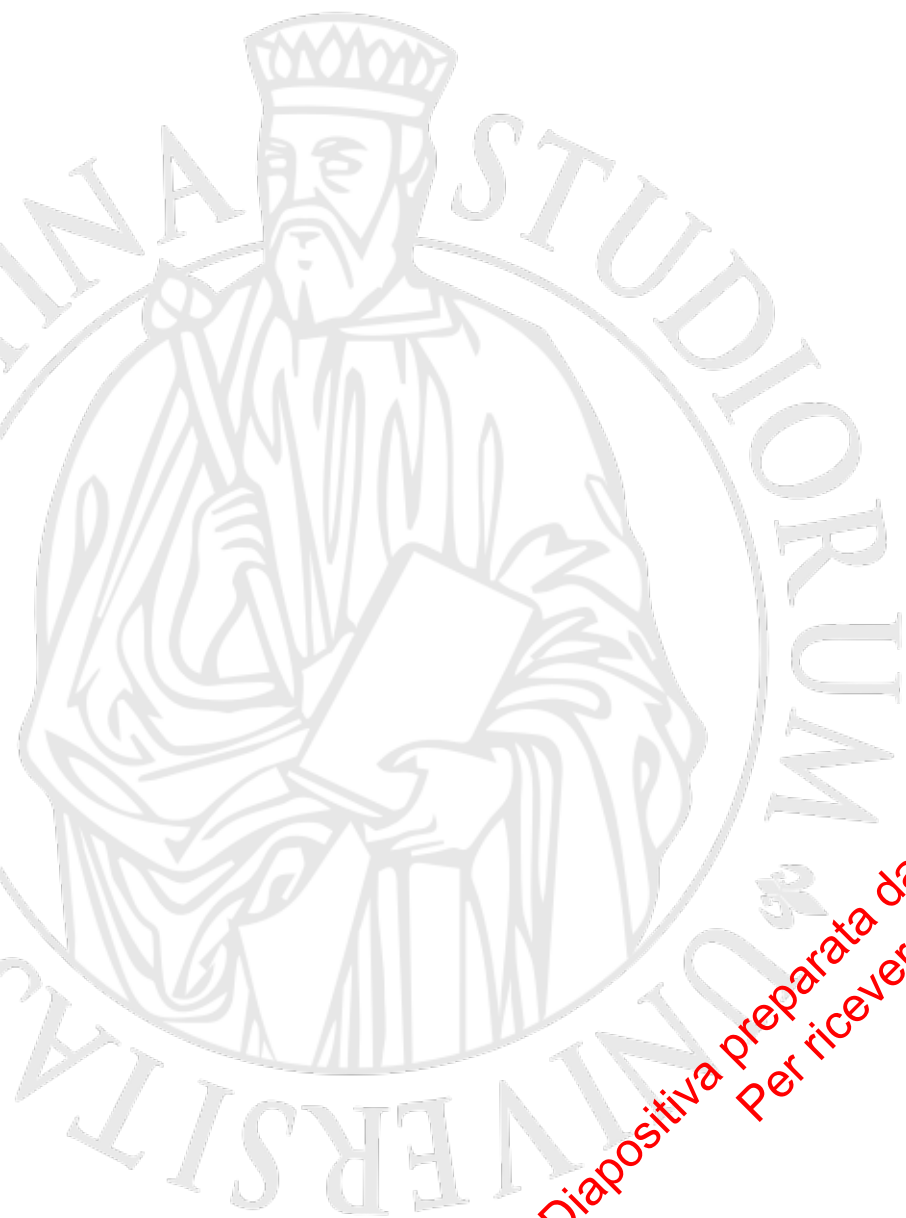




Sicurezza dei SGLT2i: c'è qualcosa a cui stare attenti?

Edoardo Mannucci

Diapositiva preparata da EDOARDO MANNUCCI e ceduta alla Società Italiana di Diabetologia.
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Consensus tra esperti con metodo DELPHI

IL GIUSTO POSTO DELLE **GLIFLOZINE** NEL TRATTAMENTO DEL **DIABETE DI TIPO 2**

9 LUGLIO 2022

ROMA Starhotels Metropole

Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto compensi per relazioni/consulenze da

Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi

La struttura di appartenenza di E. Mannucci ha ricevuto :

- Finanziamenti per ricerca indipendente non condizionata da ***Abbott***
- Compensi per studi clinici sponsorizzati da ***Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Molteni, Novo Nordisk***

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Tolerability and safety issues

- Genital infections
- Urinary infections
- Fournier's gangrene
- Ketoacidosis
- Dehydration
- Fractures
- Amputations

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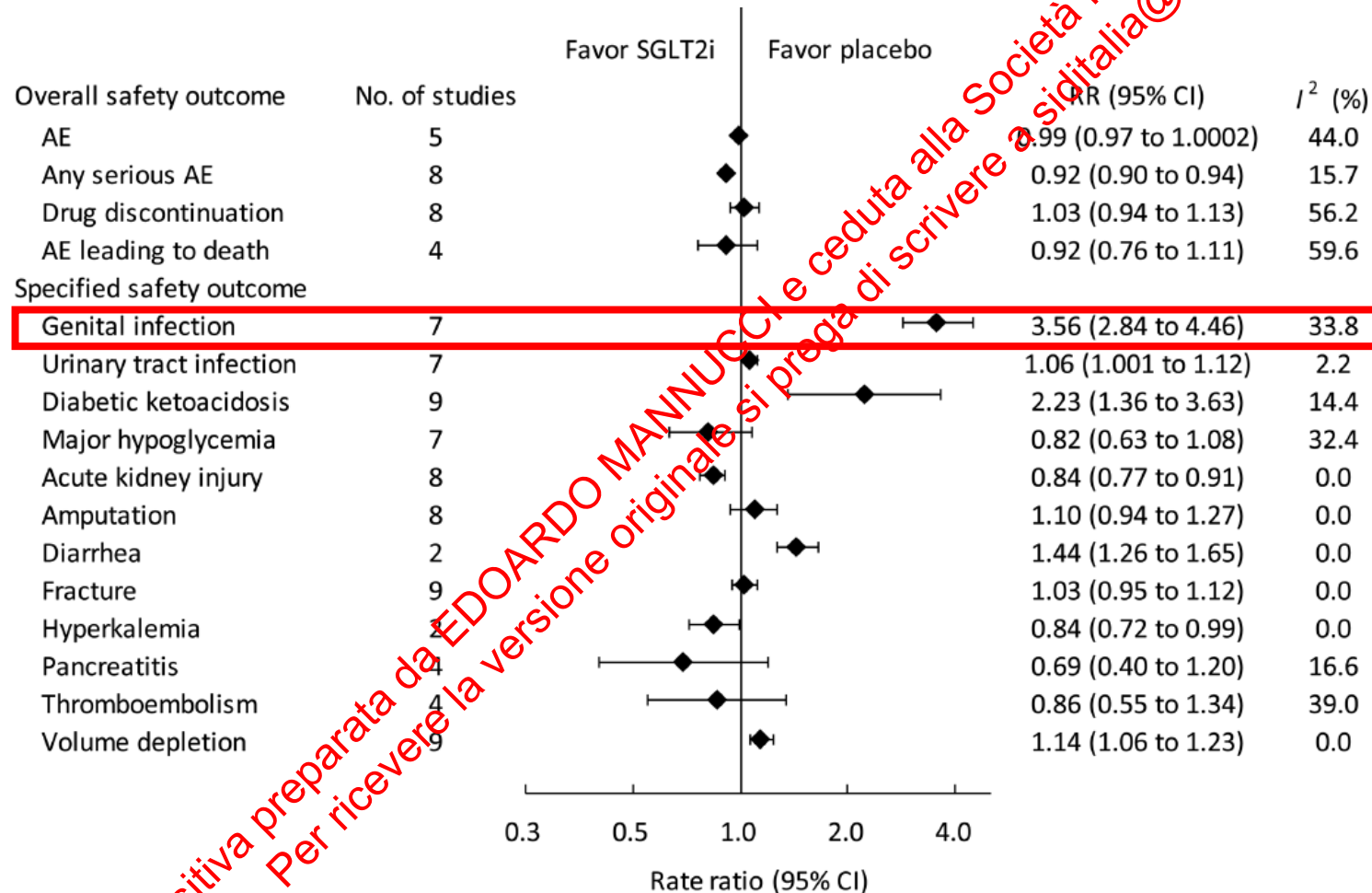
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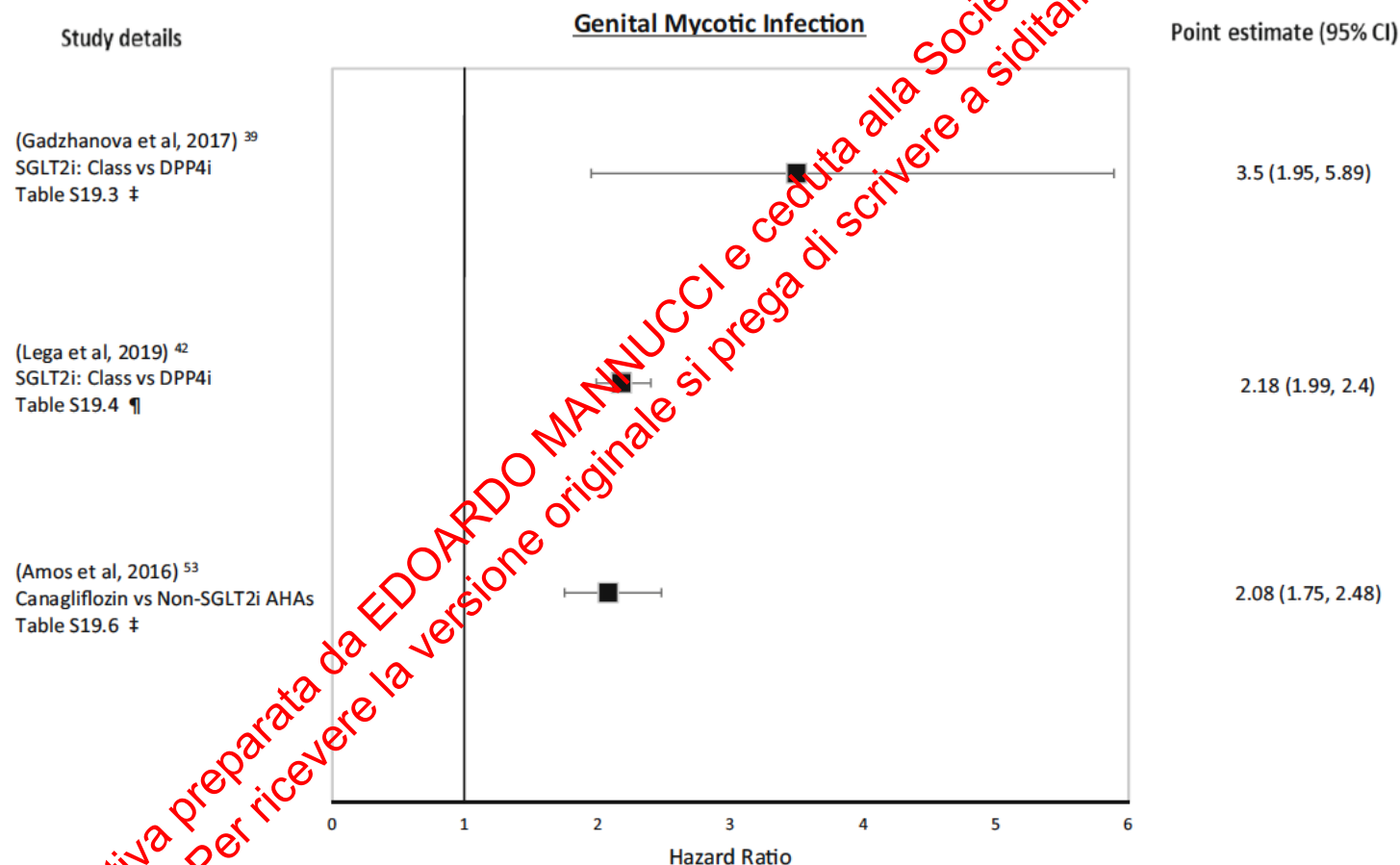
SGLT2i and genital infections

