

SGLT2i e terapia di combinazione all'inizio: sempre con metformina?

Riccardo C. Bonadonna

**Dipartimento di Medicina e Chirurgia
Università di Parma e AOU di Parma**

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Riccardo C. Bonadonna dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Finanziamenti ricerca: Nessuno

Relatore a convegni: Sanofi, Eli Lilly Ltd, Boehringer-Ingelheim, Astra Zeneca

Board Member/Advisory Panel: Eli Lilly Ltd, Sanofi

Stock/Shareholder: Nessuno

Consulente: Nessuno

Dipendente: Nessuno

Altro: Nessuno

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Perché iniziare subito una terapia di combinazione?

- Grave scompenso glicometabolico
- Tempo come endpoint
- Paradigma «treat to benefit»
- Altro

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Dove trovare le indicazioni?

- Studi di «efficacy» (RCT)
- Analisi post-hoc degli RCT
- Studi di «effectiveness» (RWE)

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Dove trovare le indicazioni?

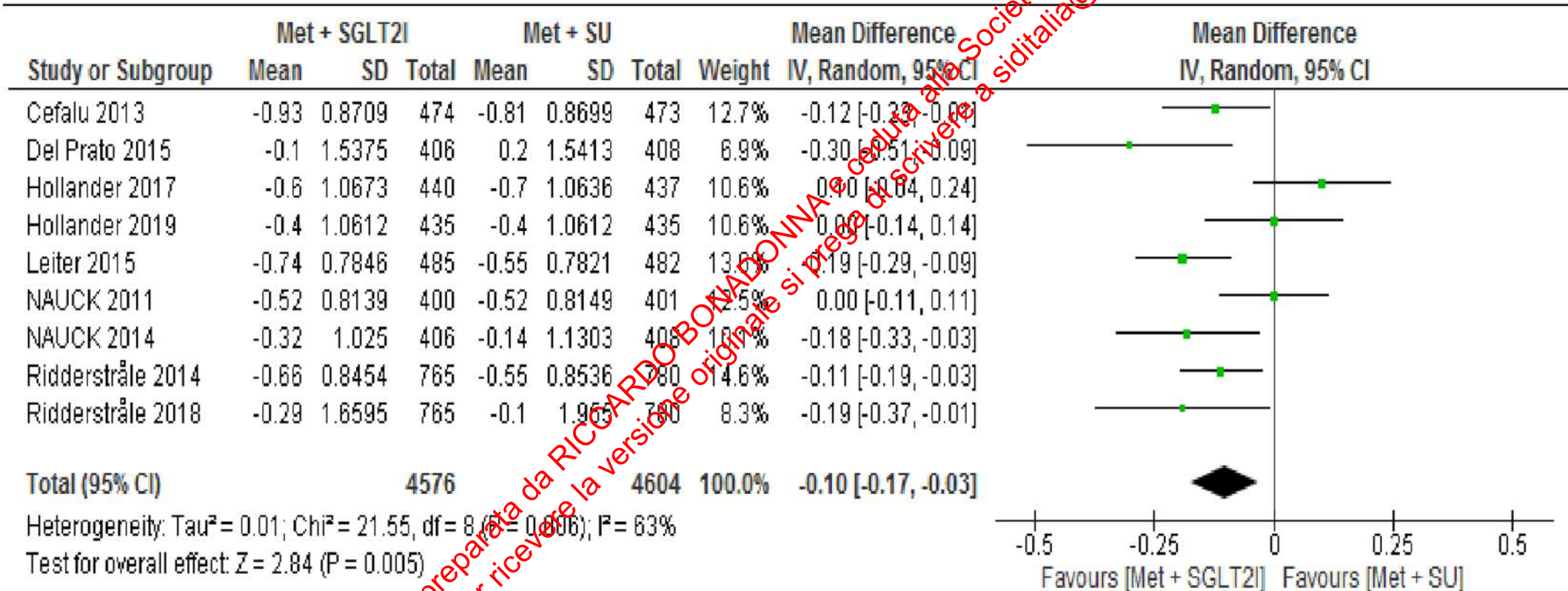
➤ Studi di «efficacy» (RCT)

- Analisi post-hoc degli RCT

- Studi di «effectiveness» (RWE)

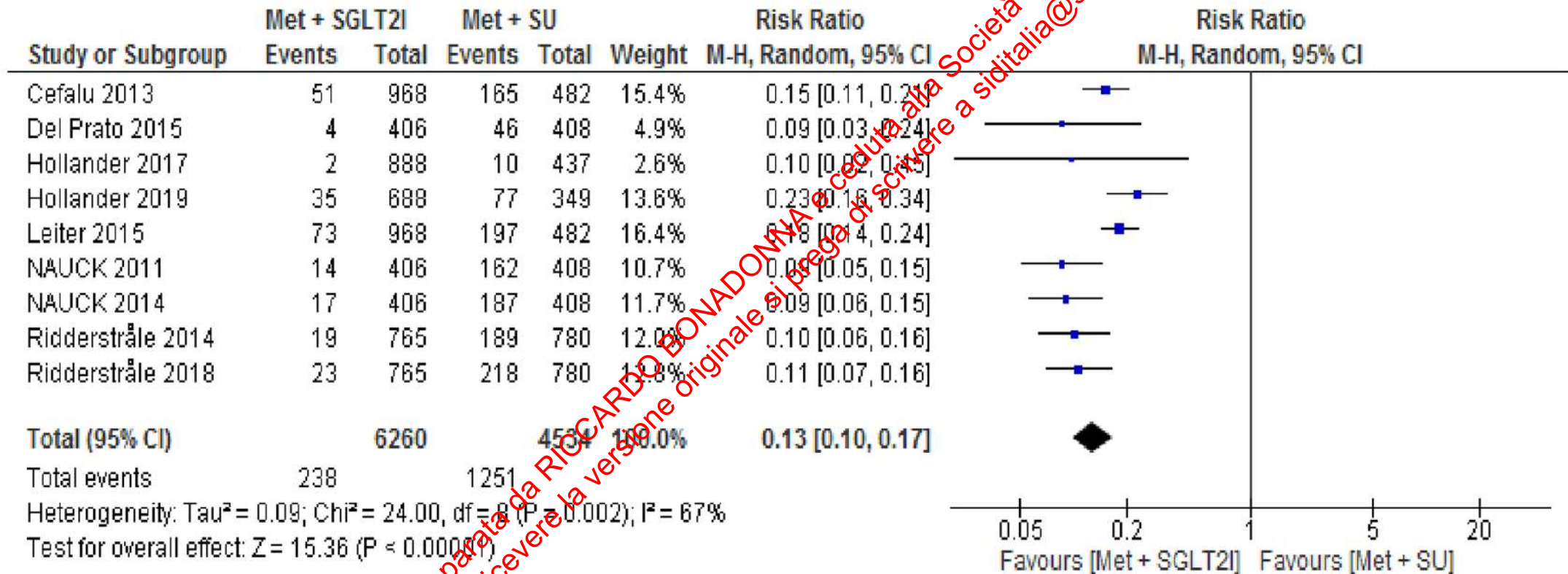
Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Comparison of **change in HbA1c (%)** from baseline between patients who were on metformin-SGLT2i or metformin-SU combination therapies – a meta-analysis of RCTs



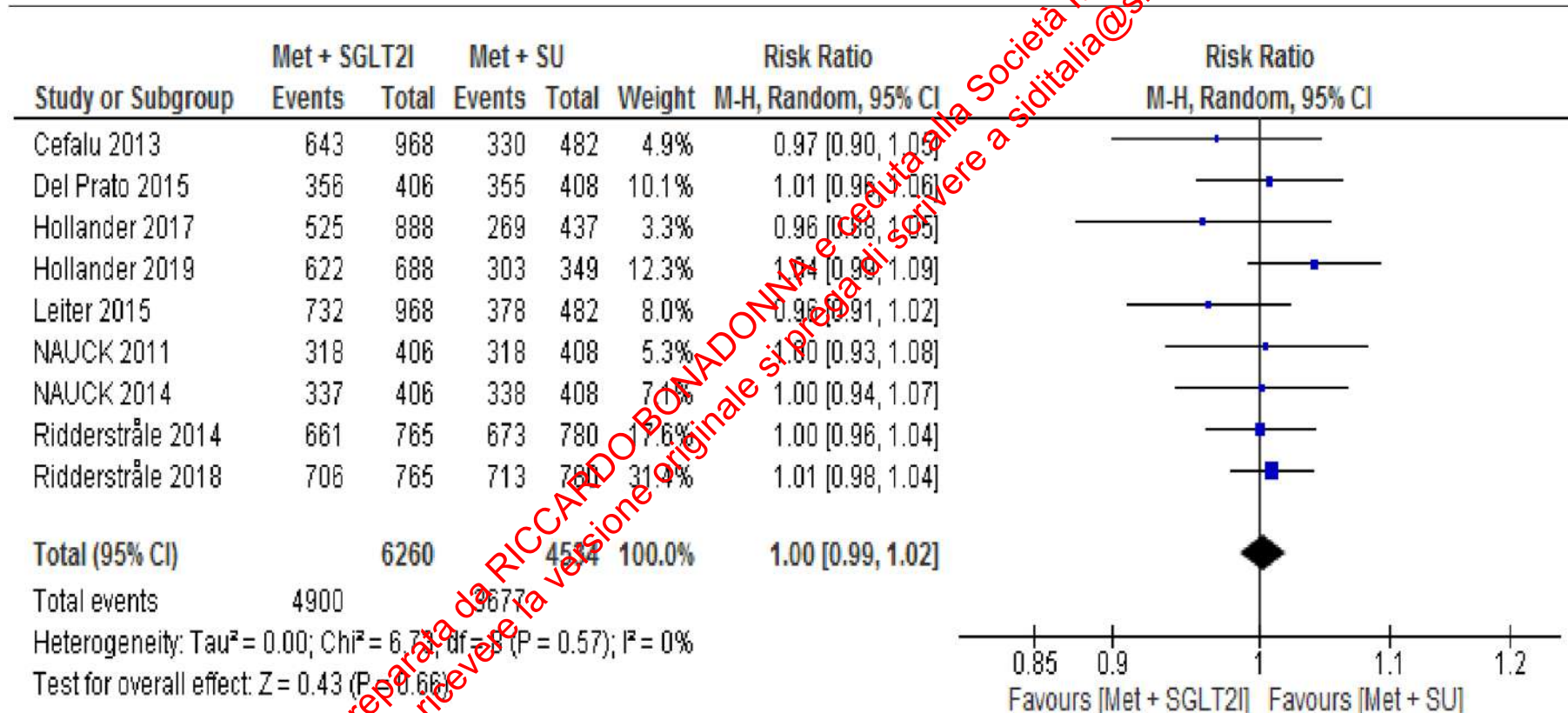
SD= standard deviation; CI= confidence interval; MD= mean difference; Met=metformin; SGLT2i= Sodium glucose co-transporter 2 inhibitor; SU= sulfonylurea

