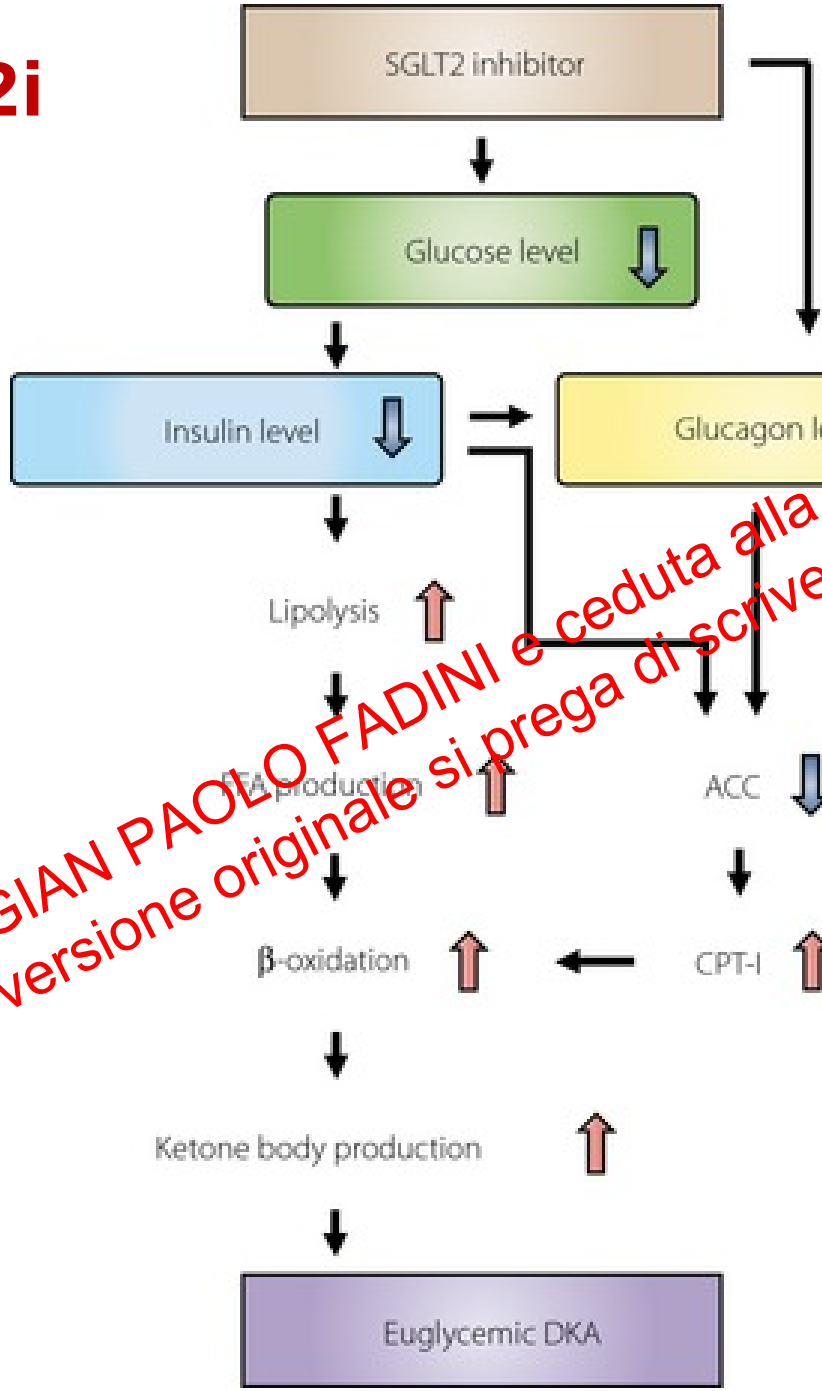
- **FDA warning with 73 cases → now thousands of cases reported worldwide**
- **Can be «normoglycemic» → delayed diagnosis**
- **Variable presentation**
- **No clear precipitating event in ¼ cases**
- **Potentially fatal**