A meta-analysis of placebo-controlled RCTs



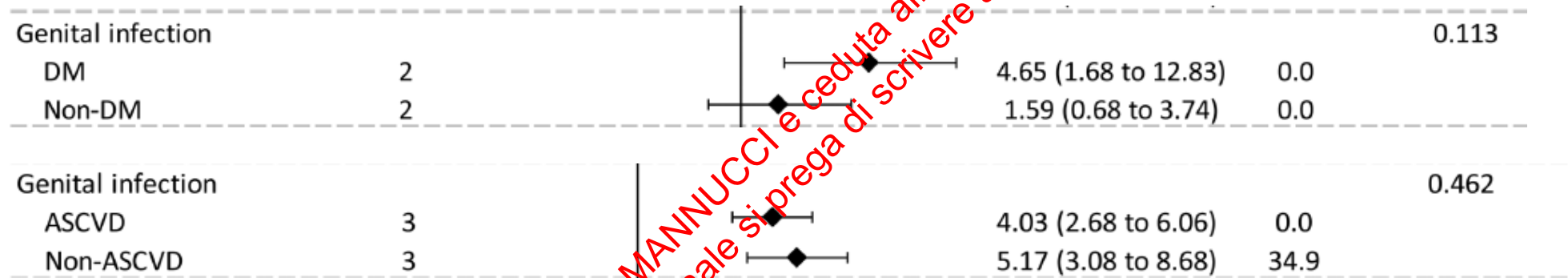
SGLT2i and genital infections

A systematic review of observational studies



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Empagliflozin: effect on genital infections

Pooled analysis of phase III trials



Empagliflozin: effect on genital infections

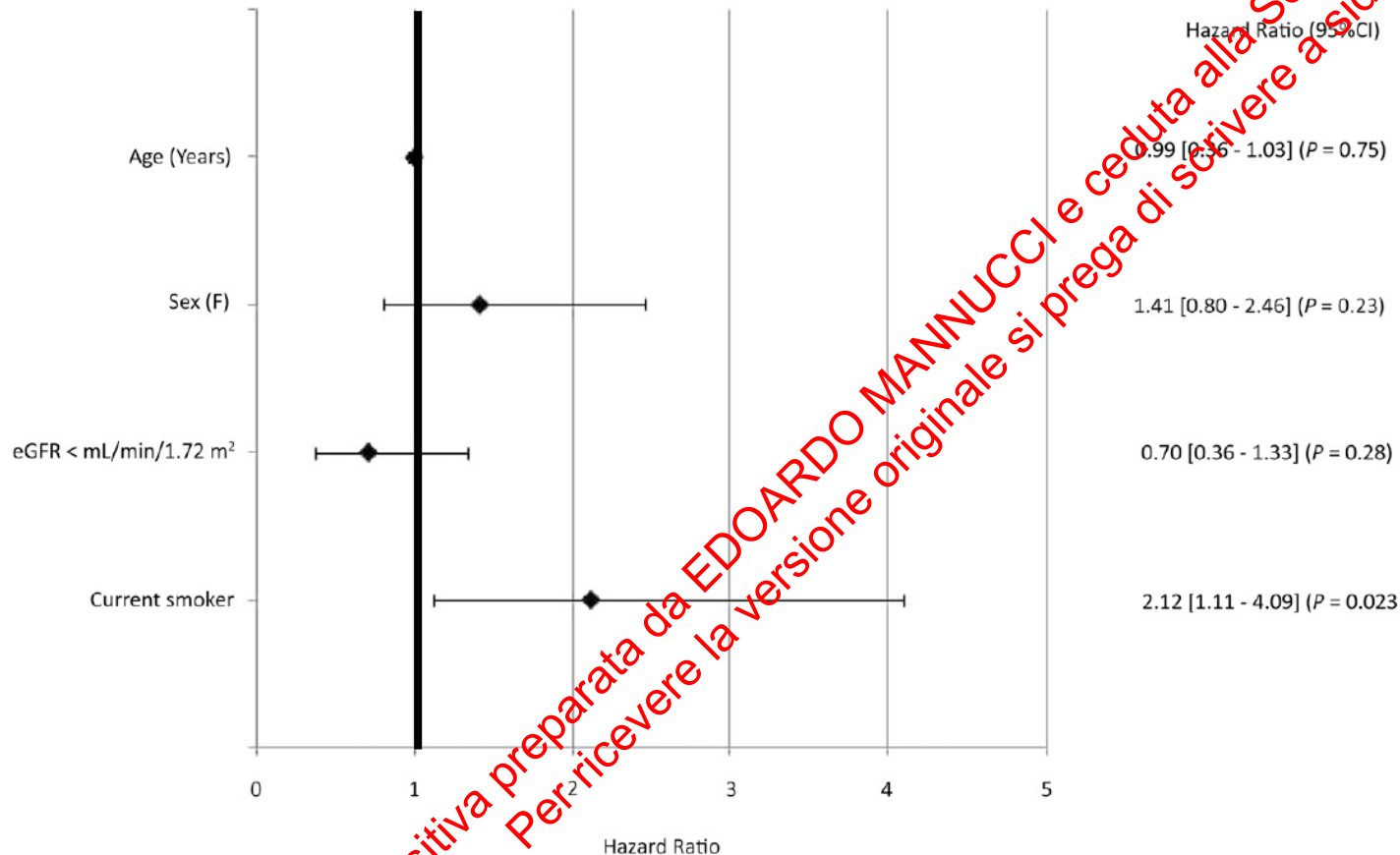
Results of a retrospective 3-year study in Japan

Table 3. Adverse drug reactions by age of patient (safety analysis set).

ADR	All patients (N = 7931)	≥65 years (n = 5024)	≥65 to <75 years (n = 2077)	≥75 years (n = 830)
Total ADRs	1024 (12.91)	594 (11.82)	310 (14.93)	120 (14.46)
ADR of special interest				
Hypoglycemia ^a	35 (0.44)	18 (0.36)	9 (0.43)	8 (0.96)
Urinary tract infection ^b	85 (1.07)	47 (0.94)	26 (1.25)	12 (1.45)
Genital infection ^c	52 (0.66)	34 (0.68)	12 (0.58)	6 (0.72)
Volume depletion ^d	40 (0.50)	25 (0.50)	13 (0.63)	2 (0.24)
Cardiovascular event ^e	53 (0.67)	25 (0.50)	18 (0.87)	10 (1.20)
Renal impairment ^f	22 (0.28)	9 (0.18)	7 (0.34)	6 (0.72)
Liver injury ^g	44 (0.55)	34 (0.68)	8 (0.39)	2 (0.24)
Bone fracture ^h	10 (0.13)	5 (0.10)	3 (0.14)	2 (0.24)
Malignancy ⁱ	36 (0.45)	7 (0.14)	21 (1.01)	8 (0.96)
Excessive urination/frequent urination ^j	102 (1.29)	63 (1.25)	31 (1.49)	8 (0.96)
AEs relating to an increase in ketones ^k	39 (0.49)	35 (0.70)	4 (0.19)	0
Diabetic ketoacidosis ^l	0	0	0	0
Lower limb amputation ^m	3 (0.04)	2 (0.04)	1 (0.05)	0

SGLT2i and risk of genital infections

Results of a retrospective cohort study



Retrospective cohort study.

