



**A chi non prescrivere
i farmaci innovativi**

Anziano

Anna Solini

Università di Pisa

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

Disclosure

Grant: Novo, Sankyo, sanofi (University of Pisa)

Advisory Board: Bayer, Boehringer Ingelheim, Lilly, Novo, Sankyo

Talks: Bayer, Lilly, Novo, sanofi, Boehringer Ingelheim

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

The frail, elderly subject might take multiple advantages from the use of innovative drugs

- ✓ Efficacy
- ✓ AKI
- ✓ Falls
- ✓ Cognitive impairment

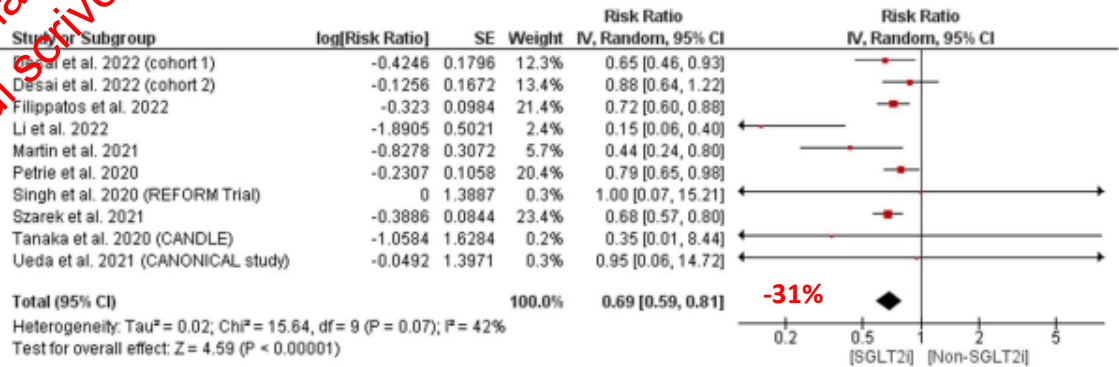
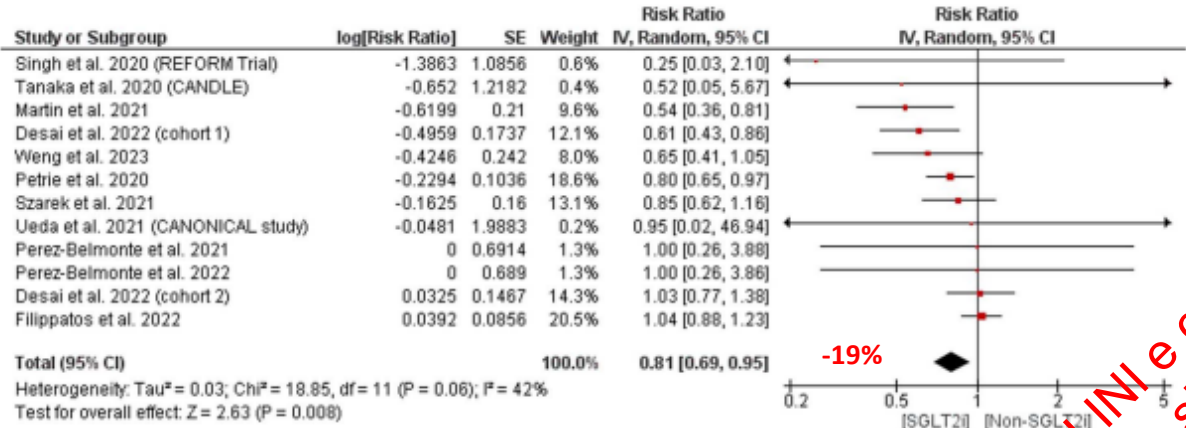
Diapositiva preparata da ANNA SOLINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Benefit-risk profile of SGLT2i in older frail adults

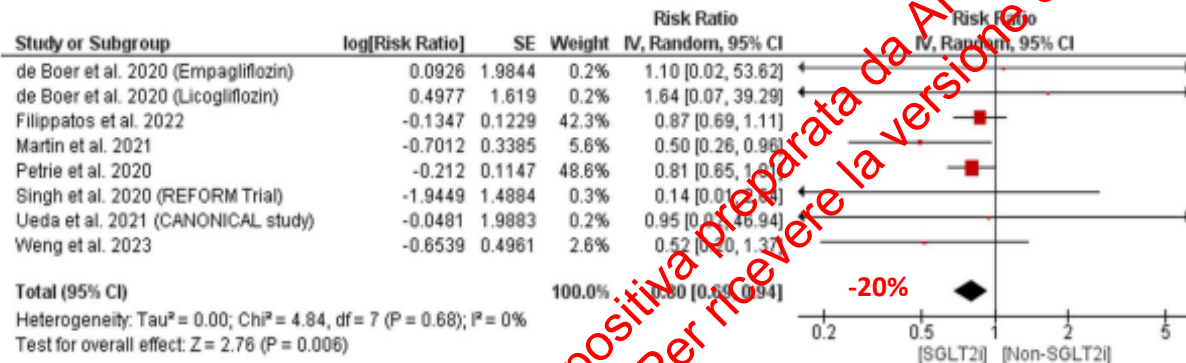


SGLT2i in frail or older people with T2D and HF (n>77,000)