Risk of hypoglycemia between patients who were on metformin-SGLT2i or metformin-SU combination therapies – a meta-analysis of RCTs



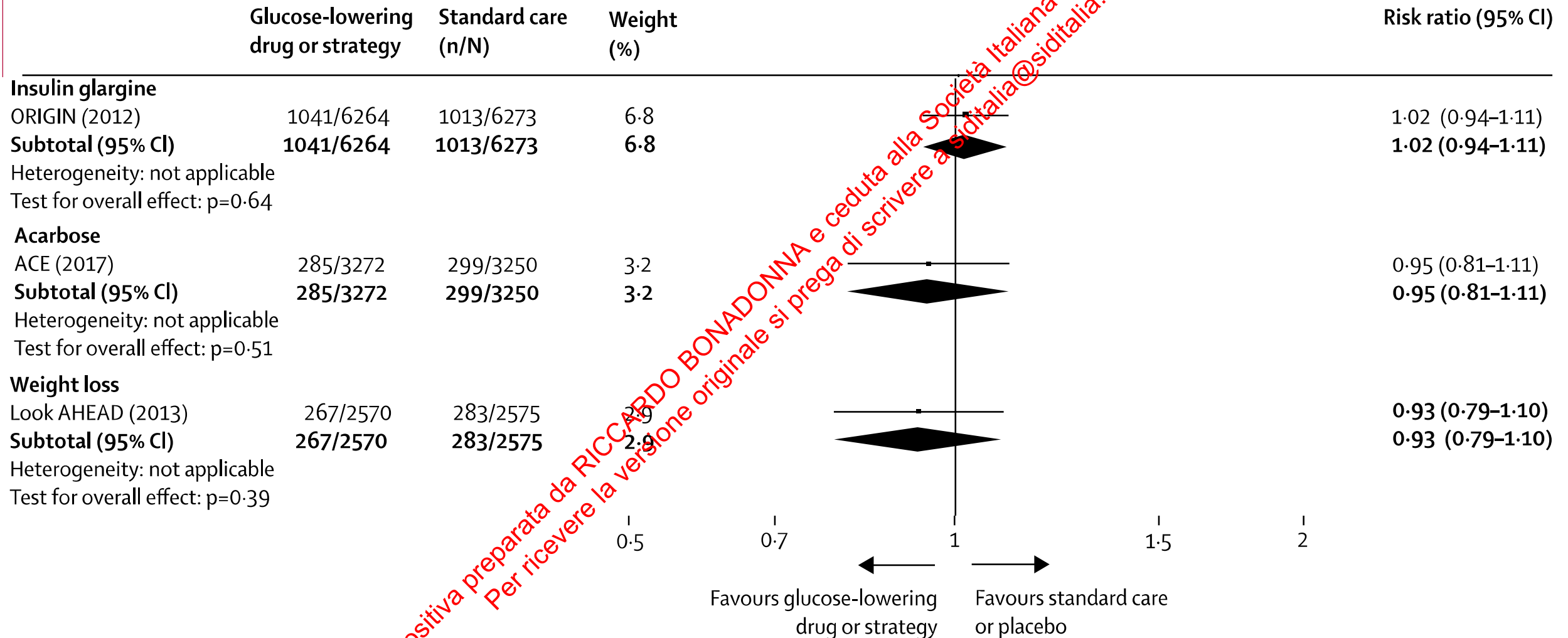
RR= Risk Ratio; CI= confidence interval; df= degrees of freedom; Met=Metformin; SGLT2i= Sodium-glucose co-transporter 2 inhibitor; SU= Sulfonylurea

Risk of adverse events between patients who were on metformin-SGLT2i or metformin-SU combination therapies – a meta-analysis of RCTs



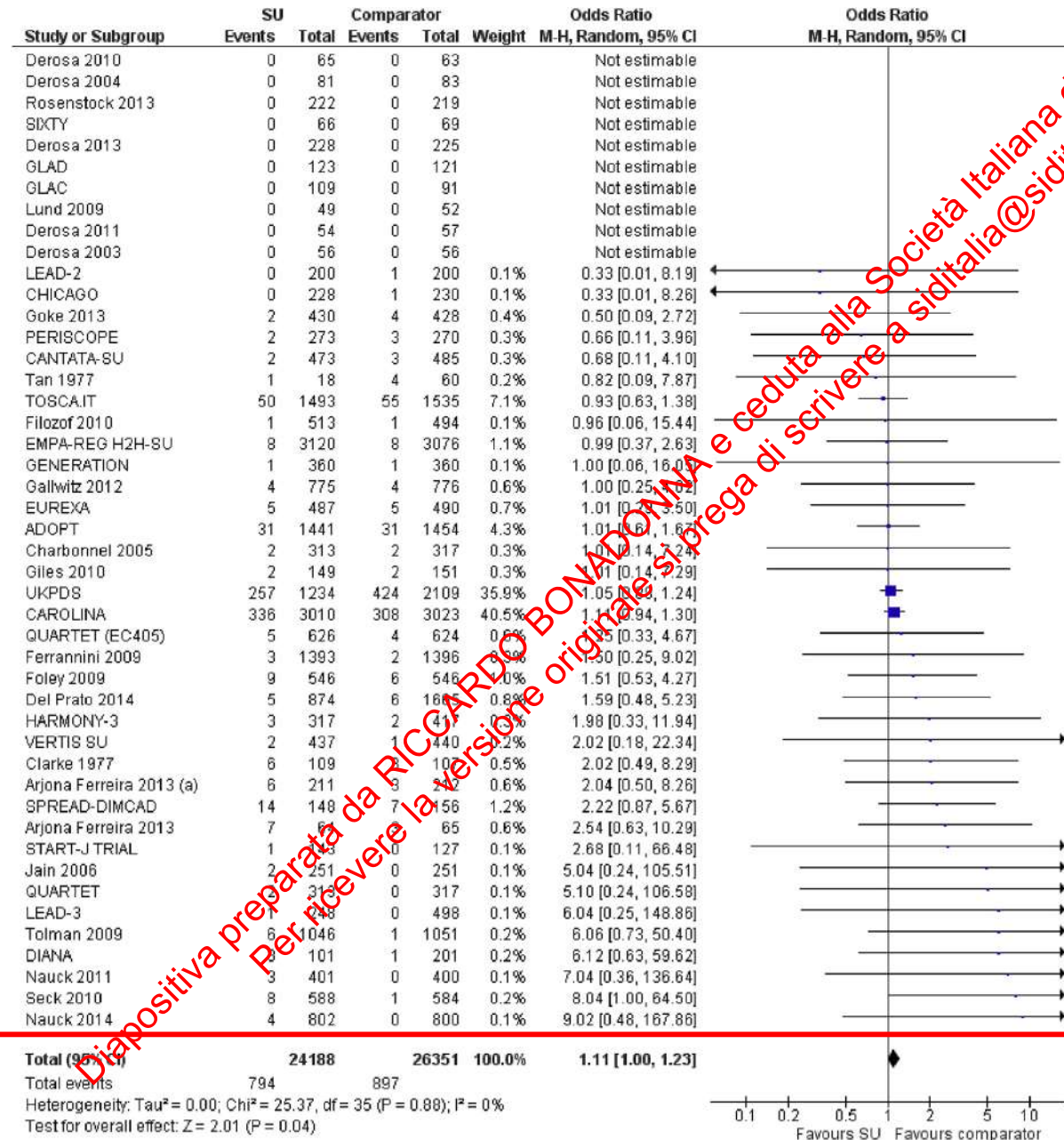
RR= Risk Ratio; CI= confidence interval; df= degrees of freedom; Met=Metformin; SGLT2i= Sodium-glucose co-transporter 2 inhibitor; SU= Sulfonylurea

Meta-analysis of insulin, acarbose and weight loss CVOT for the endpoint MACE in T2DM



Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia
 Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Insulin secretagogues (slightly) increase all-cause mortality, do not they?

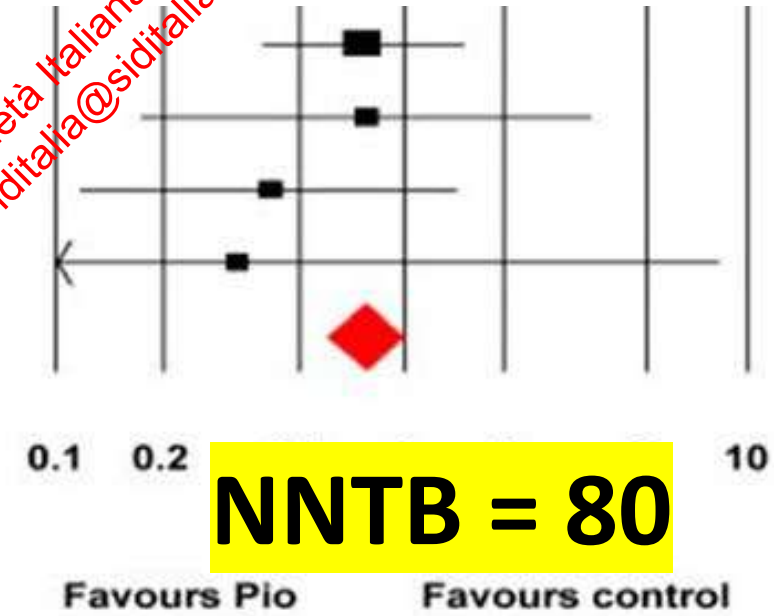


Meta-analysis of DPP4i trials for the endpoint MACE in T2DM



Pioglitazone reduces the risk of first MACE: a meta-analysis of RCTs in patients with type 2 diabetes

TOSCA.IT	0.776	0.400	1.503	0.452
PROFIT-J	0.789	0.175	3.563	0.758
J-SPIRIT	0.415	0.118	1.462	0.171
PERISCOPE	0.336	0.014	8.279	0.505
	0.773	0.600	0.997	0.007