Fadini et al. Diabetologia 2017
Bonora et al. Diabetes Obes Metab 2018

DKA during SGLT2i



Fracture risk & SGLT2i

- **A signal has been reported for Canagliflozin**
- **Not significant for Empa & Dapa**
- **Possible mechanisms linking Cana and bone biology via FGF23**

JCI insight

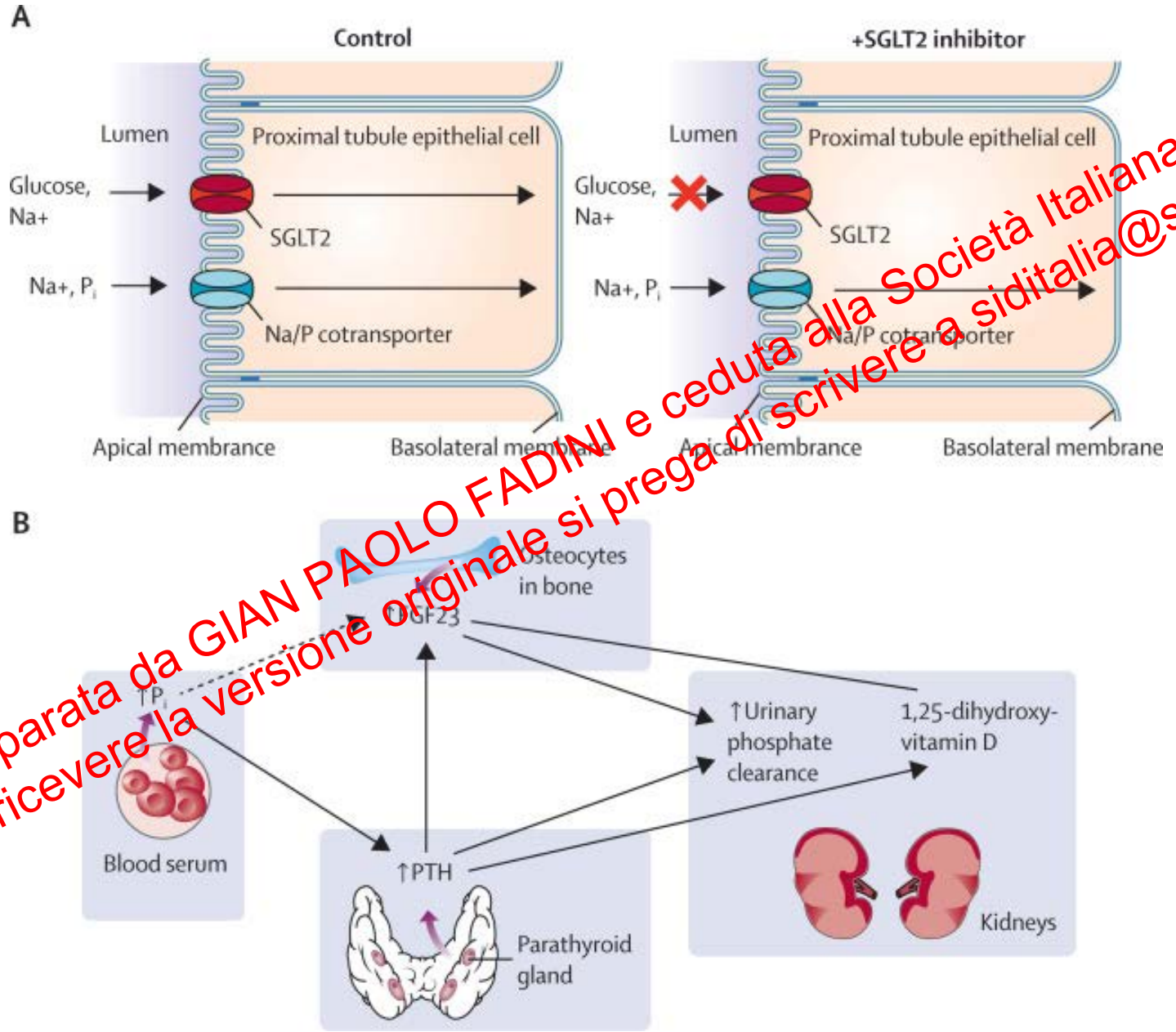
CLINICAL MEDICINE

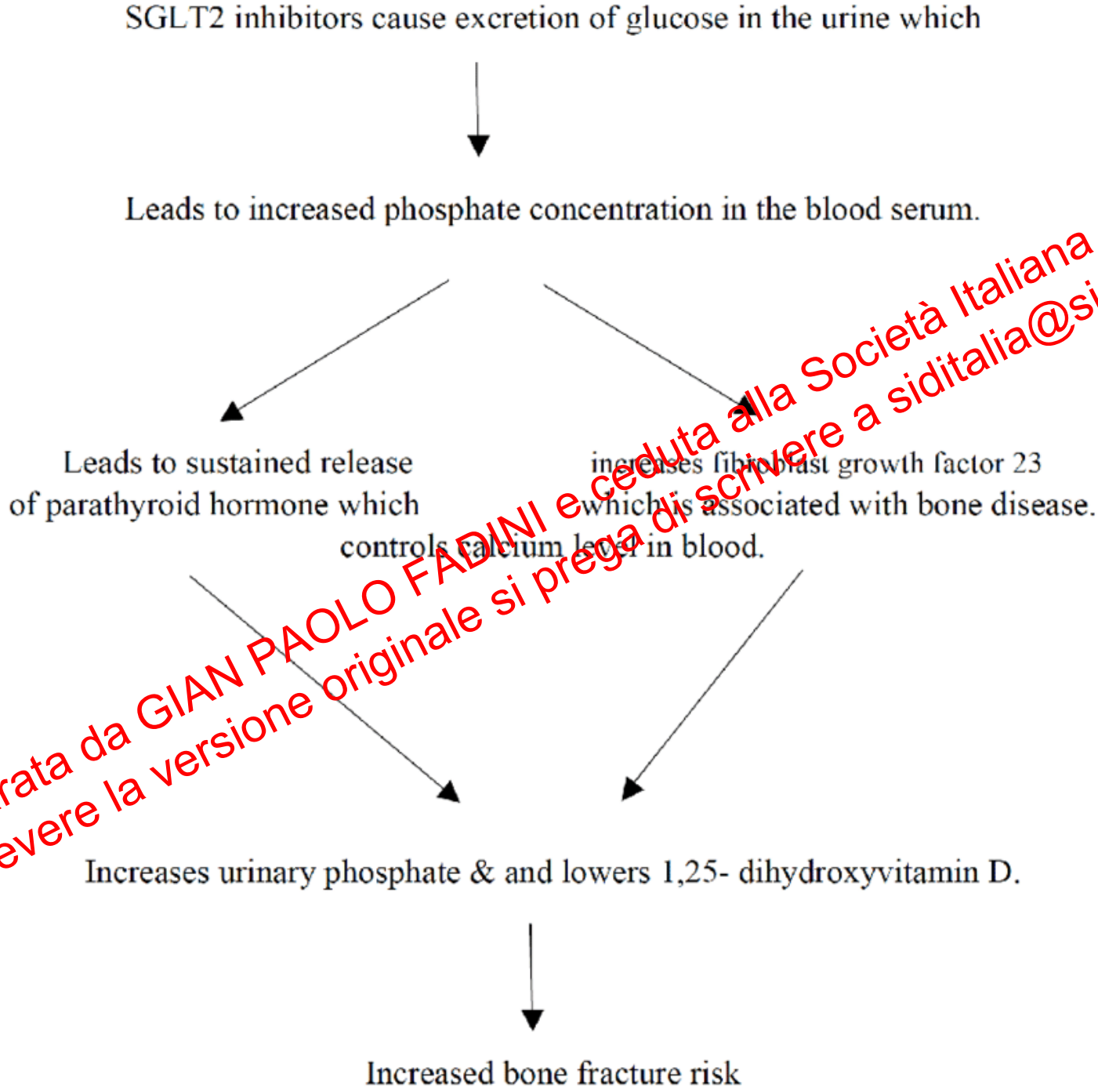
Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study