All-cause mortality



Cardiac death



SGLT2i in frail or older people with T2D and HF

Safety profile

	Studies	RR (IV, Random) 95% CI	P(Z)-value	P(Q) Hetero.; I-Sqr (Q)
Thromboembolic (ACS or Cerebral vascular occlusion)	8	0.93 [0.76, 1.13]	0.46	$P = 0.71$; $I^2 = 0\%$
All-cause mortality	12	0.84 [0.69, 0.95]	0.008	$P = 0.06$; $I^2 = 42\%$
Cardiac death	8	0.80 [0.69, 0.94]	0.006	$P = 0.68$; $I^2 = 0\%$
HHF	10	0.69 [0.59, 0.81]	< 0.00001	$P = 0.07$; $I^2 = 42\%$
Atrial fibrillation	3	1.67 [0.29, 9.49]	0.56	$P = 0.86$; $I^2 = 0\%$
Worsening HF	3	0.55 [0.22, 1.37]	0.2	$P = 0.84$; $I^2 = 0\%$
Renal progression/Composite renal end point	4	0.88 [0.69, 1.13]	0.31	$P = 0.39$; $I^2 = 1\%$
AKI	3	0.92 [0.29, 2.91]	0.89	$P = 0.01$; $I^2 = 77\%$
DKA	3	0.94 [0.33, 2.67]	0.91	$P = 0.68$; $I^2 = 0\%$

Diapositiva preparata da ANNA SOLINI e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Comparative effectiveness of empagliflozin in reducing the burden of recurrent cardiovascular hospitalizations among older T2D adults in routine clinical care

Incidence of total CV events

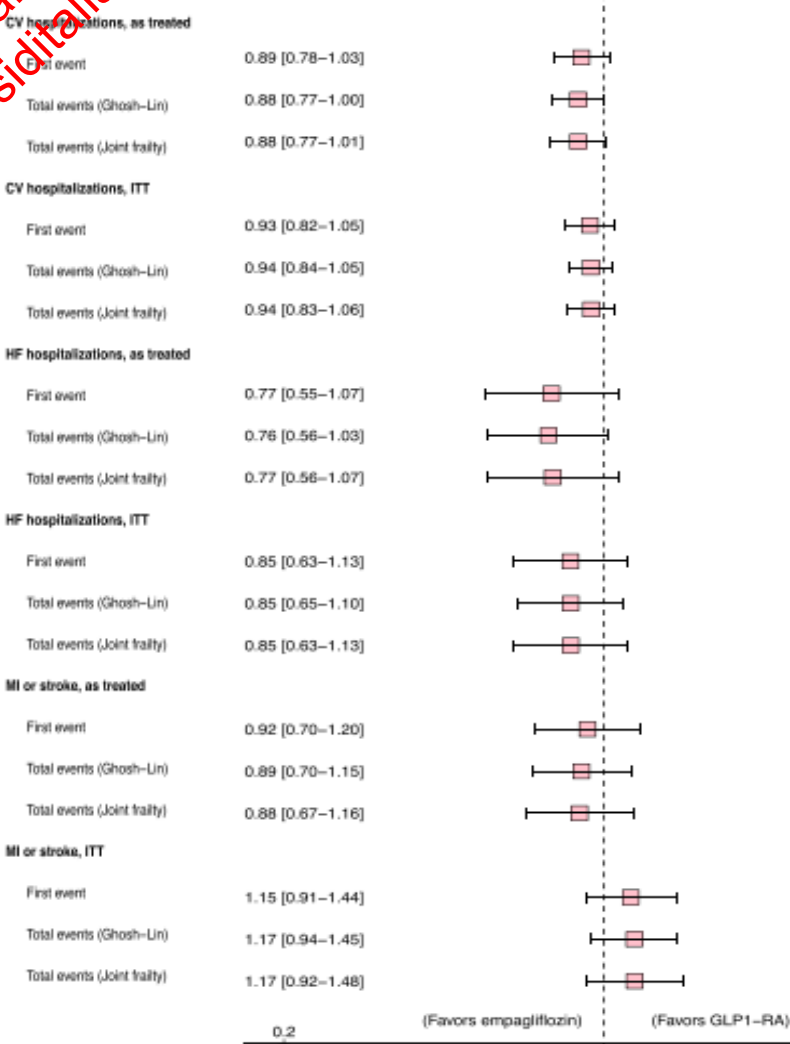
Cohort 2			
Empagliflozin (n = 17,502)		GLP-1RA (n = 17,502)	
Total events/person-y	Incidence rate/100 py (95% CI)	Total events/person-y	Incidence rate/100 py (95% CI)
389/8,950	5.3 (4.7-5.9)	389/7,892	6.1 (5.5-6.8)
490/11,058	5.4 (4.9-6.0)	521/10,979	5.8 (5.3-6.4)
67/8,950	0.9 (0.7-1.1)	76/7,892	1.1 (0.9-1.5)
86/11,058	0.9 (0.7-1.2)	101/10,979	1.1 (0.9-1.4)
109/8,950	1.4 (1.1-1.7)	106/7,892	1.6 (1.3-1.9)
159/11,058	1.6 (1.4-1.9)	138/10,979	1.4 (1.2-1.7)
94/8,950	1.1 (0.8-1.3)	91/7,892	1.2 (0.9-1.5)
126/11,058	1.1 (0.9-1.4)	139/10,979	1.3 (1.1-1.5)