Forest plot comparing Pioglitazone (Pio) Vs. Control on Stroke

Study name

Statistics for each study

MH odds ratio and 95% CI

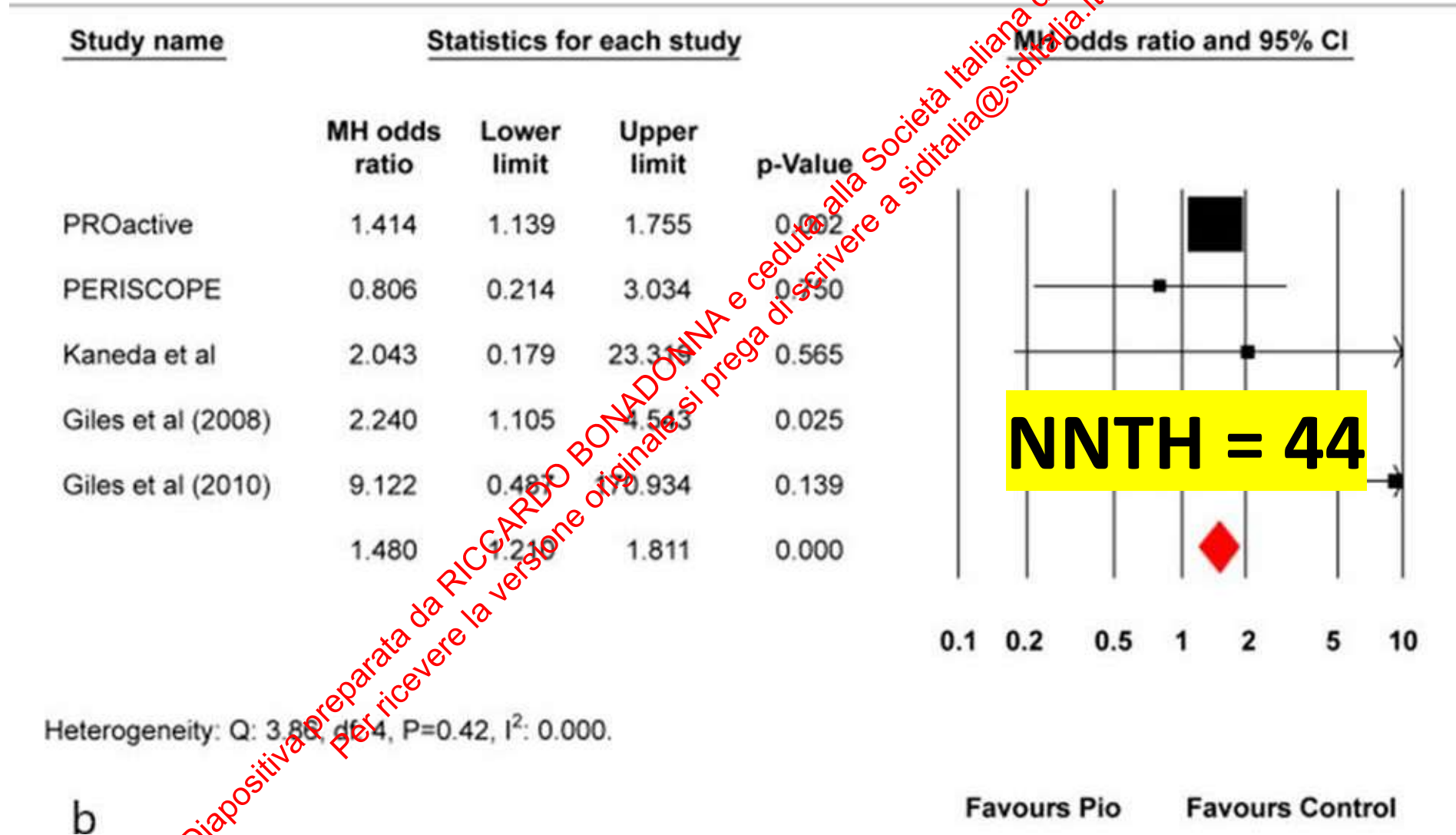
MH odds
ratio

Lower
limit

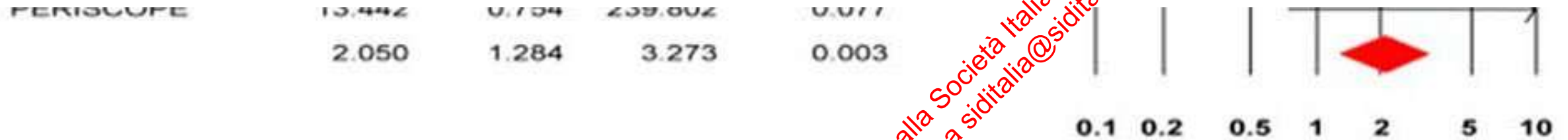
Upper
limit

P-Value

Pioglitazone increases the risk of hospitalization for heart failure: a meta-analysis of RCTs in patients with type 2 diabetes



Pioglitazone increases the risk of bone fractures in women: a meta-analysis of RCTs in patients with type 2 diabetes



Forest plot comparing Pioglitazone (Pio) Vs. Control on fracture risk (Female)

Study name

Statistics for each study

MH odds ratio and 95% CI

MH odds
ratio

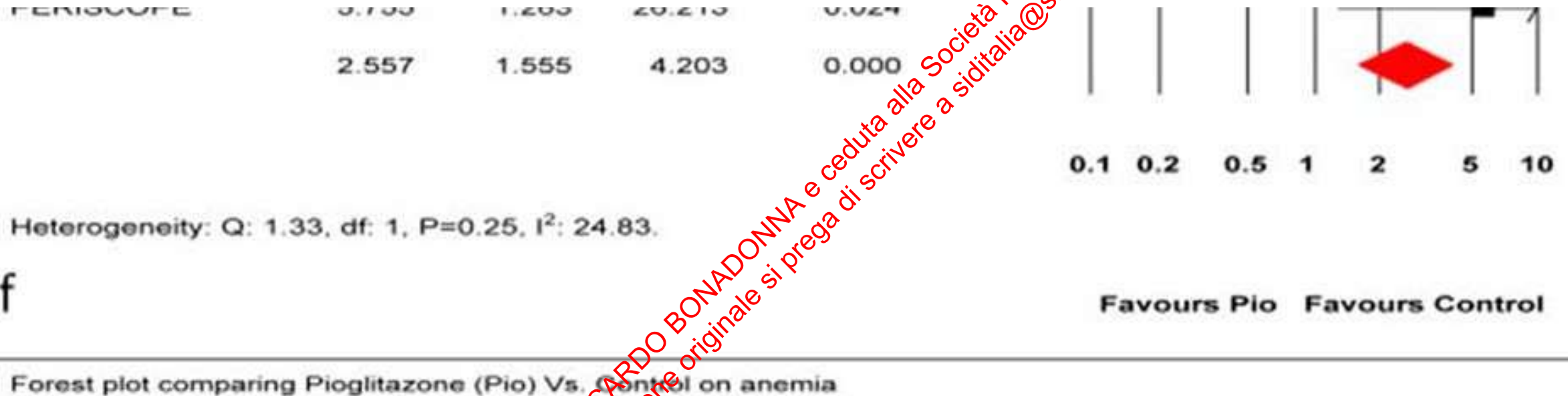
Lower
limit

Upper
limit

p-Value

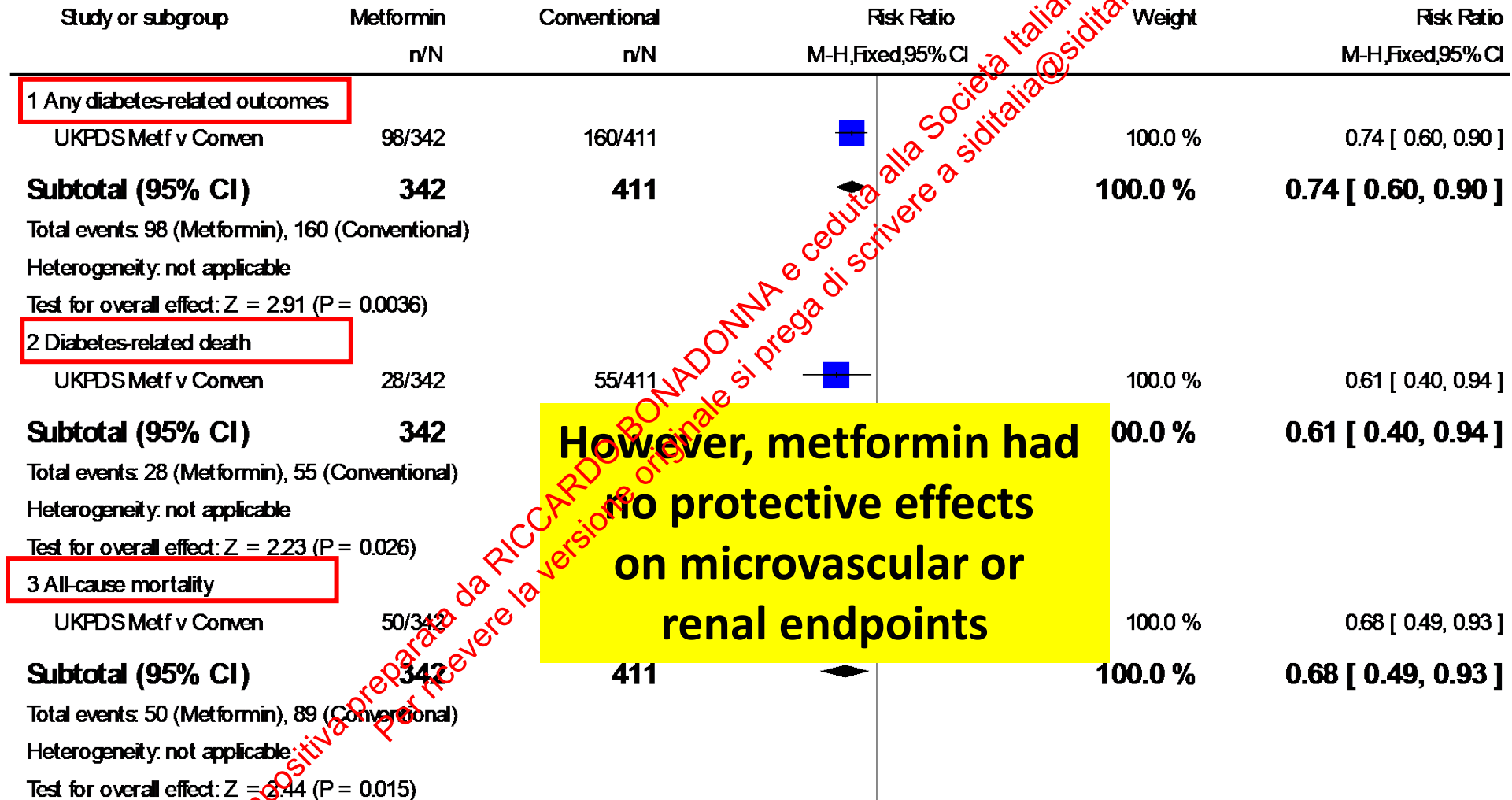
Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Pioglitazone and the risk of bladder cancer: a meta-analysis of RCTs in patients with type 2 diabetes