508 patients initiating a treatment with SGLT2i before Oct 1st, 2018

2-y follow-up

Reported genital infections (from clinical records):

10.8%

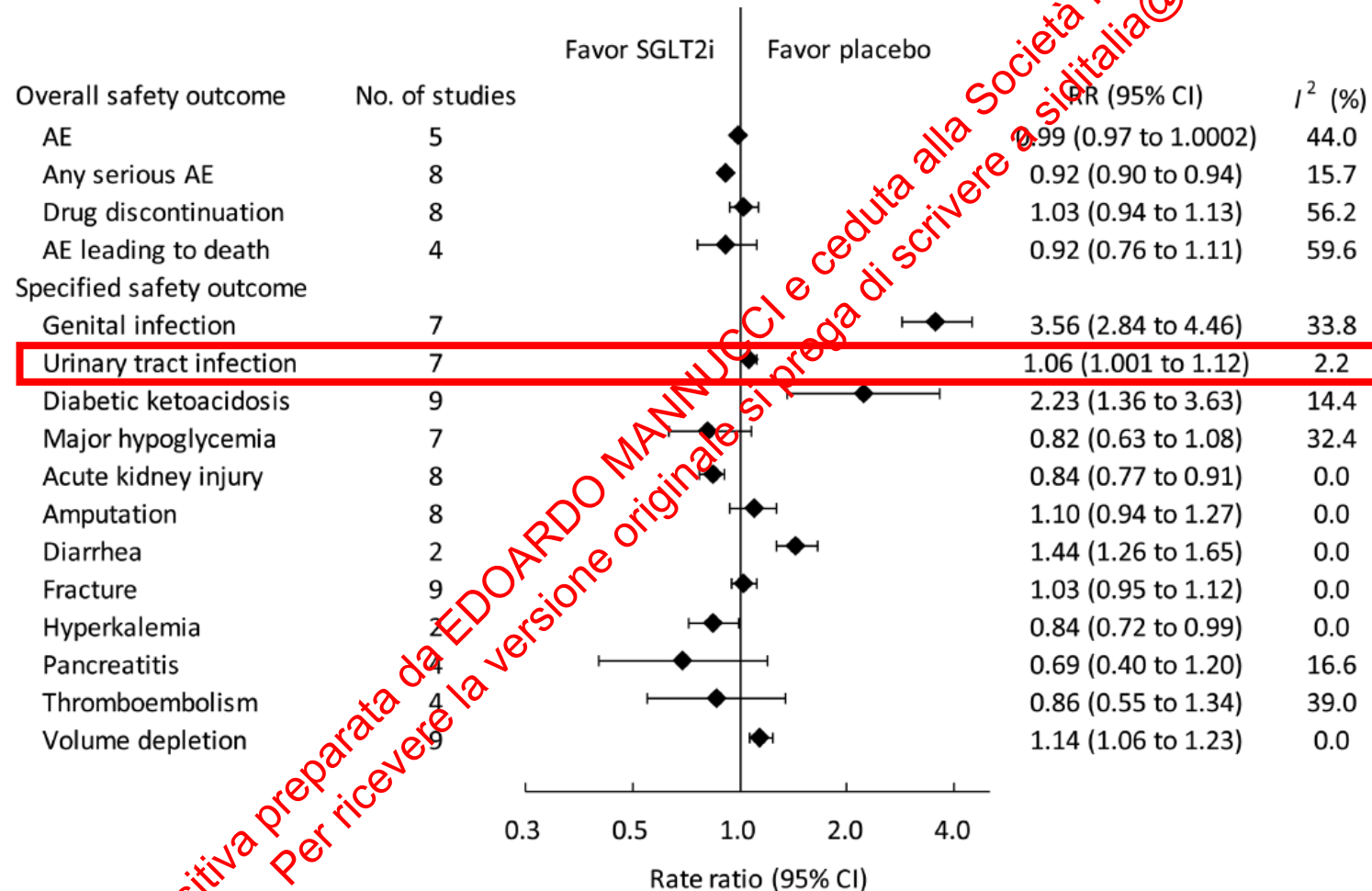
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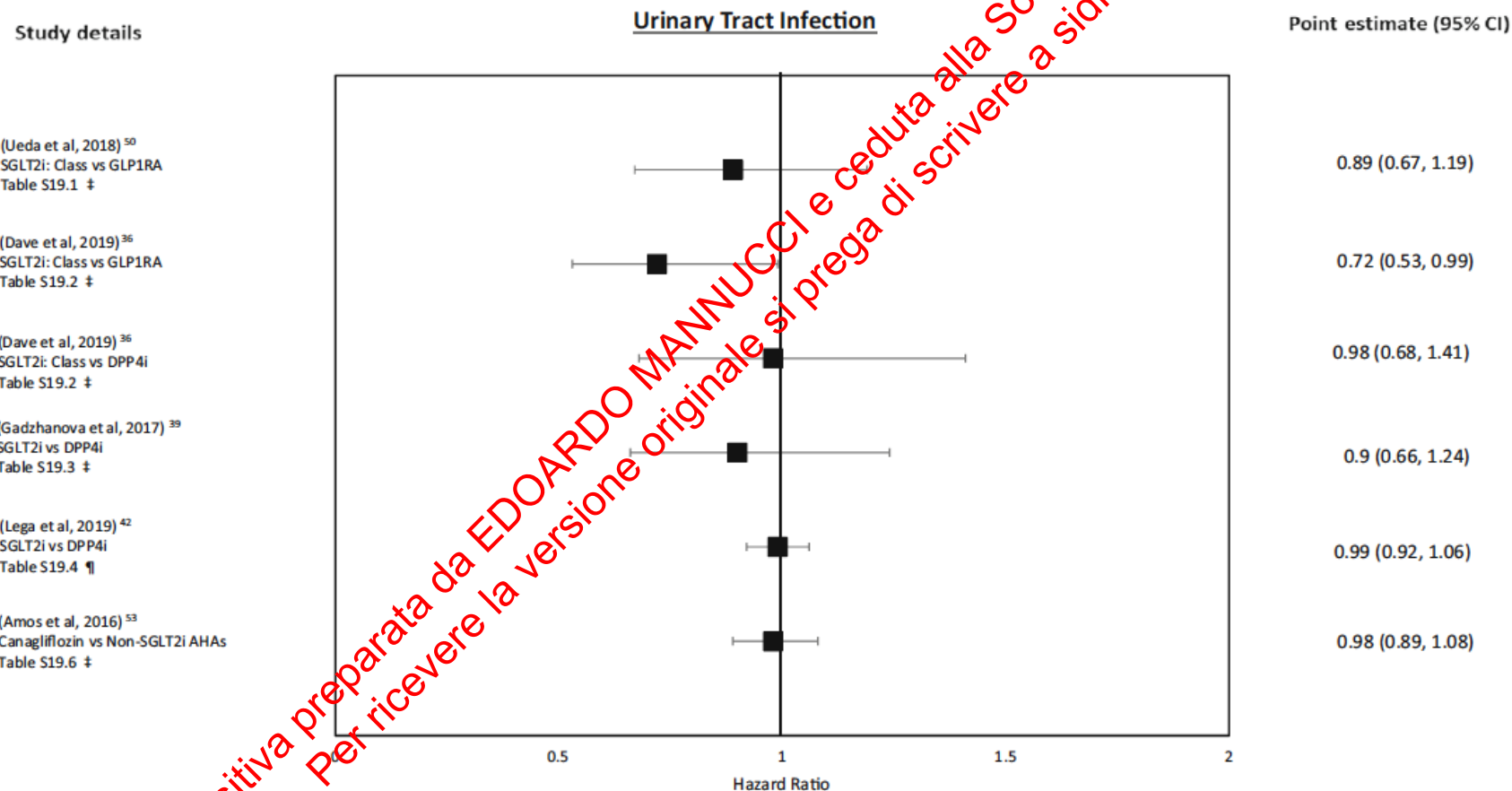
SGLT2i and urinary tract infections

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SGLT2i and risk of Fournier gangrene

Results from the US FDA pharmacovigilance reporting system

TABLE 4: The association between different SGLT2 inhibitors and FG occurrence.

Drug	N	ROR (95% two-sided CI)	IRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Canagliflozin	190	18.76 (16.22, 21.70)	18.60 (3058.02)	4.17 (3.61)	18.00 (15.94)
Canagliflozin/metformin	9	20.12 (10.43, 38.81)	19.93 (161.61)	4.31 (2.24)	19.90 (11.48)
Dapagliflozin	96	22.89 (18.68, 28.04)	22.64 (1952.68)	4.48 (3.65)	22.27 (18.79)
Dapagliflozin/saxagliptin	0	—	—	—	—
Dapagliflozin/metformin	12	34.86 (19.89, 60.73)	34.28 (387.09)	5.10 (2.88)	34.21 (21.21)
Empagliflozin	209	46.70 (40.64, 53.70)	45.70 (8798.23)	5.46 (4.75)	44.02 (39.16)
Empagliflozin/linagliptin	10	24.82 (12.76, 44.46)	23.55 (215.66)	4.56 (2.44)	23.51 (13.95)
Empagliflozin/metformin	13	54.73 (31.56, 95.12)	53.36 (666.70)	5.73 (3.30)	53.24 (33.56)
Ertugliflozin	3	18.68 (5.99, 58.24)	18.51 (49.70)	4.21 (1.35)	18.50 (7.15)

SGLT2i and risk of Fournier gangrene

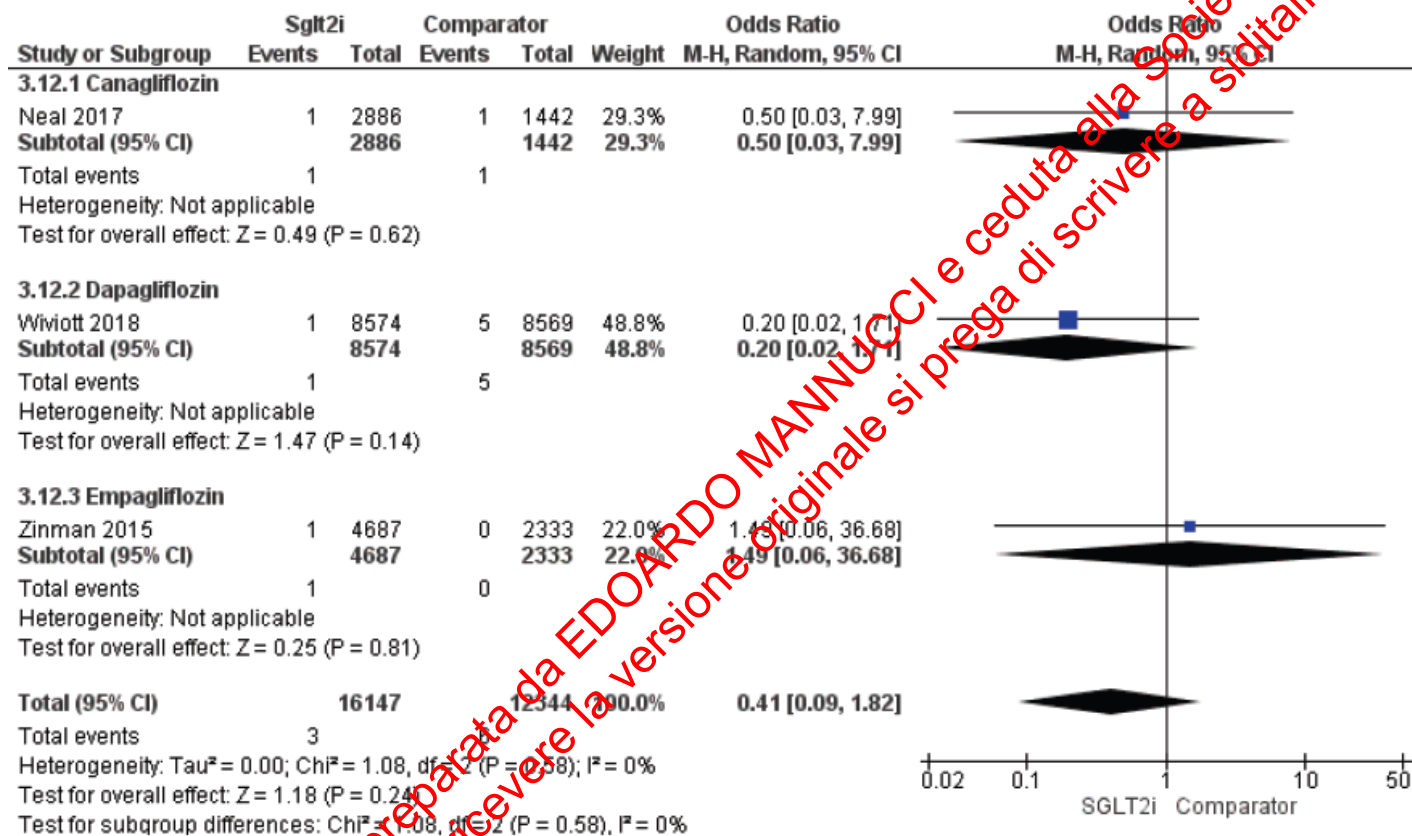
Results from the US FDA pharmacovigilance reporting system

TABLE 3: Detailed information on FFG reports.