Jenny E. Blau,[1,2] Viviana Bauman,[1] Ellen M. Conway,[1] Paolo Piaggi,[3] Mary F. Walter,[1] Elizabeth C. Wright,[1] Shanna Bernstein,[4] Amber B. Courville,[4] Michael T. Collins,[5] Kristina I. Rother,[1] and Simeon I. Taylor[1,6]

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

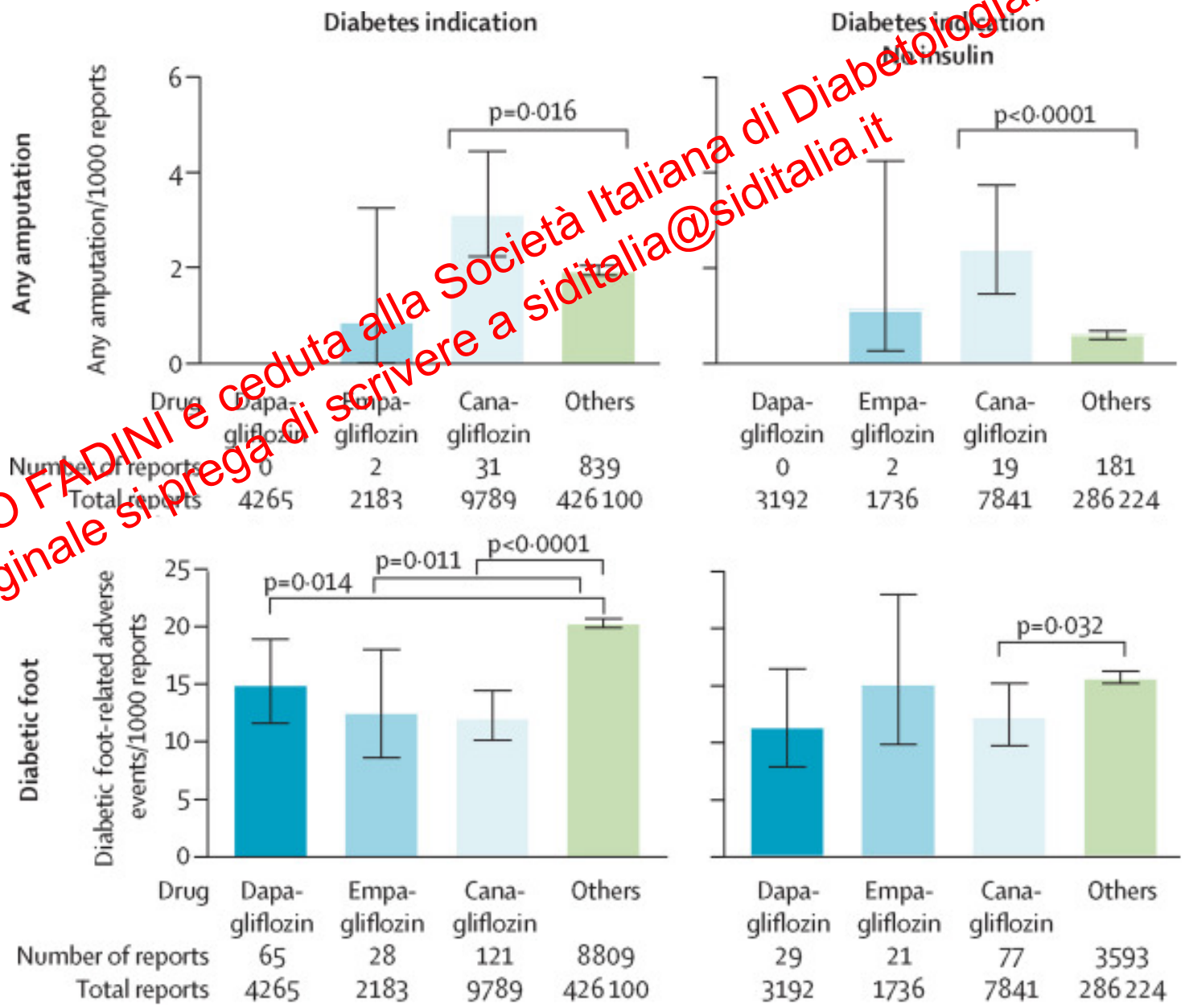
Fracture risk & SGLT2i





Amputations risk & SGLT2i

- FDA warning from CANVAS
- Below-knee amputations
- Mostly with Canagliflozin
- Confirmed in RW (not all)
- Confirmed in pharmacovigilance
- Mechanisms largely unknown?