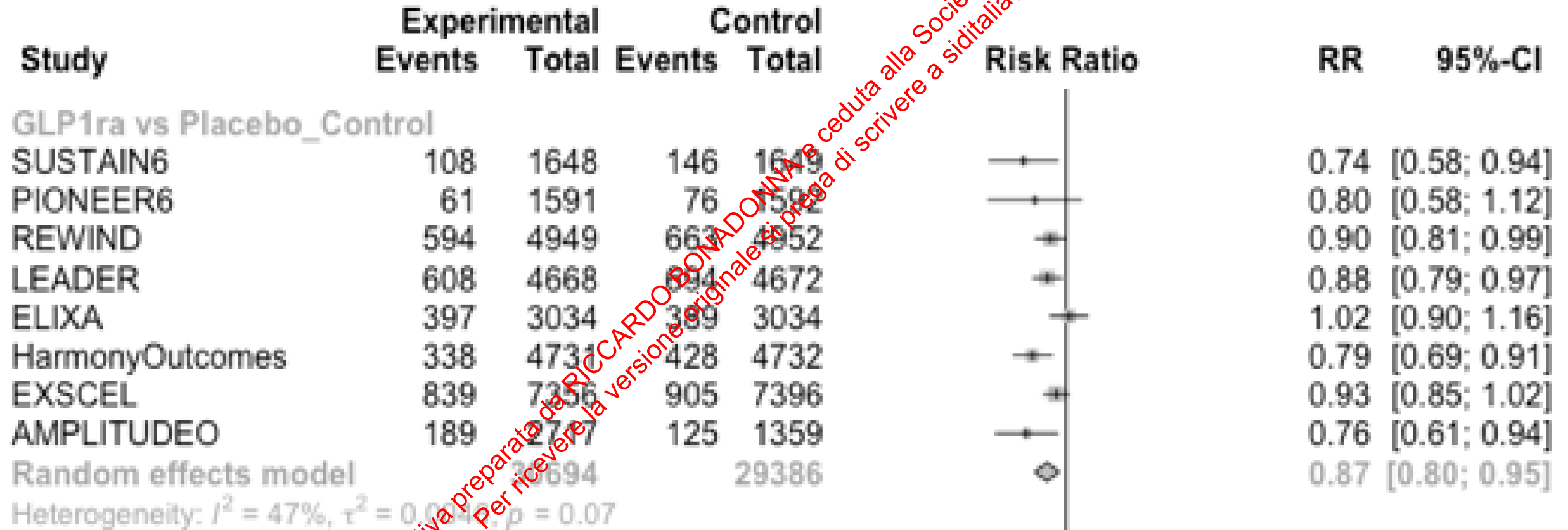
Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

UKPDS. Metformin vs Conventional treatment: diabetes related outcomes, mortality



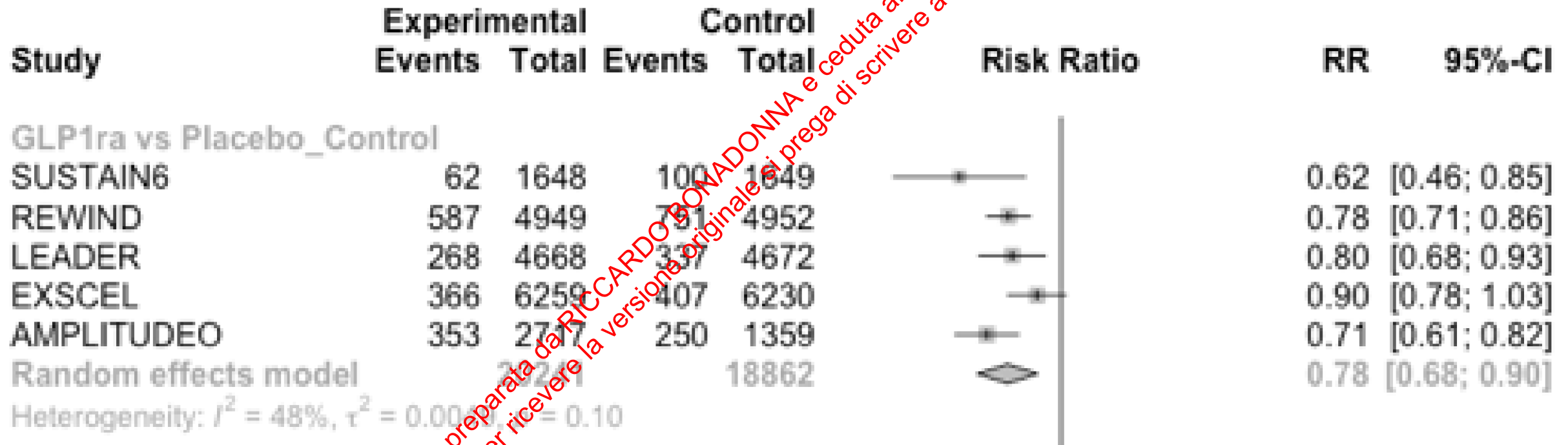
**However, metformin had
no protective effects
on microvascular or
renal endpoints**

GLP1Ra and the risk of first MACE: meta-analysis of RCTs in patients with type 2 diabetes



Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

GLP1Ra and the risk of composite renal outcome: meta-analysis of RCTs in patients with type 2 diabetes



Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Dove trovare le indicazioni?

✓ Studi di «efficacy» (RCT)

✎ Analisi post-hoc degli RCT

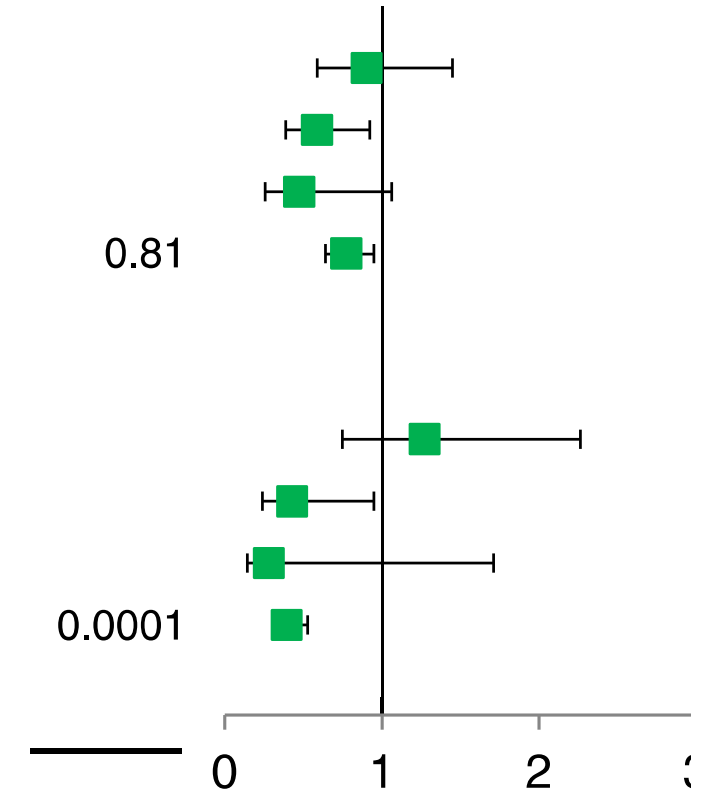
• Studi di «effectiveness» (RWE)

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Pioglitazone and «treat to benefit»: does the dose matter?

The IRIS Study

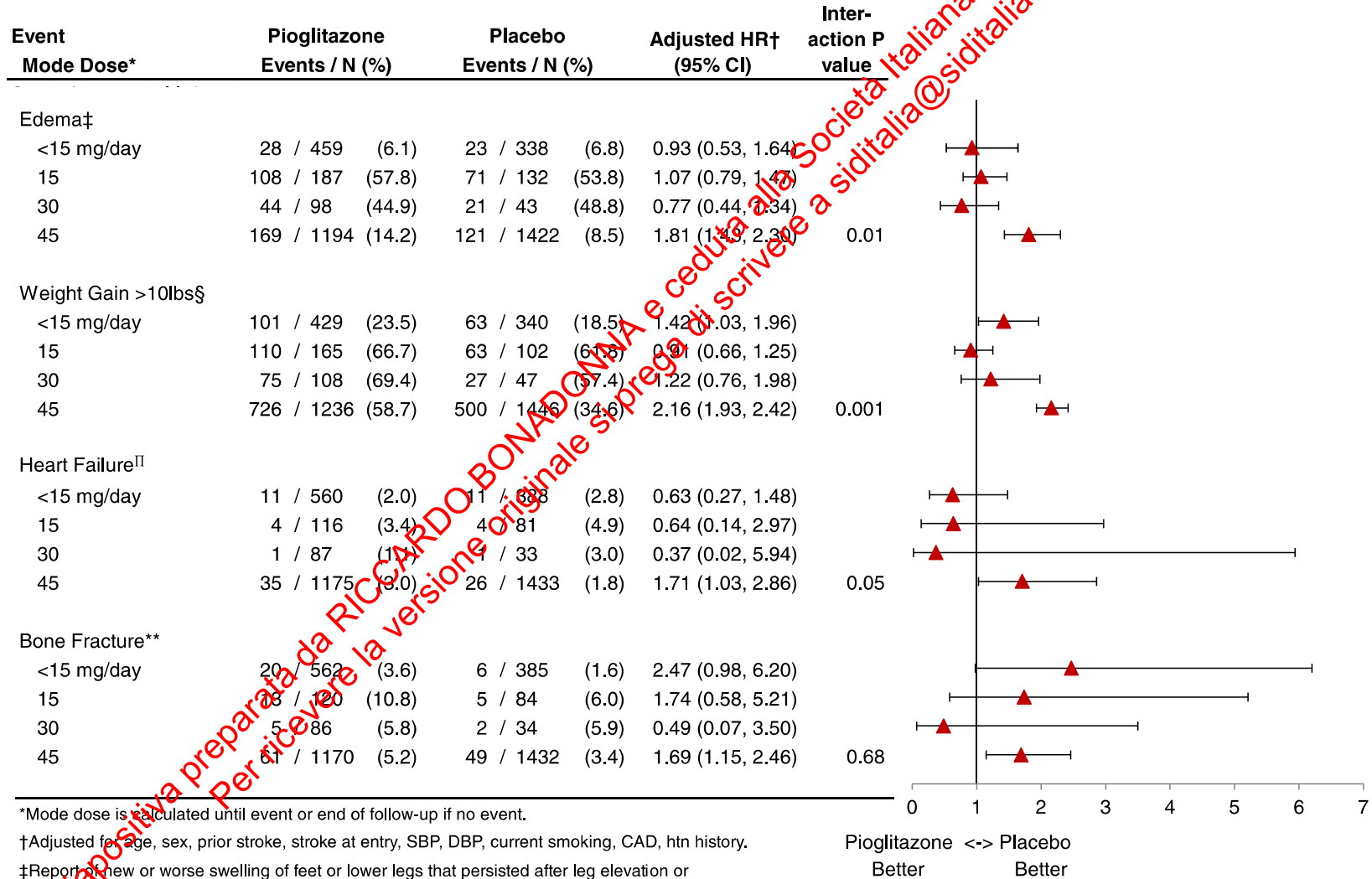
Event	Pioglitazone		Placebo		Adjusted HR†	Inter-action P
Mode Dose*	Events / N (%)		Events / N (%)		(95% CI)	value
Stroke/Myocardial Infarction						
<15 mg/day	32 / 546	(5.9)	25 / 366	(6.8)	0.89 (0.53, 1.51)	0.81
15	23 / 128	(18.0)	34 / 105	(32.4)	0.53 (0.30, 0.91)	
30	12 / 89	(13.5)	7 / 35	(20.0)	0.40 (0.15, 1.07)	
45	114 / 1175	(9.7)	179 / 1429	(12.5)	0.74 (0.59, 0.94)	
New Onset Diabetes						
<15 mg/day	29 / 573	(5.1)	16 / 389	(4.1)	1.31 (0.71, 2.44)	0.0001
15	7 / 114	(6.1)	11 / 81	(13.6)	0.35 (0.13, 0.94)	
30	3 / 86	(3.5)	2 / 33	(6.1)	0.18 (0.02, 1.81)	
45	34 / 1165	(2.9)	120 / 1432	(8.4)	0.31 (0.21, 0.46)	



Pioglitazone <-> Placebo
Better Better

Pioglitazone and adverse effects: does the dose matter?