	Canagliflozin (n)	Dapagliflozin (n)	Empagliflozin (n)	Ertugliflozin (n)	Total (n, %)
Reported year					
2019	153	68	183	3	407 (75.09%)
2018	31	27	45	0	103 (19.00%)
2017	2	1	1	0	4 (0.74%)
2016	2	7	1	0	10 (1.85%)
2015	10	4	1	0	15 (2.77%)
2014	0	1	0	0	1 (0.18%)
Unknown	1	0	1	0	2 (0.36%)

SGLT2i and risk of Fournier gangrene

Meta-analysis of available RCTs



SGLT2i and risk of Fournier gangrene

Results of a retrospective nested case-control study

Treatment ^a	Overall	
	Cases (N = 216)	Controls (N = 1296)
SGLT2i (with or without other AHAs)	9 (4.2%)	100 (7.7%)
Two or more non-SGLT2i AHAs or insulin alone	97 (44.9%)	474 (36.6%)
Two or more non-SGLT2i AHAs	59 (27.3%)	411 (31.7%)
Insulin alone	38 (17.6%)	63 (4.9%)
Single AHAs excluding insulin or no current exposure	110 (50.9%)	722 (55.7%)

Nested case-control study within a cohort

Cohort: 1,897,935 subjects with T2DM between 2013 and 2018 enrolled in Trueven Health MarketScan (including insurance companies and Medicare administrative data).

Cases: 216 patients hospitalized for Fournier gangrene, 2013-2018

Controls: 1,296 matched patients

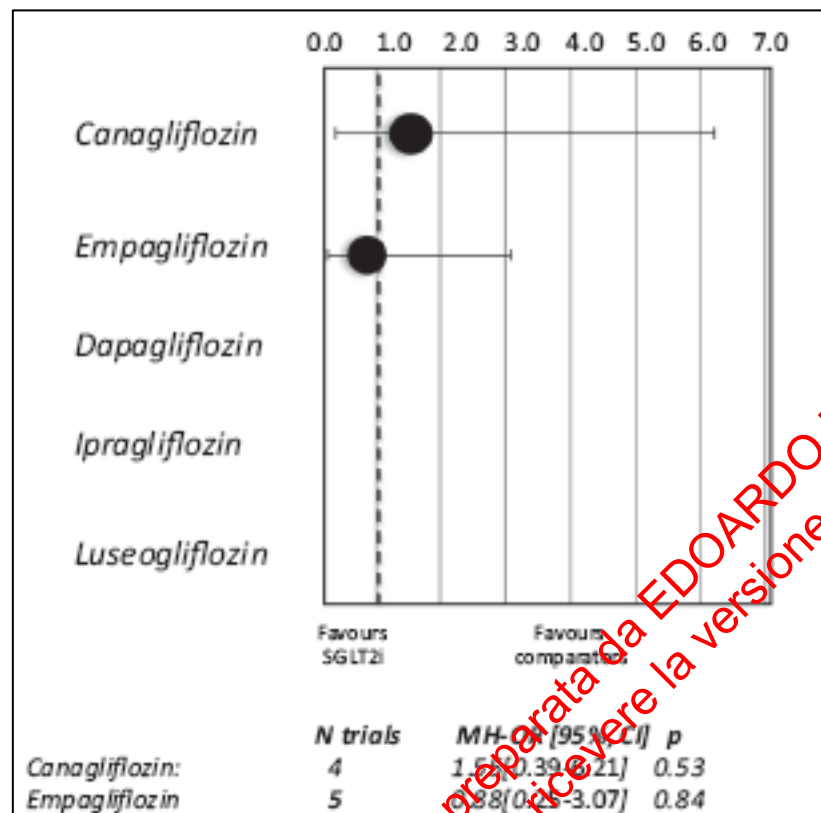
Tolerability and safety issues

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SGLT-2 inhibitors and ketoacidosis in type 2 diabetes

Meta-analysis of RCTs



RCT of at least 12 weeks in T2DM.

Number of trials: 88

Trials reporting information on DKA: 72

Trials with at least one event of DKA: 9

Patients enrolled in trials with DKA events:

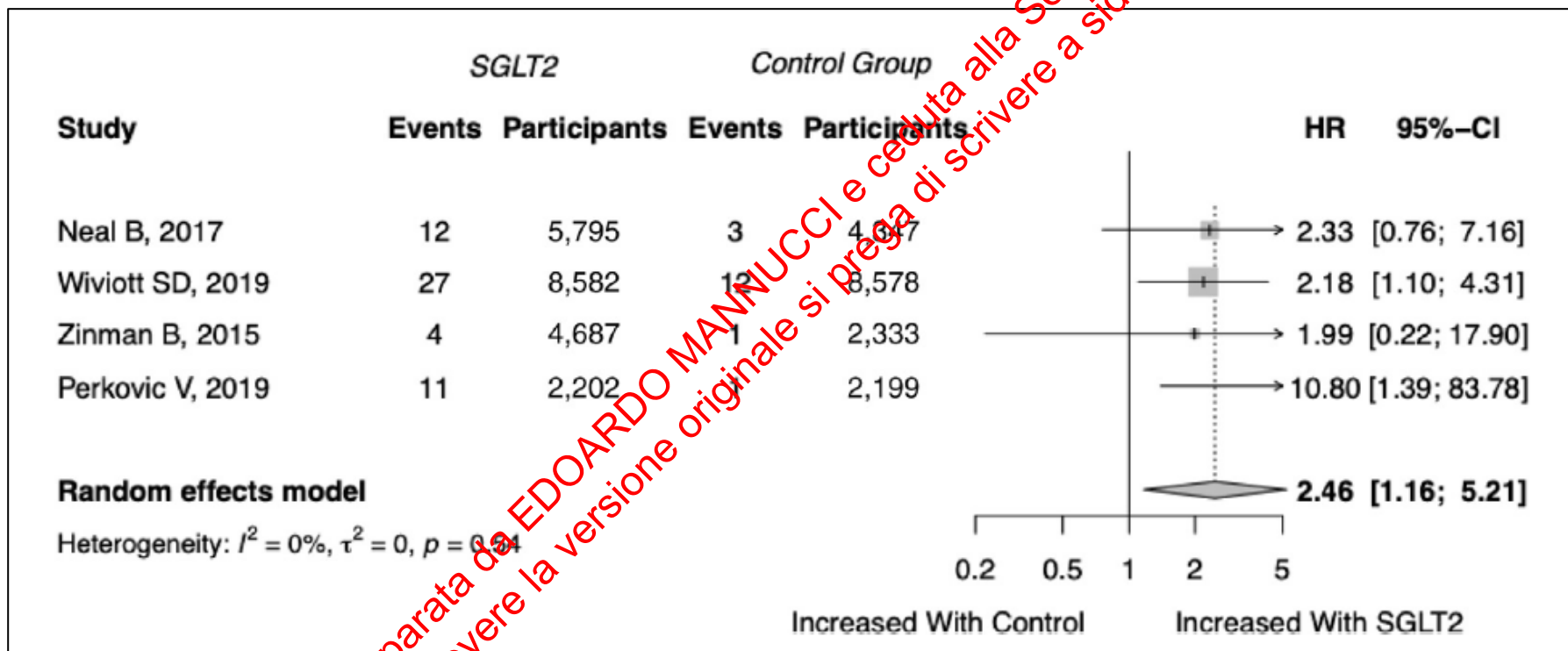
- 10,157 with SGLT-2 inhibitors
- 5,396 with comparator

Number of events of DKA:

- 16 with SGLT-2 inhibitors
- 6 with comparators

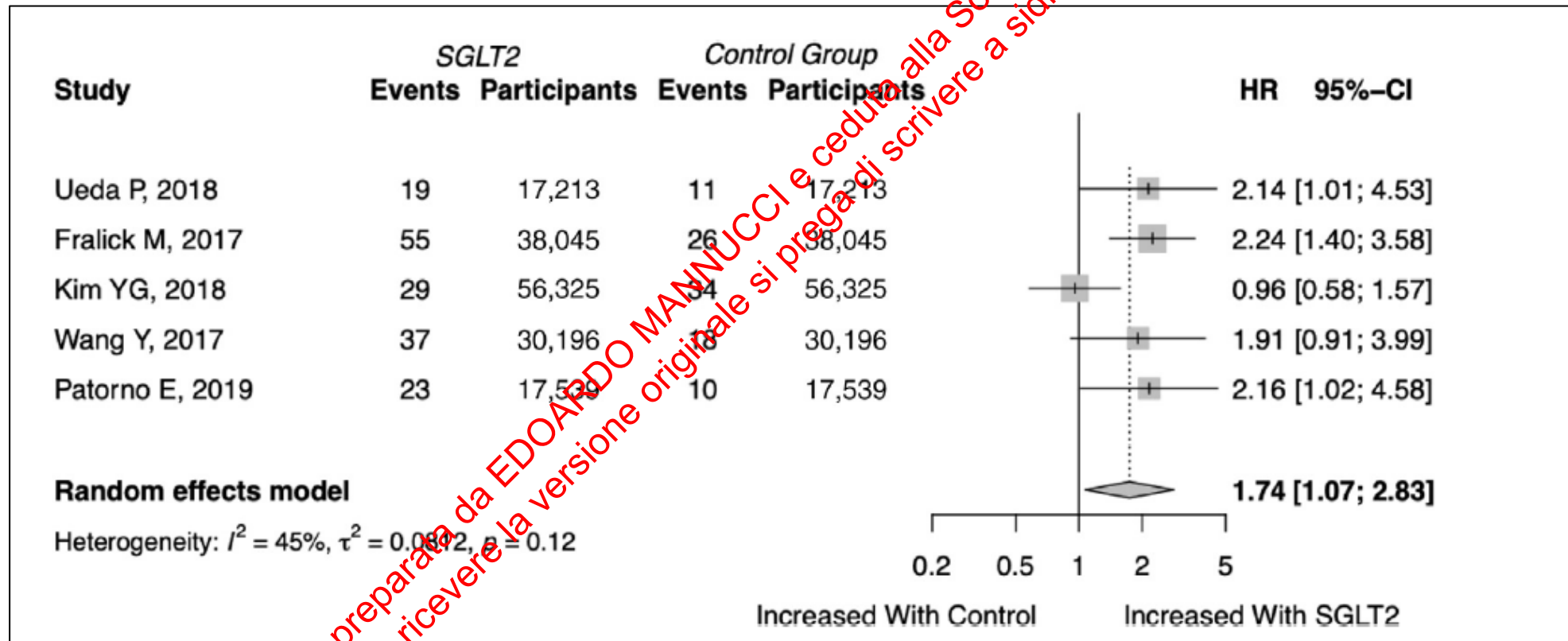
SGLT2i and ketoacidosis

A meta-analysis of placebo-controlled RCTs



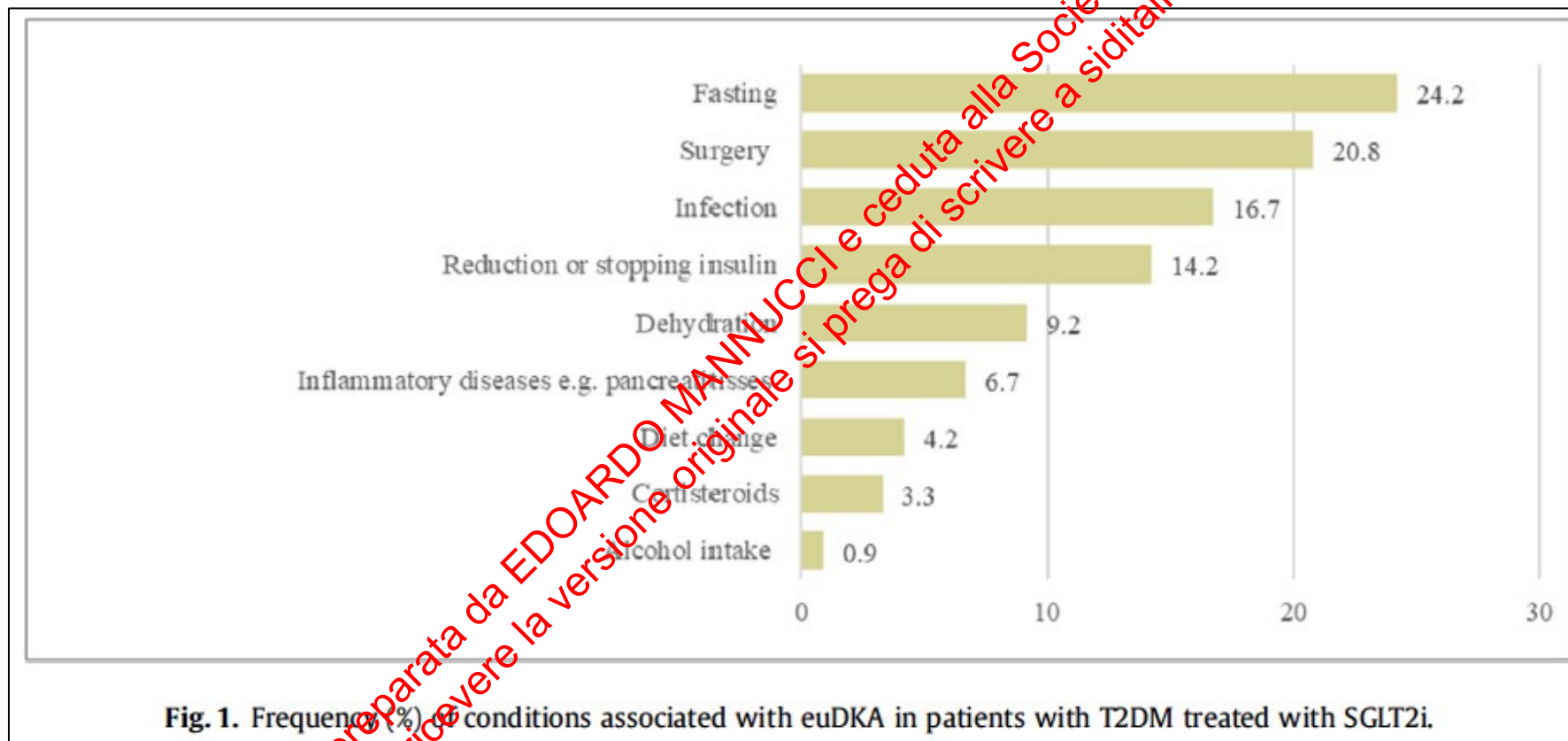
SGLT2i and ketoacidosis

A meta-analysis of observational studies



SGLT2i and ketoacidosis: risk factors

An analysis of a series of case reports



SGLT2i, ketogenis diets, and ketoacidosis

Case reports

Reported Cases of SGLT2 Inhibitor Use Associated With euDKA and Low-Carbohydrate Diets in Patients With T2DM

Patient age (y)	Gender	Number of years patient had T2DM	Number of days on a low-carbohydrate diet before developing euDKA	Number of days patient took SGLT2 inhibitor before developing euDKA	Plasma blood glucose (mg/dL) on admission to the hospital for euDKA	HbA1C at the time of admission for euDKA	Number of days patient required insulin drip	Reference
32	Female	22	~3960	13	191	9.3% (78 mmol/mol IFCC)	Unknown	17
44	Male	16	Unknown	3-4	180	9.3% (78 mmol/mol)	Unknown	18
64	Female	Unknown	60	365	~185.59	7.5% (58 mmol/mol IFCC)	Unknown	19
73	Male	10	7	Unknown	Unknown	Unknown	Unknown	20
					Point-of-care blood glucose: 143			
31	Female	Unknown	14	Unknown	139	Unknown	Unknown	21
34 ^a	Male	>5	7	~60	251	HbA1C 8.2% (66 mmol/mol IFCC)	3	
47 ^a	Female	~0.17	~60	.1	187	HbA1C 13.6% (125 mmol/mol IFCC)	5	

Abbreviations: euDKA = euglycemic diabetic ketoacidosis; HbA1C = hemoglobin A1C; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

^a Patient case 1 and 2 from our report included for comparison.

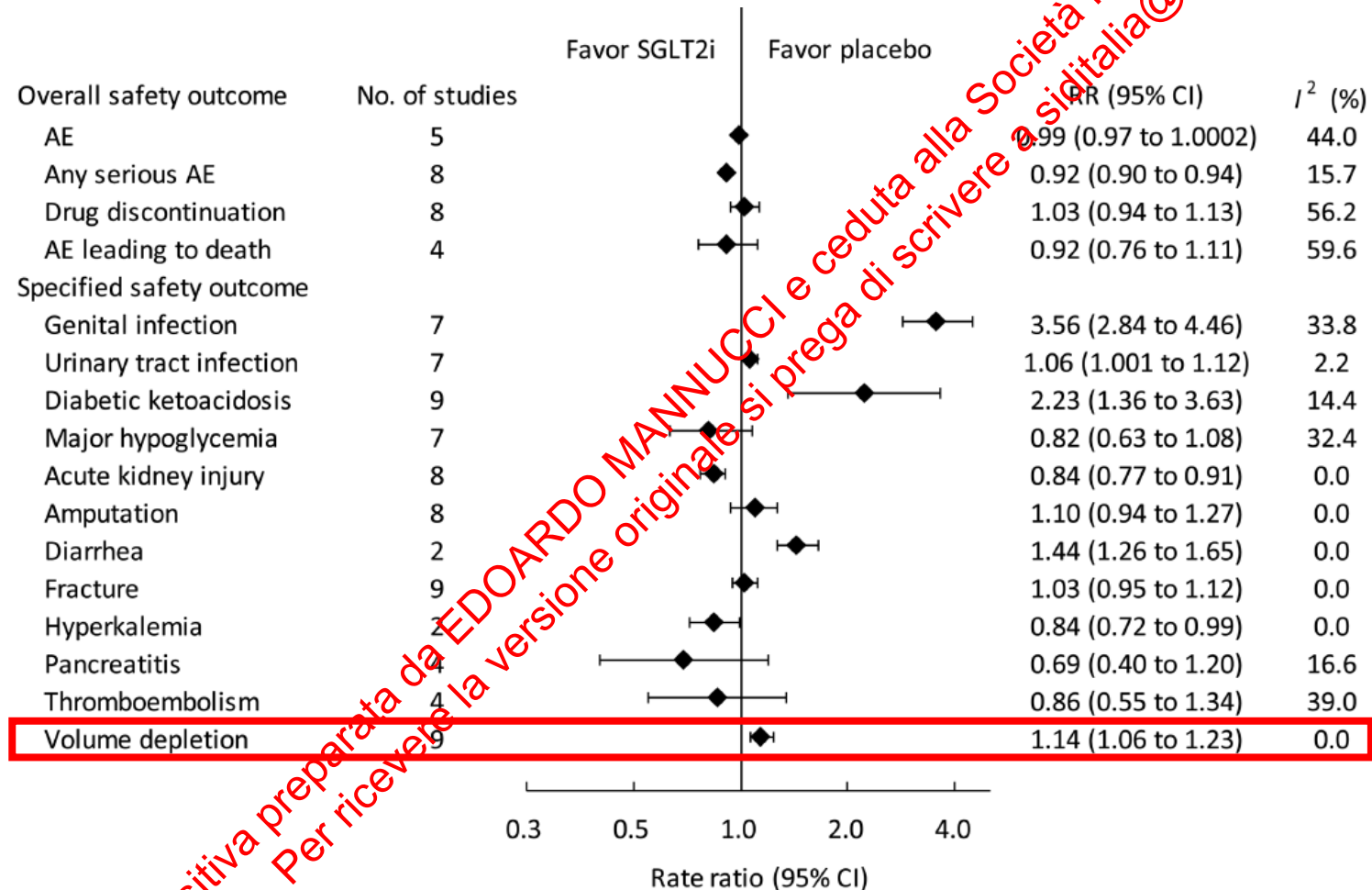
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SGLT2i and dehydration