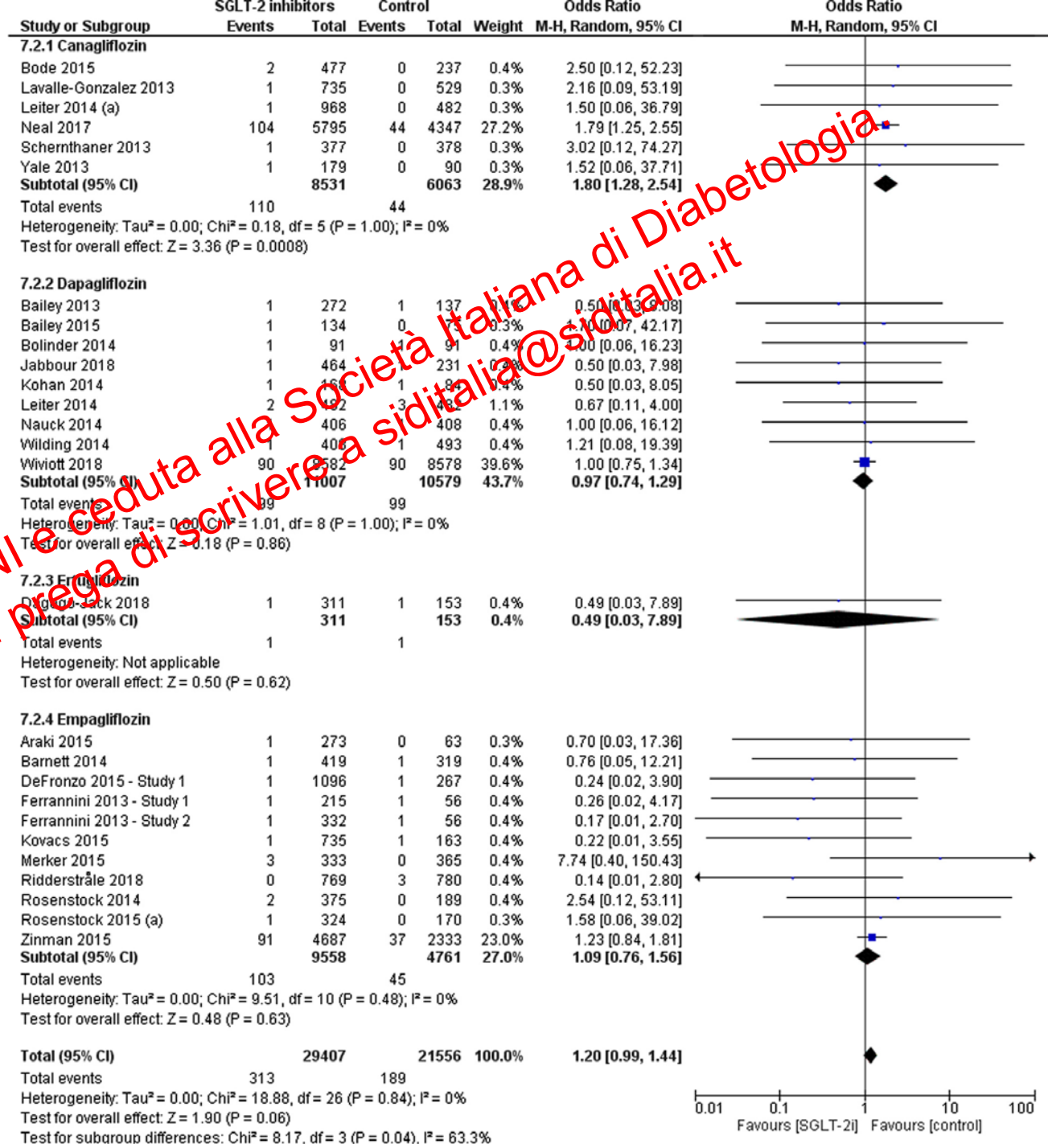
Fadini et al. Lancet DE 2018

SGLT-2i and amputations

CANA pooled RR 1,80 (1,28-2,54)

EMPA pooled RR 1.09 (0.76-1.56)

DAPA pooled RR 0.97 (0.74-1.29)