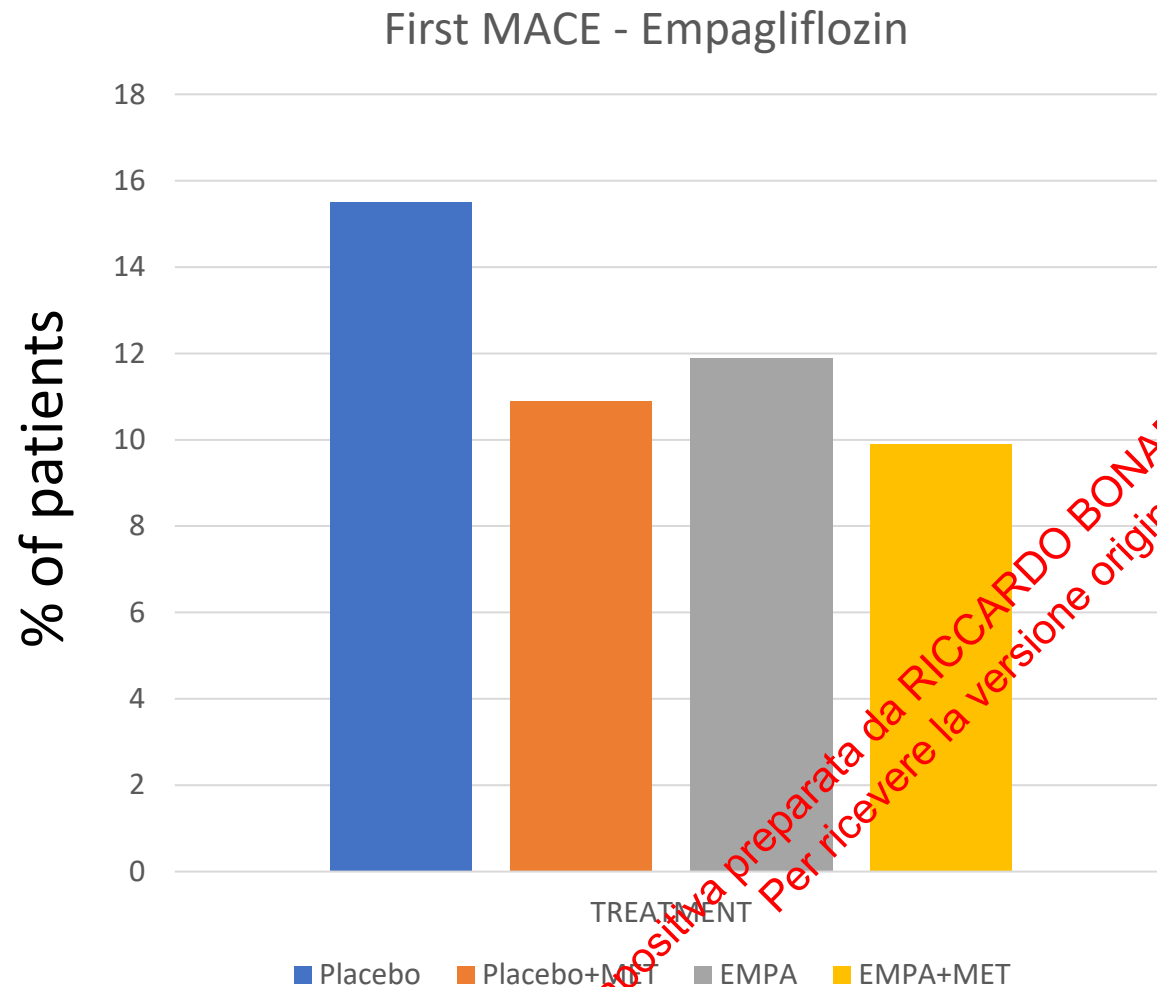
The IRIS Study



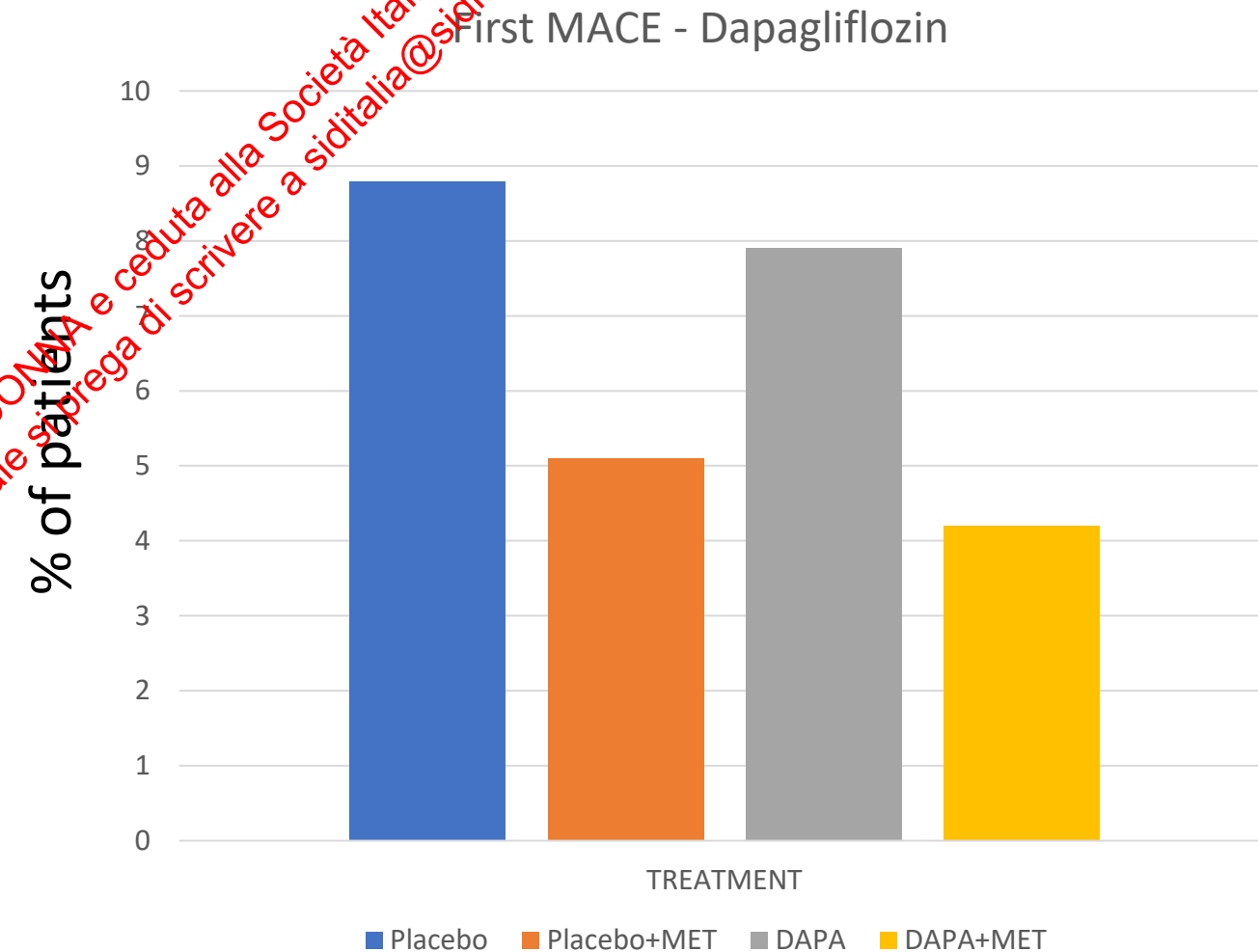
Time to any MACE in clinical trials assessing SGLT2 inhibitors.
In those without metformin, the combination SGLT2i+GLP1Ra is associated to a lower risk of MACE

Outcomes	Anticipated absolute effects* (95% CI)			N participants (studies)	Certainty of the evidence ^{a,b} (GRADE)
	Risk with other treatments	Risk with GLP1RAs without metformin	Relative effect (95% CI)		
SGLT2 inhibitors without metformin compared to placebo for prevention of cardiovascular events					
MACE	165 per 1000	85 per 1000 (72–101)	HR 0.68 (0.57–0.81)	5141 (2 RCTs ^{3,25,26})	⊕⊕○○ LOW
Cardiovascular death	88 per 1000	44 per 1000 (50–64)	HR 0.50 (0.34–0.72)	1827 (1 RCT ^{3,26})	⊕⊕⊕○ VERY LOW
First occurrence of stroke	78 per 1000	17 per 1000 (10–28)	HR 0.22 (0.13–0.36)	1827 (1 RCT ^{3,26})	⊕⊕⊕○ VERY LOW

Cumulative incidence of first MACE in the EMPA-REG Outcome and in the DECLARE-TIMI trials