A meta-analysis of placebo-controlled RCTs



Tolerability and safety issues

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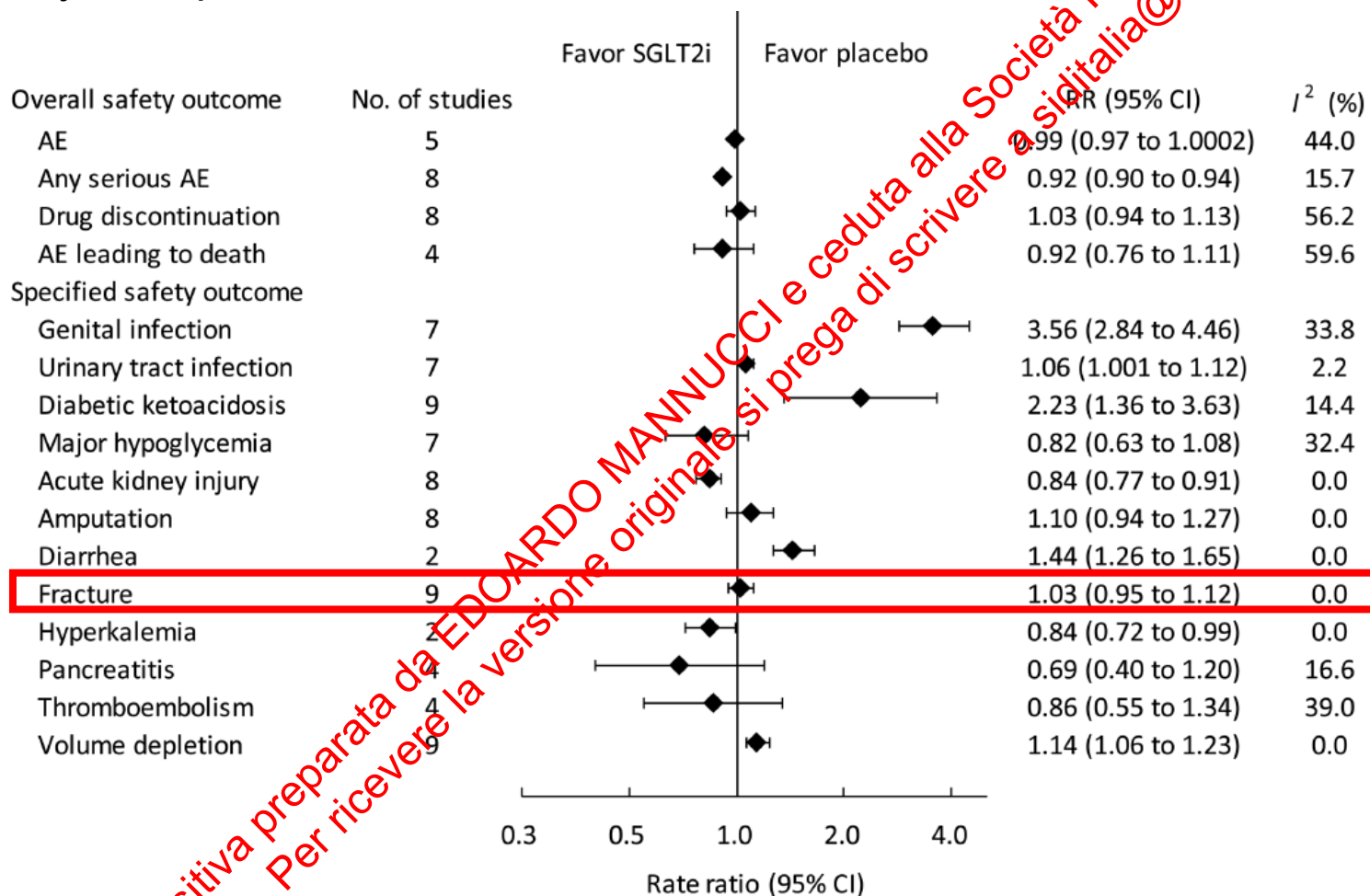
• **Fractures**

- Amputations

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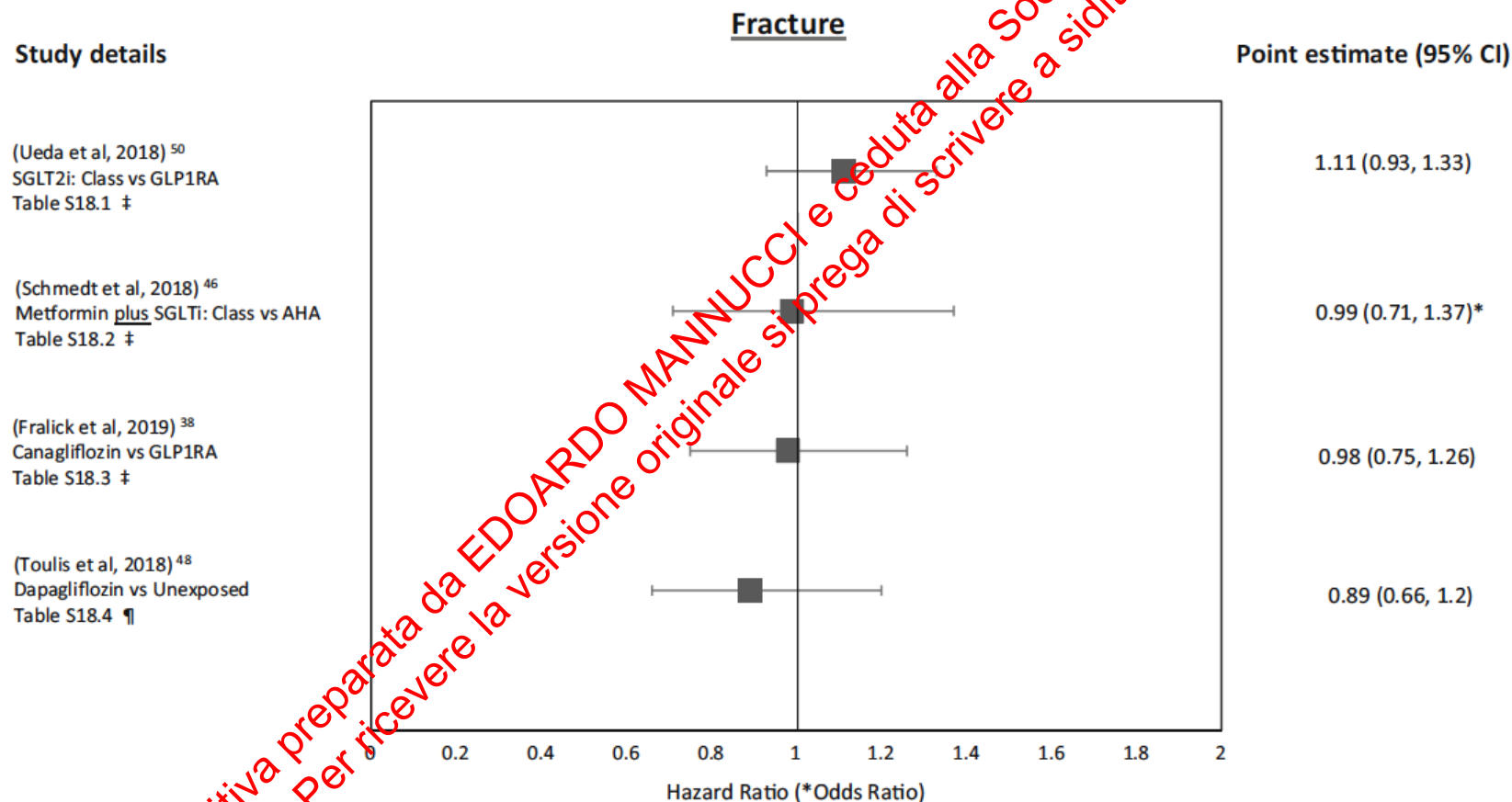
SGLT2i and bone fractures