Dicembrini et al. DRCP 2019

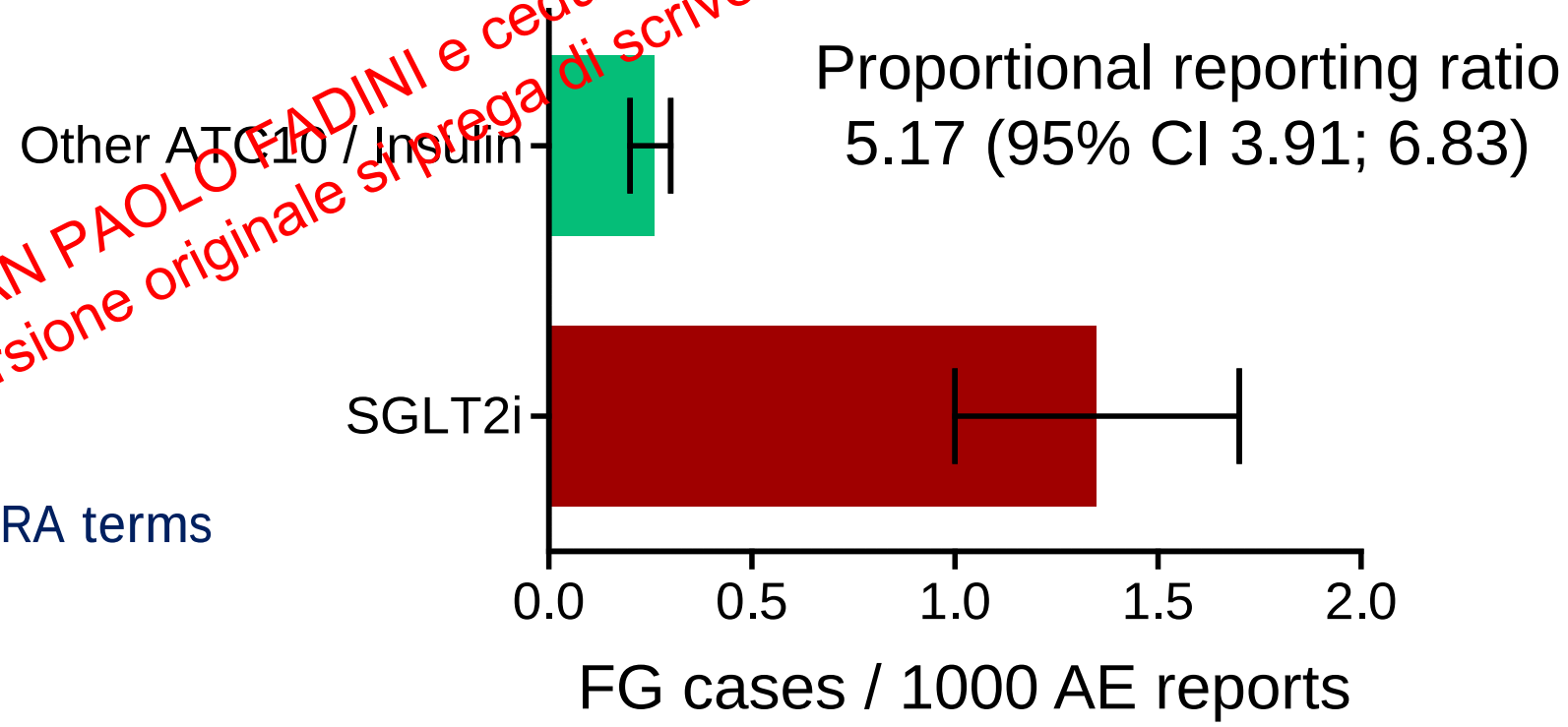
SGLT2-i and amputations

- Volume depletion → hypoperfusion?
- UTI/GTI → diabetic foot infection?
- Hyperphosphatemia → calciphylaxis?

Fournier's Gangrene & SGLT2i