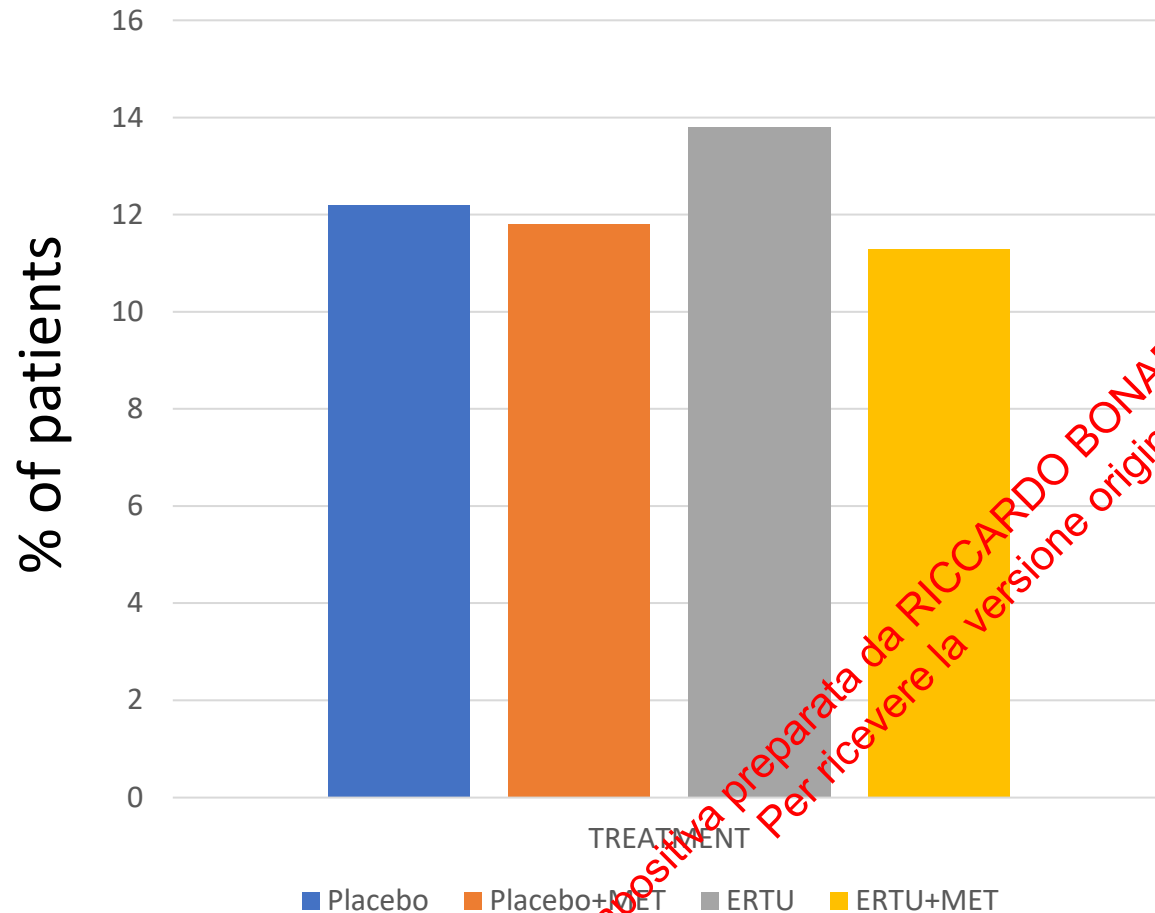
Zinman B et al.; NEJM 2015



Cahn A et al.; Diab Obes Metabol 2020

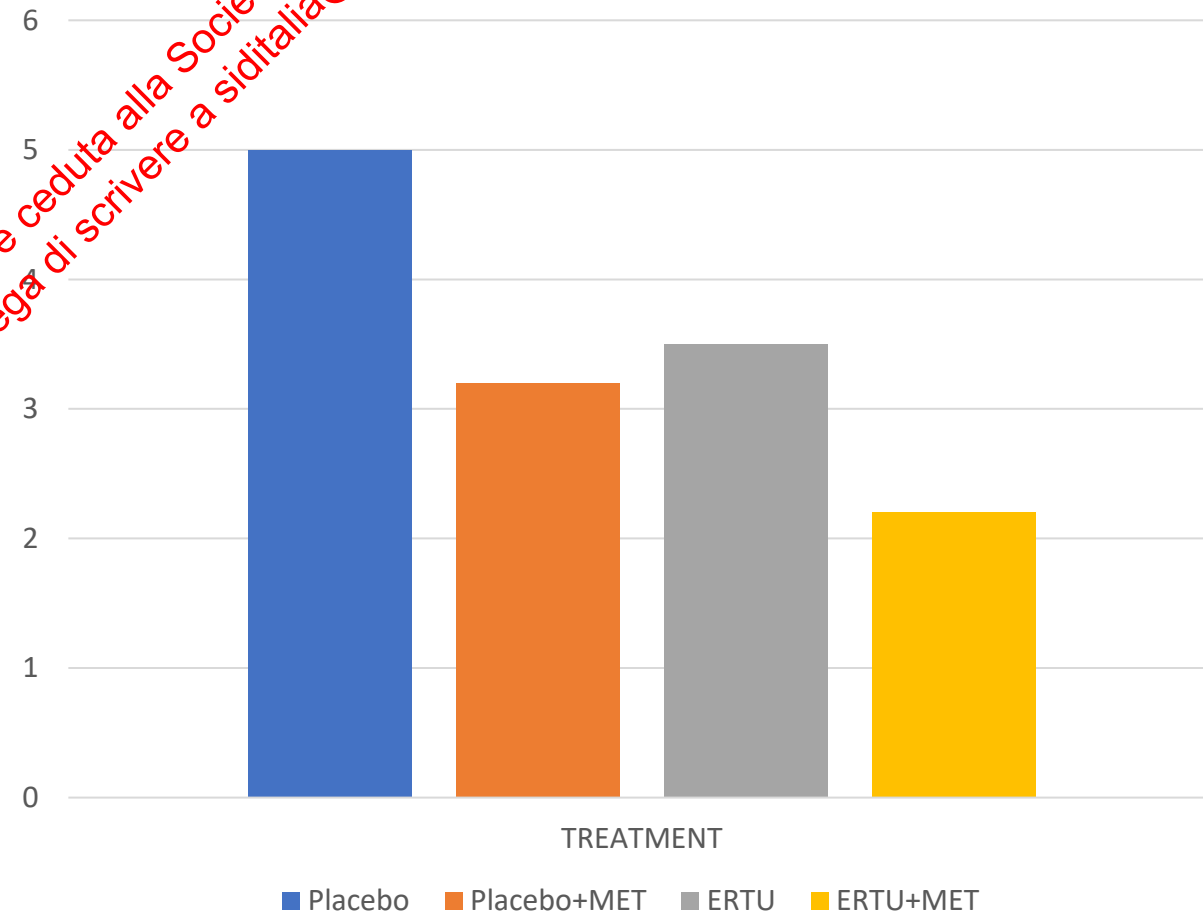
Cumulative incidence of first MACE and first HHF hospitalization in the VERTIS trial

First MACE - Ertugliflozin



Dagogo-Jack S et al.; Diab Obes Metabol 2022

First HHF hospitalization - Ertugliflozin



Cahn A et al.; Diab Obes Metabol 2020

Dove trovare le indicazioni?

✓ Studi di «efficacy» (RCT)

✓ Analisi post-hoc degli RCT

✗ Studi di «effectiveness» (RWE)

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Glucose- and weight-lowering effectiveness of DPP4i, SGLT2i and SU as add-on to metformin in type 2 diabetes: an effectiveness study in 6,310 PS-matched patients from the Mediterranean area (FU: ≥ 2 yrs)

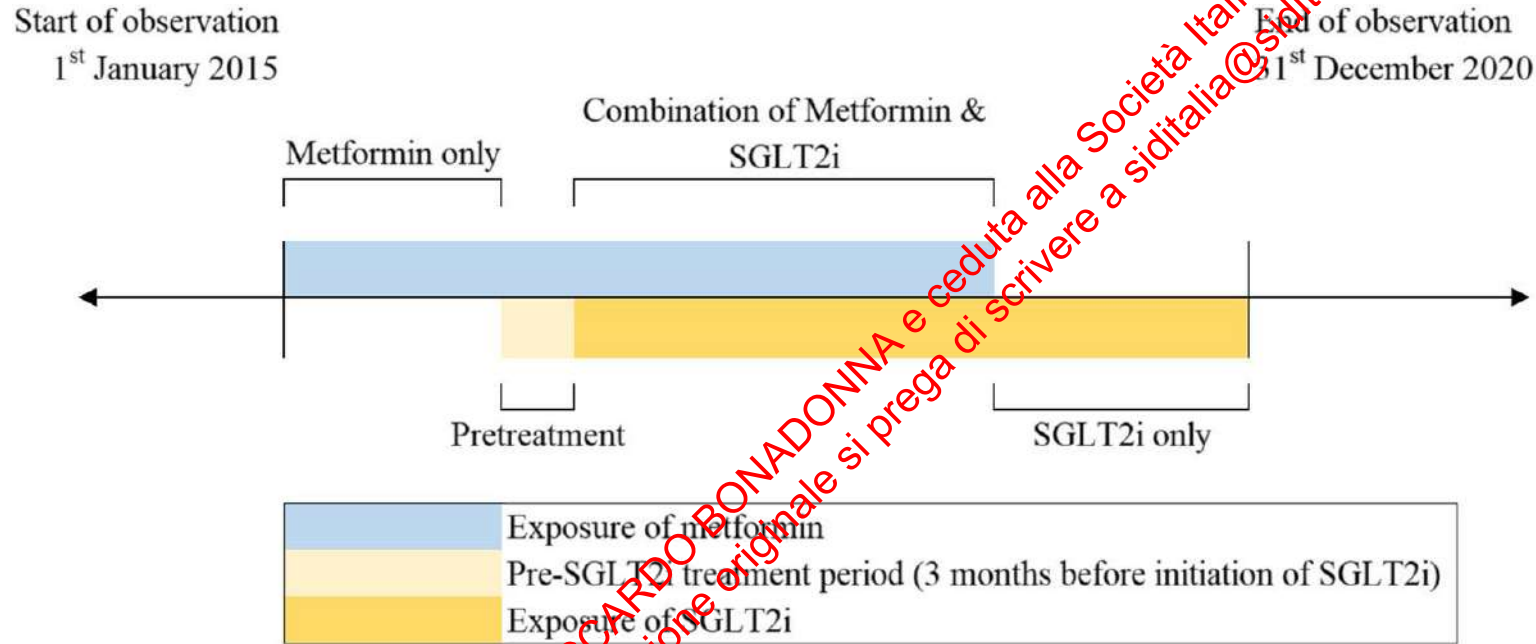
Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Magnitude of the effect size of DPP4i, SGLT2i and SU as add-on to metformin between treatments for the different outcomes in type 2 diabetes: an effectiveness study in 6,310 PS-matched patients from the Mediterranean area (FU: ≥ 2 yrs)

Clinical outcome	DPP-4i vs. SGLT-2i	DPP-4i vs. SU	SGLT-2i vs SU
HbA1c Reduction	Trivial effect	Trivial effect	Trivial effect
Weight reduction	Medium effect favouring SGLT-2i	Medium-small effect favouring DPP4i	Medium effect favouring SGLT-2i
HbA1c $\geq 0.5\%$ Reduction	Trivial effect	Trivial effect	Trivial effect
Weight reduction of $\geq 3\%$	Large effect favouring SGLT-2i	Medium effect favouring DPP4i	Large effect favouring SGLT-2i
HbA1c $\geq 0.5\%$ + weight reduction $\geq 3\%$	Medium effect favouring SGLT-2i	Medium effect favouring DPP4i	Large effect favouring SGLT-2i
Users reaching target of HbA1c $< 7\%$	Trivial effect	Trivial effect	Trivial effect
SBP and DBP decrease	Small effect favouring SGLT-2i	Trivial effect	Small effect favouring SGLT-2i
Total Cholesterol decrease	Trivial effect	Trivial effect	Small effect favouring SU
HDL increase	Medium effect favouring SGLT-2i	Trivial effect	Medium effect favouring SGLT-2i
LDL decrease	Trivial effect	Trivial effect	Trivial effect
Triglycerides decrease	Trivial effect	Trivial effect	Trivial effect