A meta-analysis of placebo-controlled RCTs



SGLT2i and bone fractures

A systematic review of observational studies



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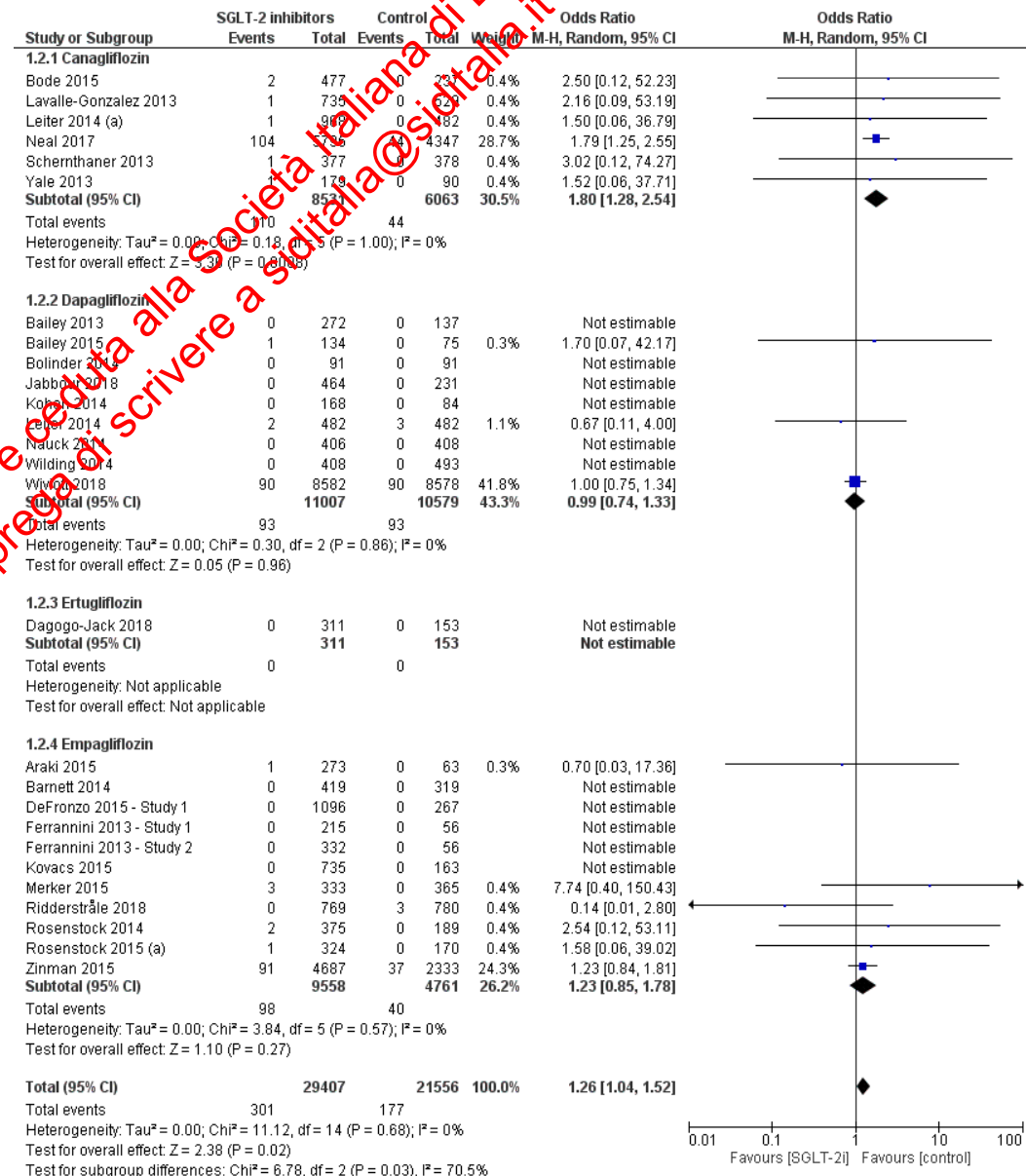
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SGLT2 inhibitors: effect on amputations

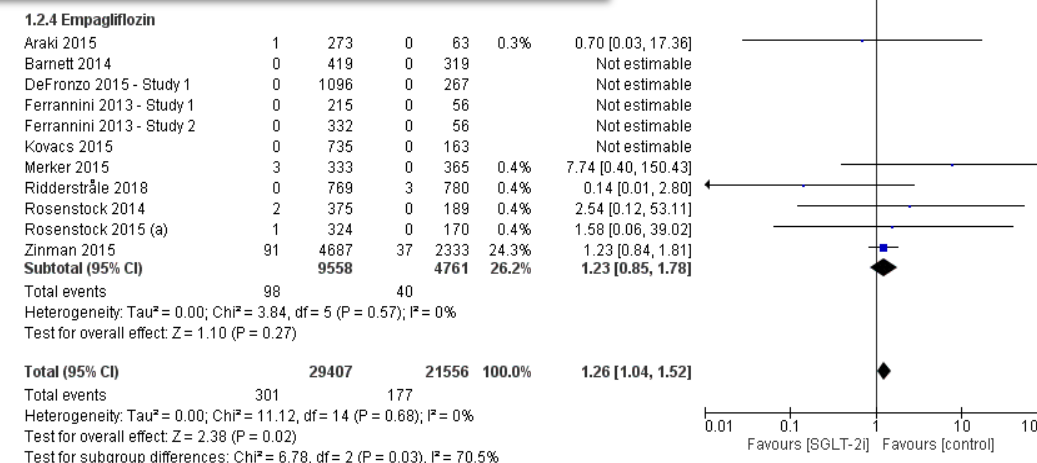
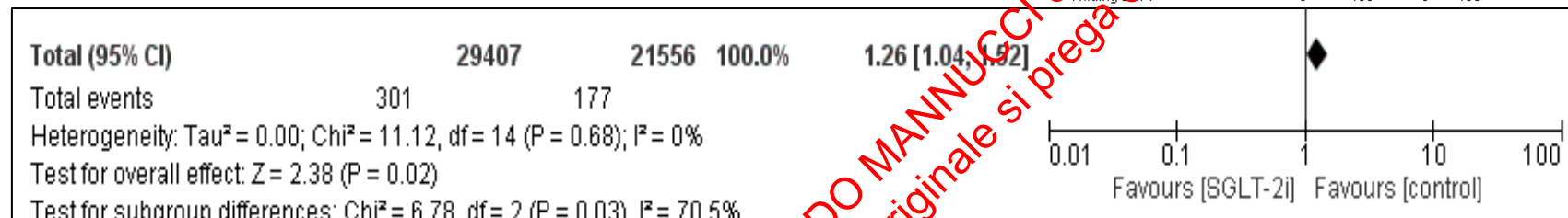
Meta-analysis of RCTs



Dicembrini I, et al. *Diabetes Res Clin Pract* 153:138-44, 2019

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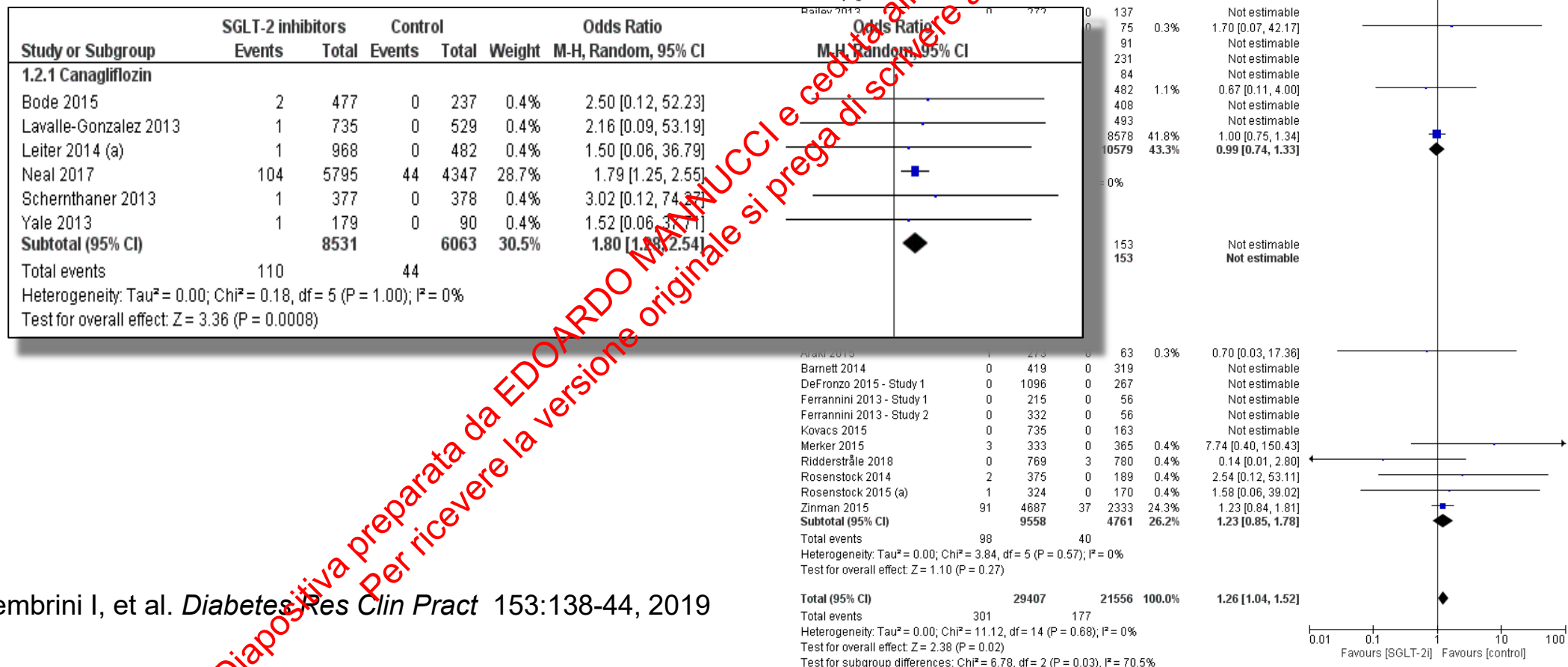
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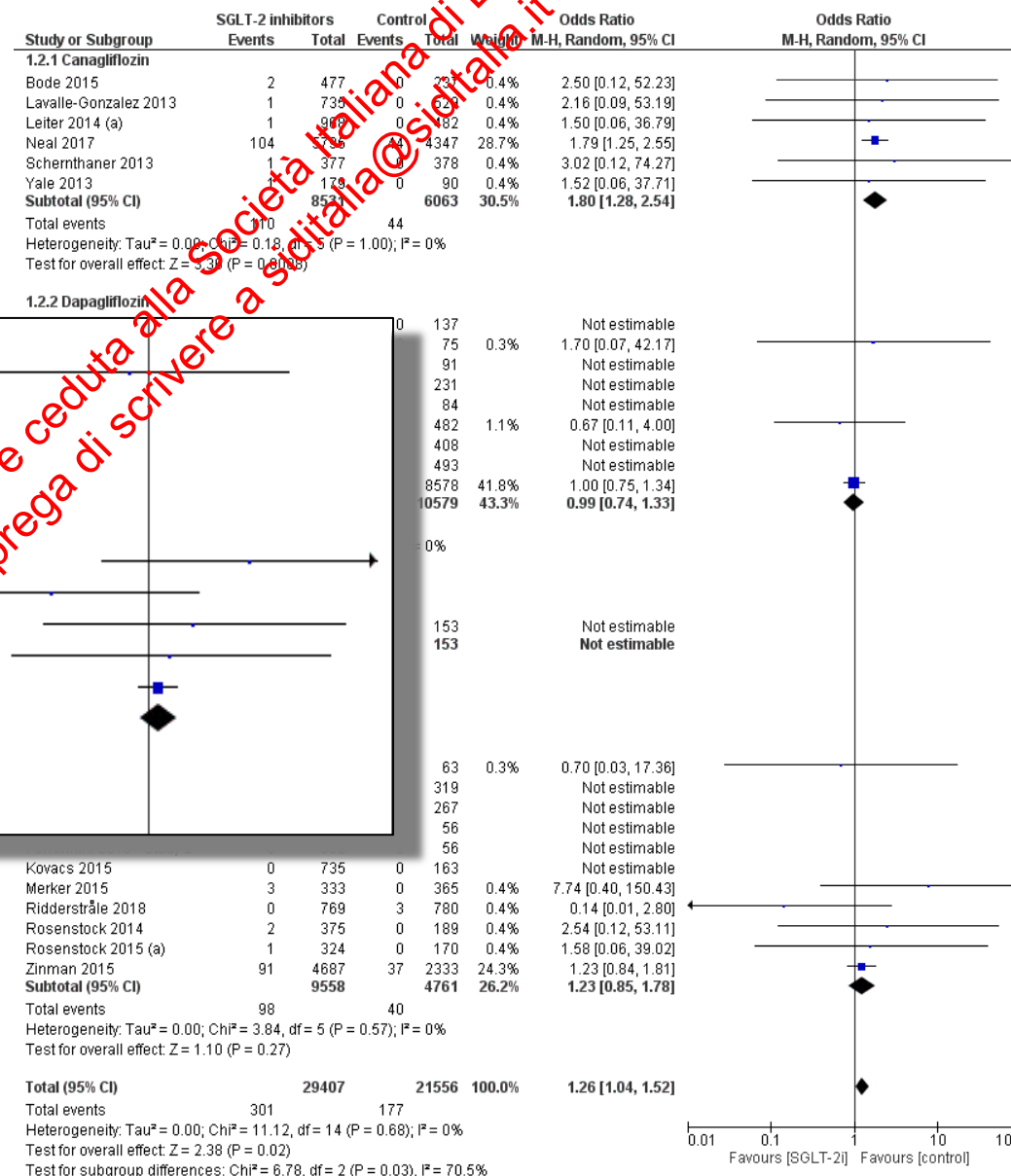
SGLT2 inhibitors: effect on amputations