- **FDA warning from 12 cases**
- **Males and females**
- **A rare serious complication of UTI / GTI?**

- **Confirmed in pharmacovigilance**



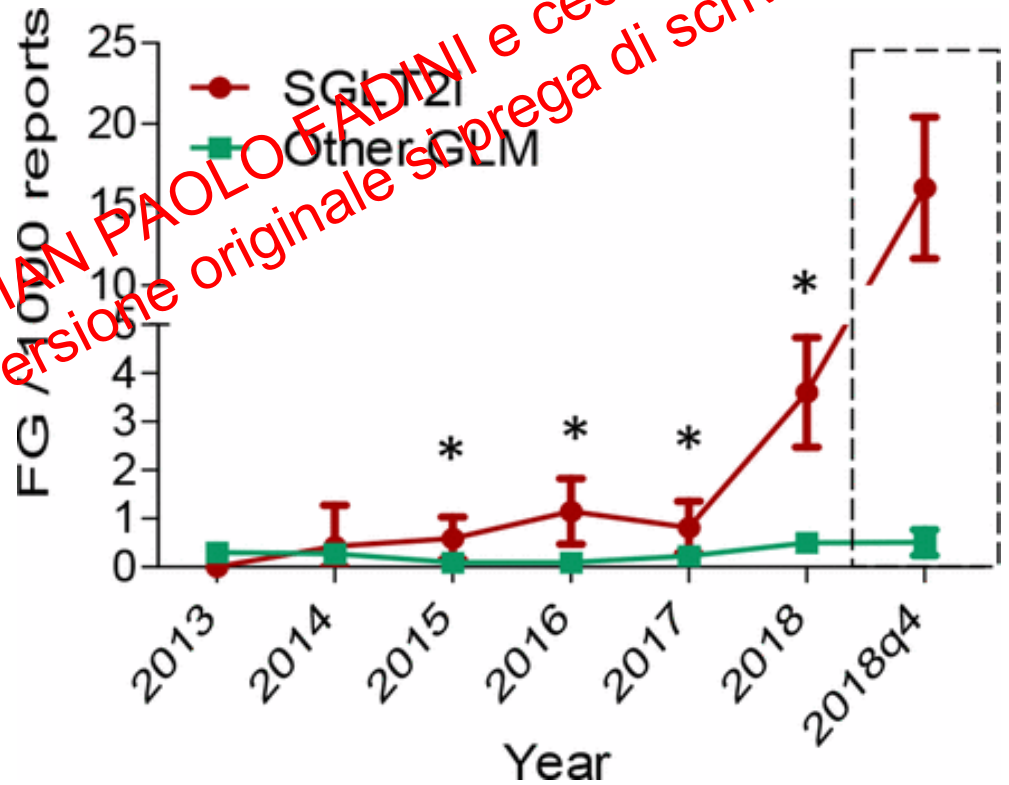
Strict definition of FG by MEDDRA terms
62 cases retrieved