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

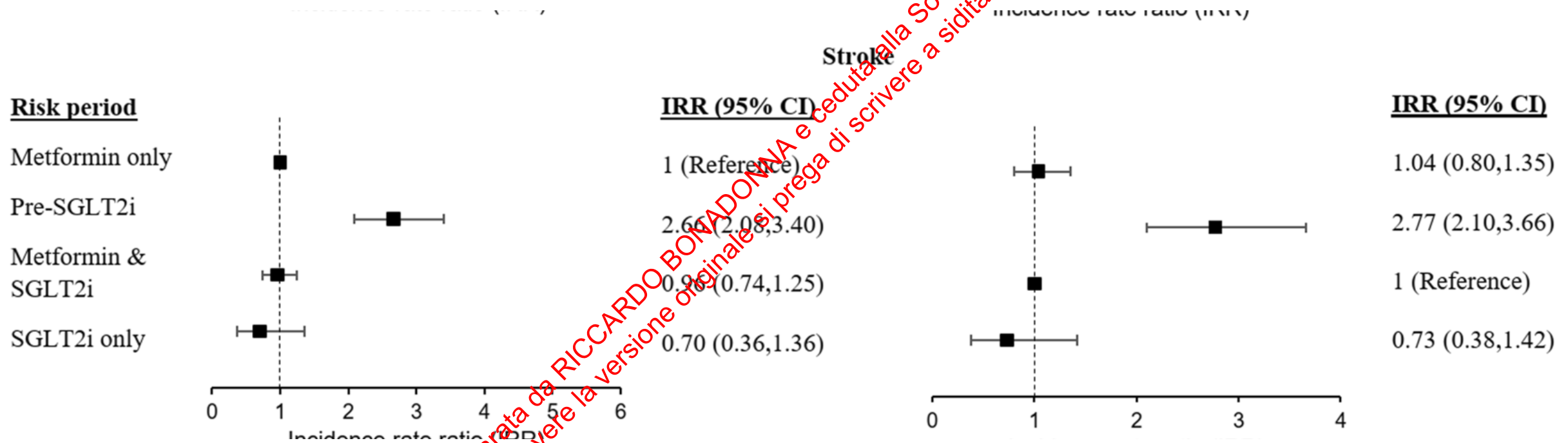
Self-controlled case-series model by exposure to metformin and SGLT2i use – a comparative effectiveness study of MACE (including HHF) and erythrocytosis risk in Hong Kong



Events/Risk periods	Metformin only		Pre-SGLT2i		Metformin & SGLT2i		SGLT2i only	
	No. of patients	Mean (SD) duration, years	No. of patients	Mean (SD) duration, years	No. of patients	Mean (SD) duration, years	No. of patients	Mean (SD) duration, years
Cardiovascular diseases	2,540	3.78 (1.46)	2,575	0.27 (0.08)	2,410	1.22 (1.13)	395	0.12 (0.43)
Coronary heart disease	2,028	3.75 (1.45)	2,061	0.27 (0.08)	1,925	1.25 (1.12)	334	0.13 (0.45)
Hospitalization for heart failure	805	3.66 (1.53)	822	0.28 (0.08)	724	0.98 (1.06)	220	0.20 (0.52)
Stroke	723	3.73 (1.46)	728	0.28 (0.08)	676	1.23 (1.17)	105	0.10 (0.38)
Erythrocytosis	1,671	3.16 (1.50)	1,700	0.28 (0.09)	1,632	1.97 (1.44)	202	0.15 (0.54)

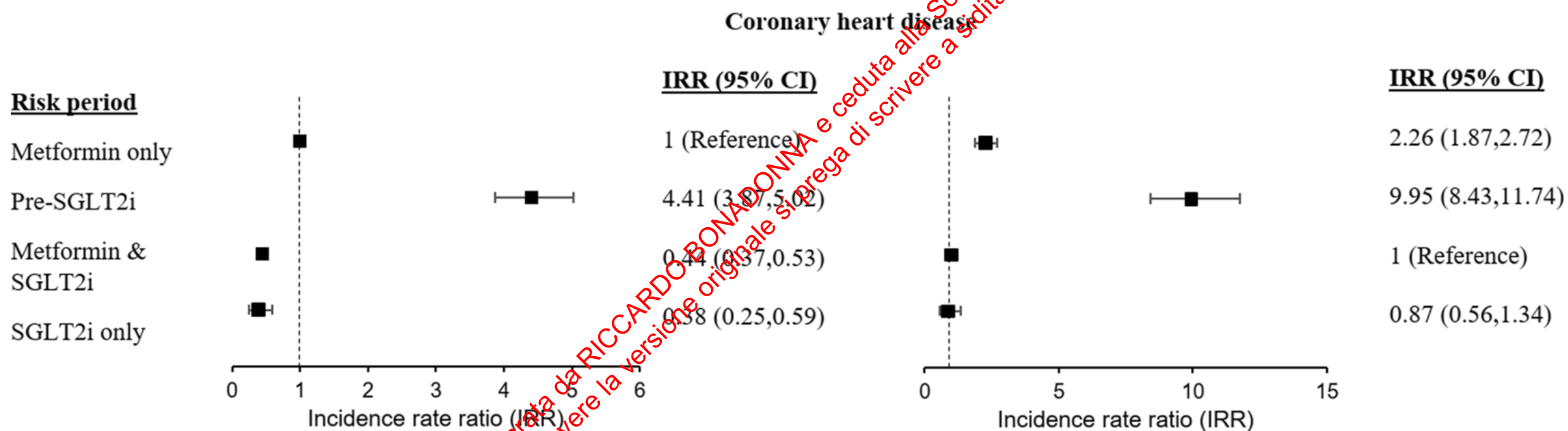
Wong CKO et al.;
Cardiovascul Diabetol 2022

Self-controlled case-series model by exposure to metformin and SGLT2i use – a comparative effectiveness study of MACE (including HHF) risk in Hong Kong

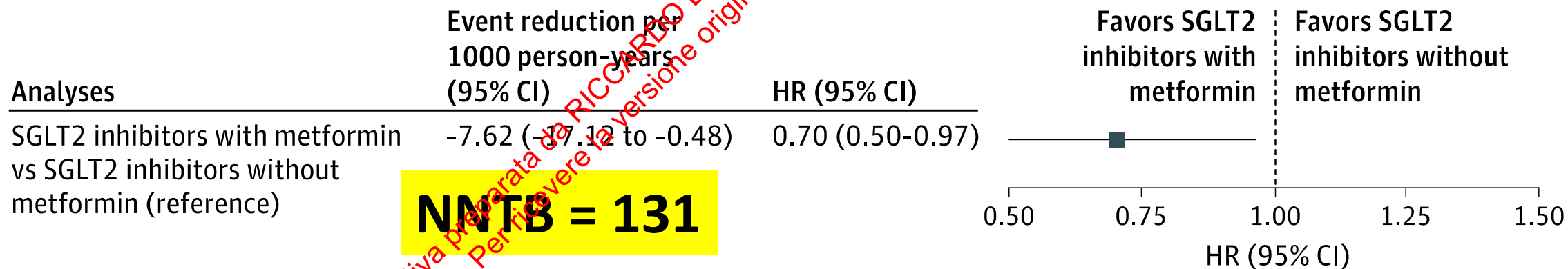
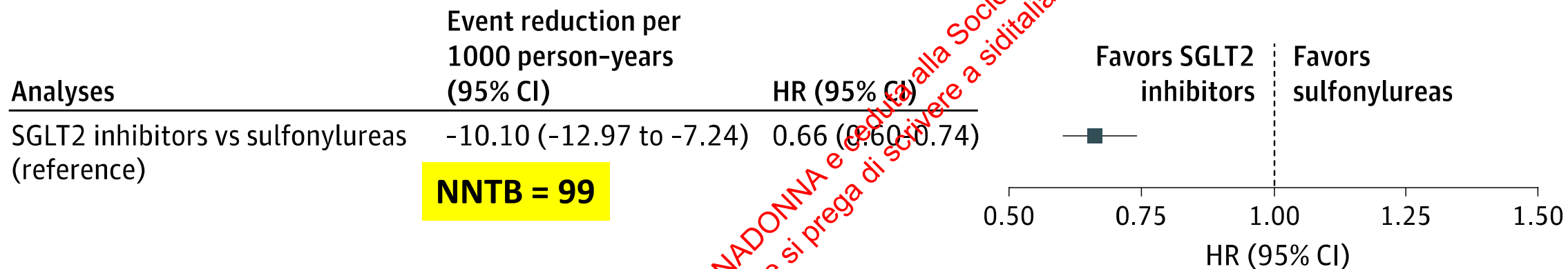


Diapositiva preparata da RICCARDO BONADONIA e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