Meta-analysis of RCTs

1.2.4 Empagliflozin

Study or Subgroup	Events	Total	Events	Total	Weight	Odds Ratio
Araki 2015	1	273	0	63	0.3%	0.70 [0.03, 17.36]
Barnett 2014	0	419	0	319		Not estimable
DeFronzo 2015 - Study 1	0	1096	0	267		Not estimable
Ferrannini 2013 - Study 1	0	215	0	56		Not estimable
Ferrannini 2013 - Study 2	0	332	0	56		Not estimable
Kovacs 2015	0	735	0	163		Not estimable
Merker 2015	3	333	0	365	0.4%	7.74 [0.40, 150.43]
Ridderstråle 2018	0	769	3	780	0.4%	0.14 [0.01, 2.80]
Rosenstock 2014	2	375	0	189	0.4%	2.54 [0.12, 53.11]
Rosenstock 2015 (a)	1	324	0	170	0.4%	1.58 [0.06, 39.02]
Zinman 2015	91	4687	37	2333	24.3%	1.23 [0.84, 1.81]
Subtotal (95% CI)		9558		4761	26.2%	1.23 [0.85, 1.78]

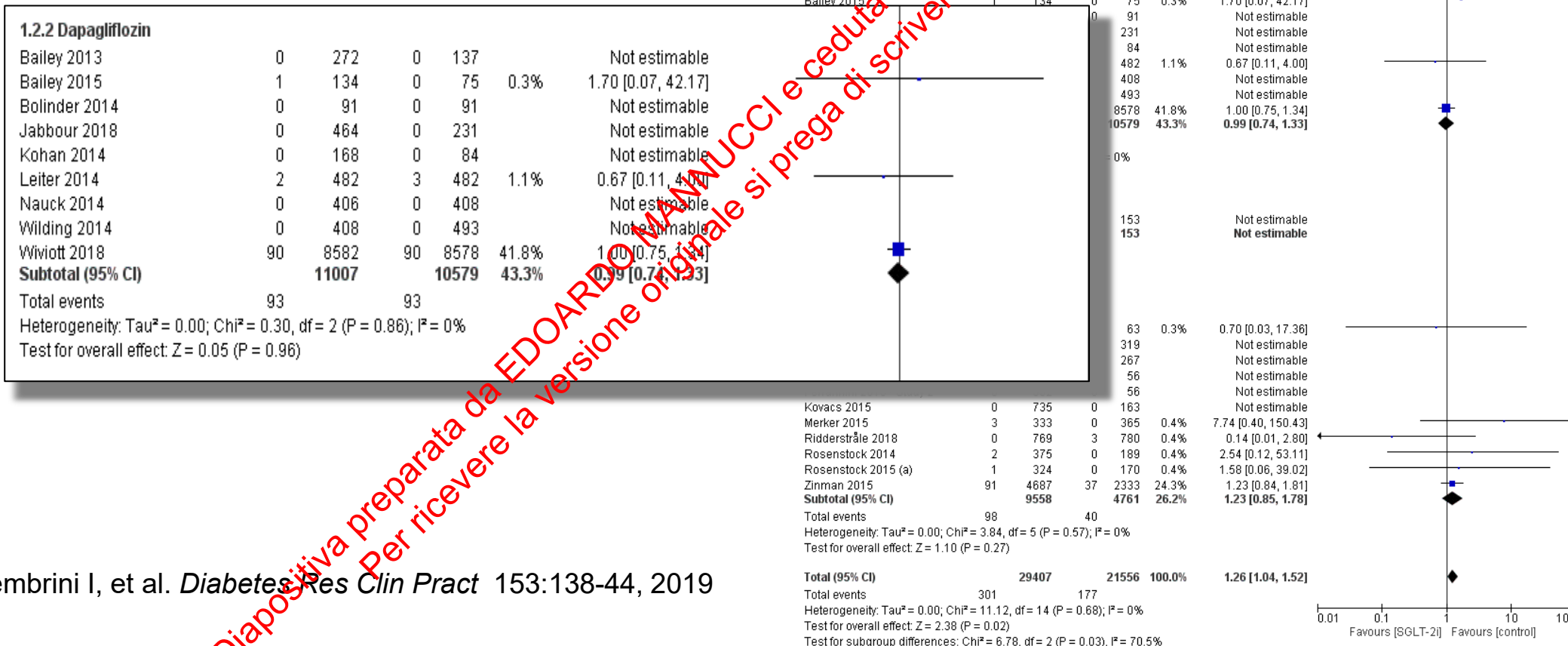
Total events 98 40
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.84$, $df = 5$ ($P = 0.57$); $I^2 = 0\%$
Test for overall effect: $Z = 1.10$ ($P = 0.27$)



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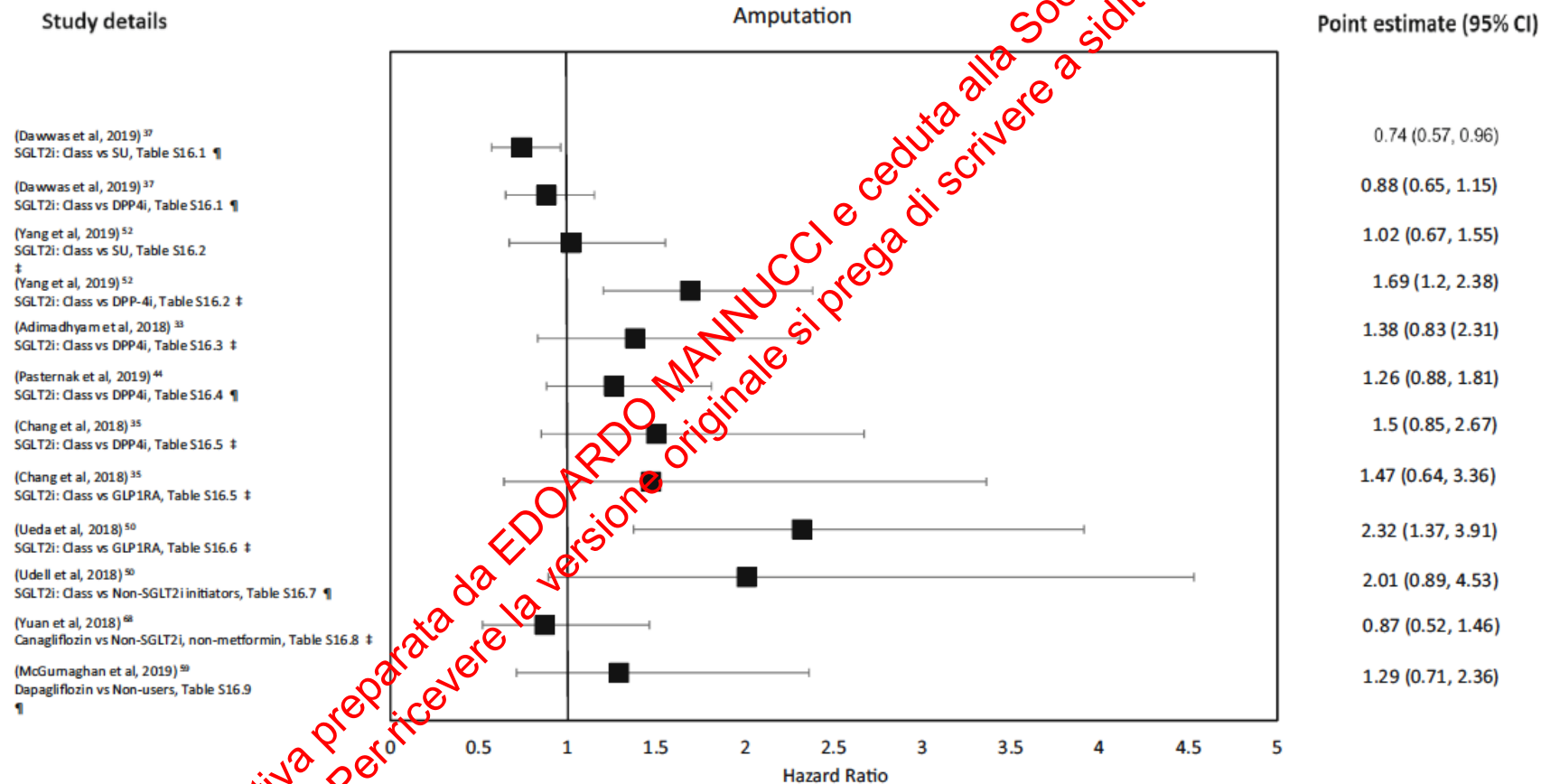
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