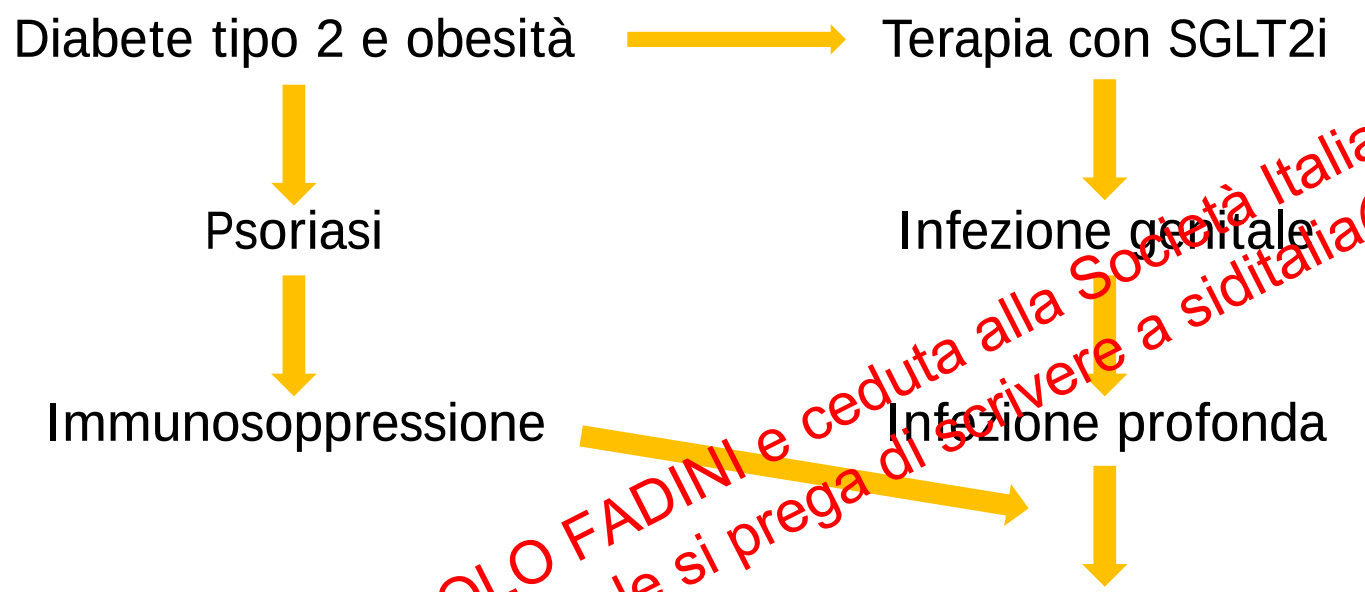
(Fadini et al. BMJ open DRC)

BMJ Open Diabetes Research & Care

Pharmacovigilance assessment of the association between Fournier's gangrene and other severe genital adverse events with SGLT-2 inhibitors

Gian Paolo Fadini ,[1] Mayur Sarangdhar,[2] Fabrizio De Ponti,[3] Angelo Avogaro,[1] Emanuel Raschi [3]





Take-home messages

- **Common non-severe AEs**
  - can be easily addressed and handled
  - do not modify the safety/efficacy balance

- **Rare severe AEs**
  - are more difficult to be predicted
  - can be life threatening and fatal
  - do not modify the safety / efficacy balance
  - become important upon enlargment of the SGLT2i population