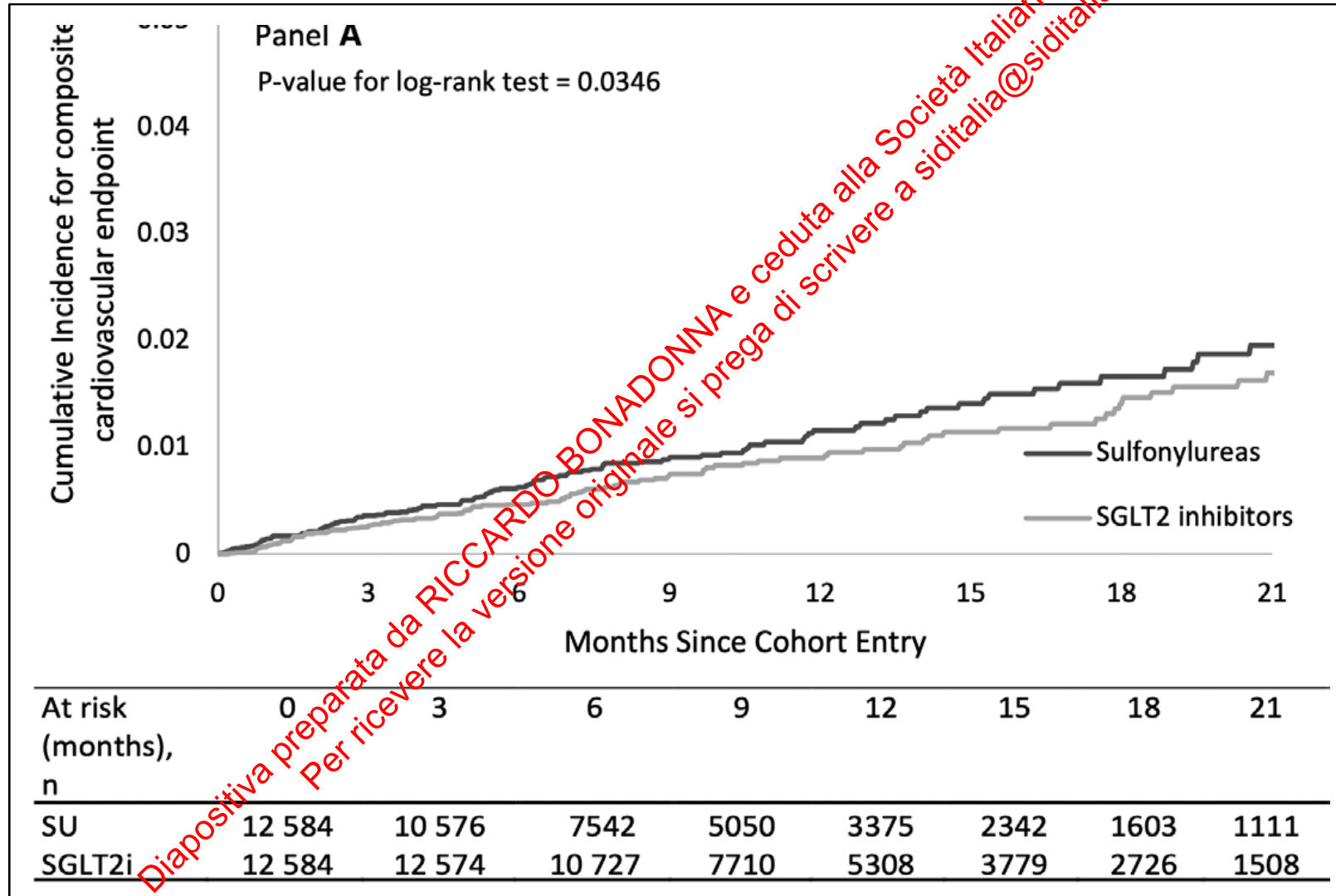
Self-controlled case-series model by exposure to metformin and SGLT2i use – a comparative effectiveness study of HHF risk in Hong Kong



Per-protocol hazard ratios (HR) and event rate reduction for all-cause mortality in the SGLT2i vs the SU treatment arms and in the SGLT2i+Met vs SGLT2i alone arms – a comparative effectiveness study

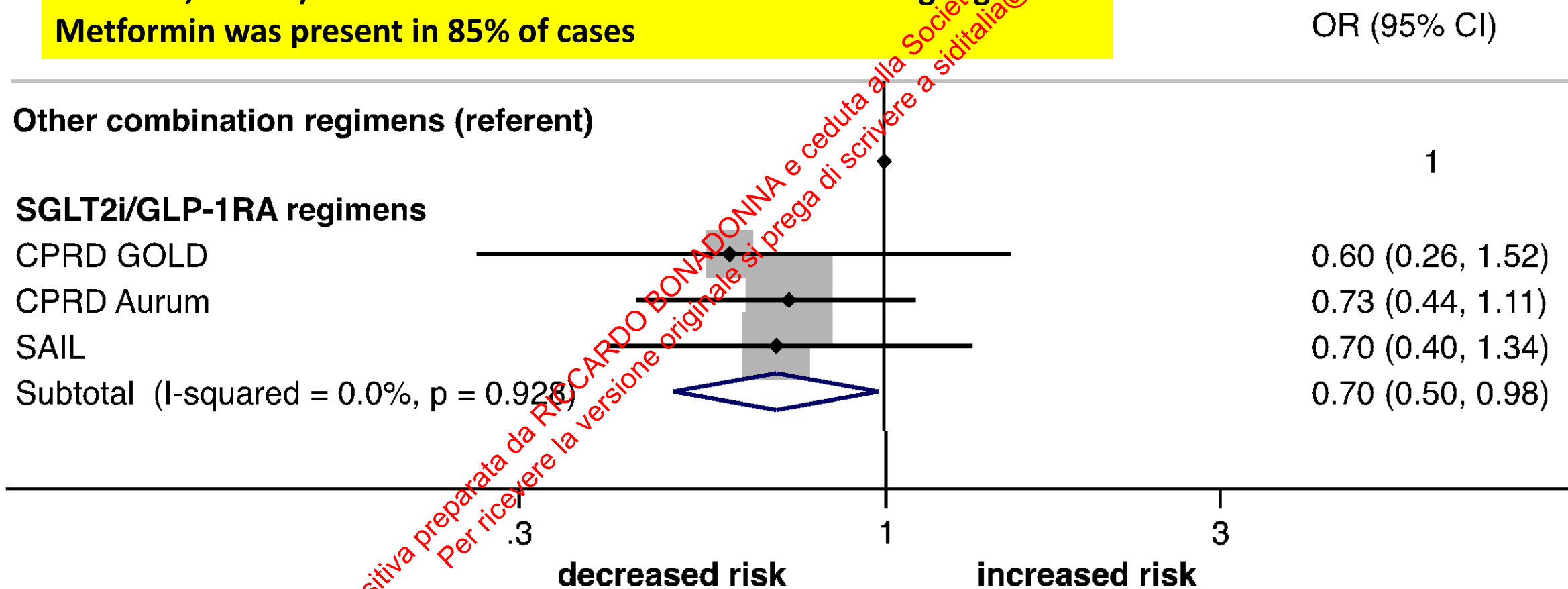


RWE from 3 HMOs: Reduced incidence of MACE in GLP1Ra+SGLT2i vs GLP1Ra+SU PS matched (95 baseline variables) cohorts of patients with type 2 diabetes



Use of SGLT2i/GLP1Ra combination therapy vs other combination regimens and risk of MACE: an effectiveness study in UK

However, SGLT2i/GLP1Ra combination was used in > 2-drug regimens
Metformin was present in 85% of cases



Dove trovare le indicazioni?

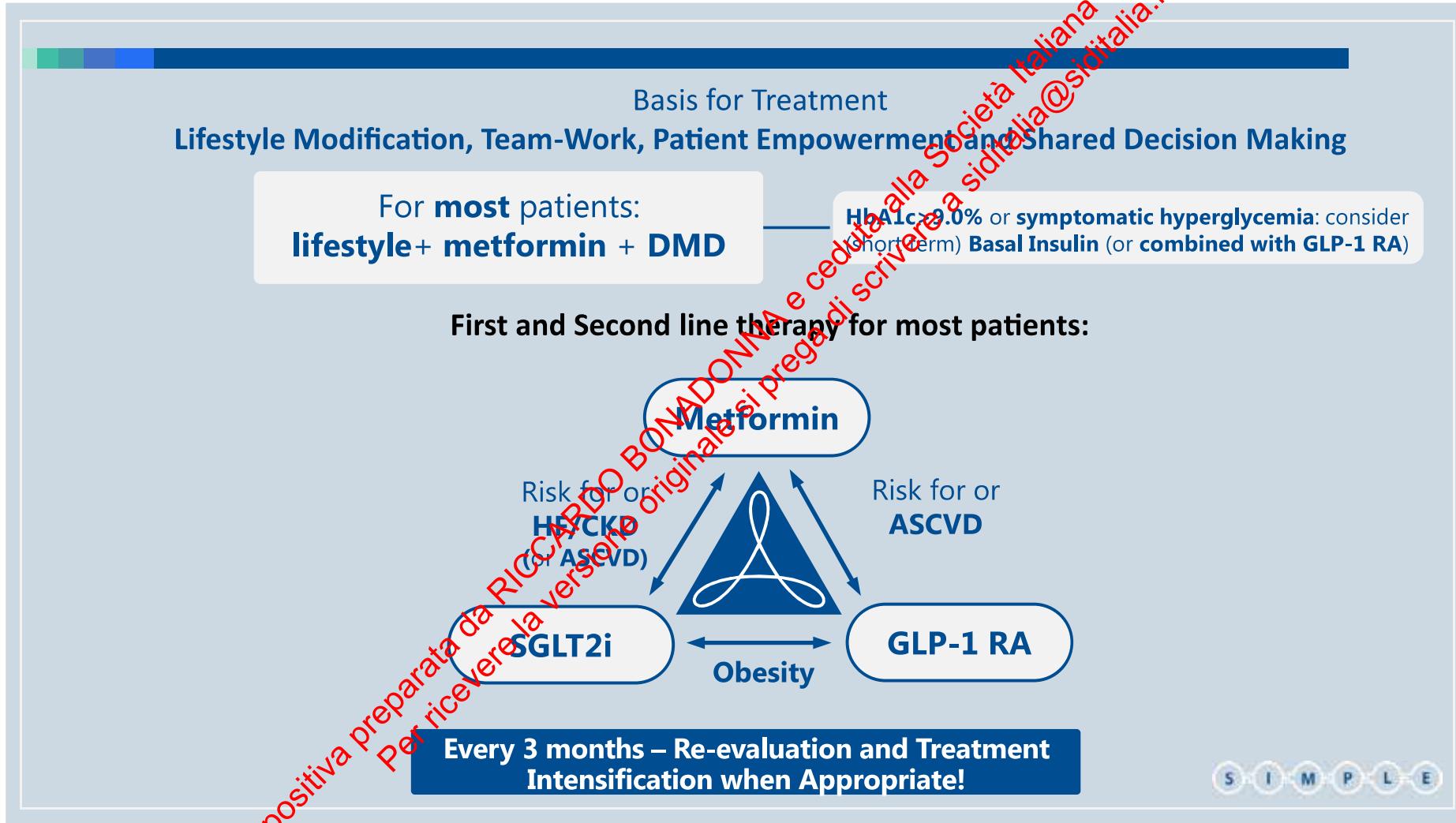
✓ Studi di «efficacy» (RCT)

✓ Analisi post-hoc degli RCT

✓ Studi di «effectiveness» (RWE)

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Terapia farmacologica del diabete di tipo 2: un triangolo equilatero?



Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Considerazioni finali per una terapia basata sul principio «treat to benefit» e sulle evidenze disponibili

- Salvo controindicazioni o intolleranza, la metformina rimane il farmaco da preferire per un trattamento di combinazione con SGLT2i all'inizio della terapia farmacologica del diabete di tipo 2
- La classe farmacologica potenzialmente in grado di contendere questo ruolo della metformina è quella dei GLP1Ra, ma le evidenze sono ancora insufficienti
- Questo non esclude che, in pazienti selezionati e/o per attenzione al vincolo della sostenibilità e al principio di equità, altre classi di farmaci possano essere considerate in combinazione con SGLT2i per una iniziale terapia di combinazione (e.g. pioglitazone, DPP4i, insuline basali...)

Grazie per l'attenzione

Diapositiva preparata da RICCARDO BONADONNA e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it