Mean age 72 yrs
Over 140 matched variables

20% RRR
Hospitalization for CV causes

30% RRR
Hospitalization for HF

Empagliflozin vs GLP1-RA RR



Mechanisms of CV protection with SGLT-2 inhibitors in Elderly with Diabetes and Heart Failure

Heart and Vessels

- ↓ arterial stiffness
- ↑ endothelial function
- ↓ circulating blood volume
- ↓ preload and afterload
- ↓ myocardial fibrosis and oxidative stress
- ↑ reverse cardiac remodeling
- ↑ myocardial energetics

Kidney

- ↑ natriuresis and diuresis
- ↓ RAAS activation
- ↑ adaptive natriuretic synergy with loop diuretics
- ↓ intraglomerular pressure and hyperfiltration

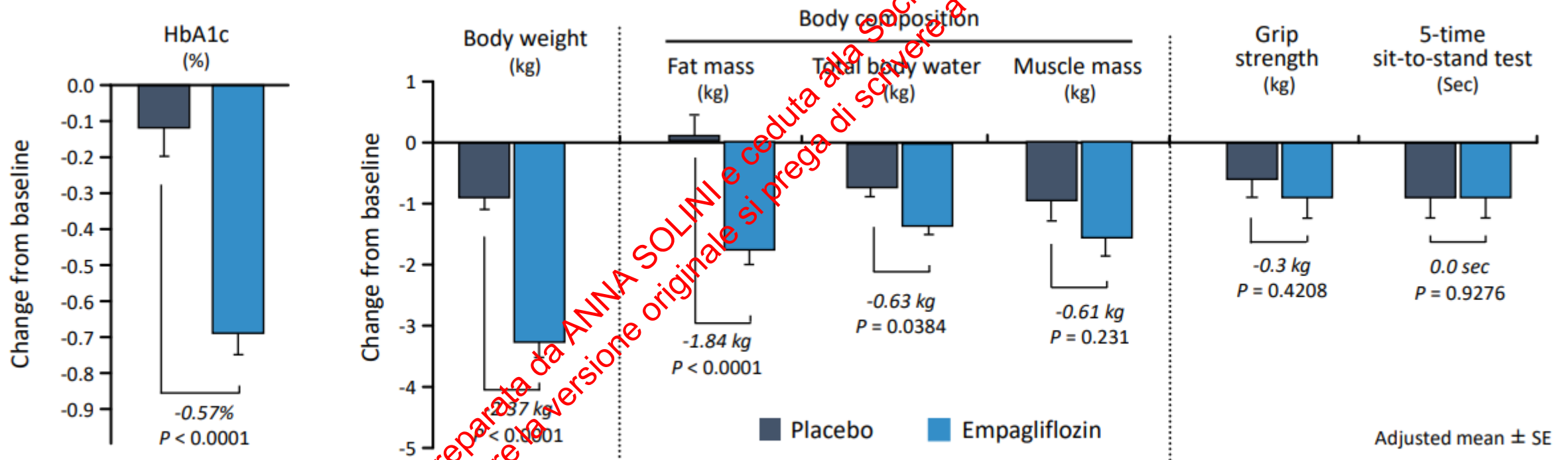
Haemodynamic and Metabolic effects

- ↓ SNS activity
- ↑ haematocrit
- ↓ blood pressure
- ↓ body weight
- ↓ total body and visceral fat
- ↓ glucotoxicity and lipotoxicity
- ↑ insulin sensitivity
- ↓ liver steatosis
- ↓ uricemia

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

Safety of empagliflozin in elderly Japanese adults: the EMPA-ELDERLY trial

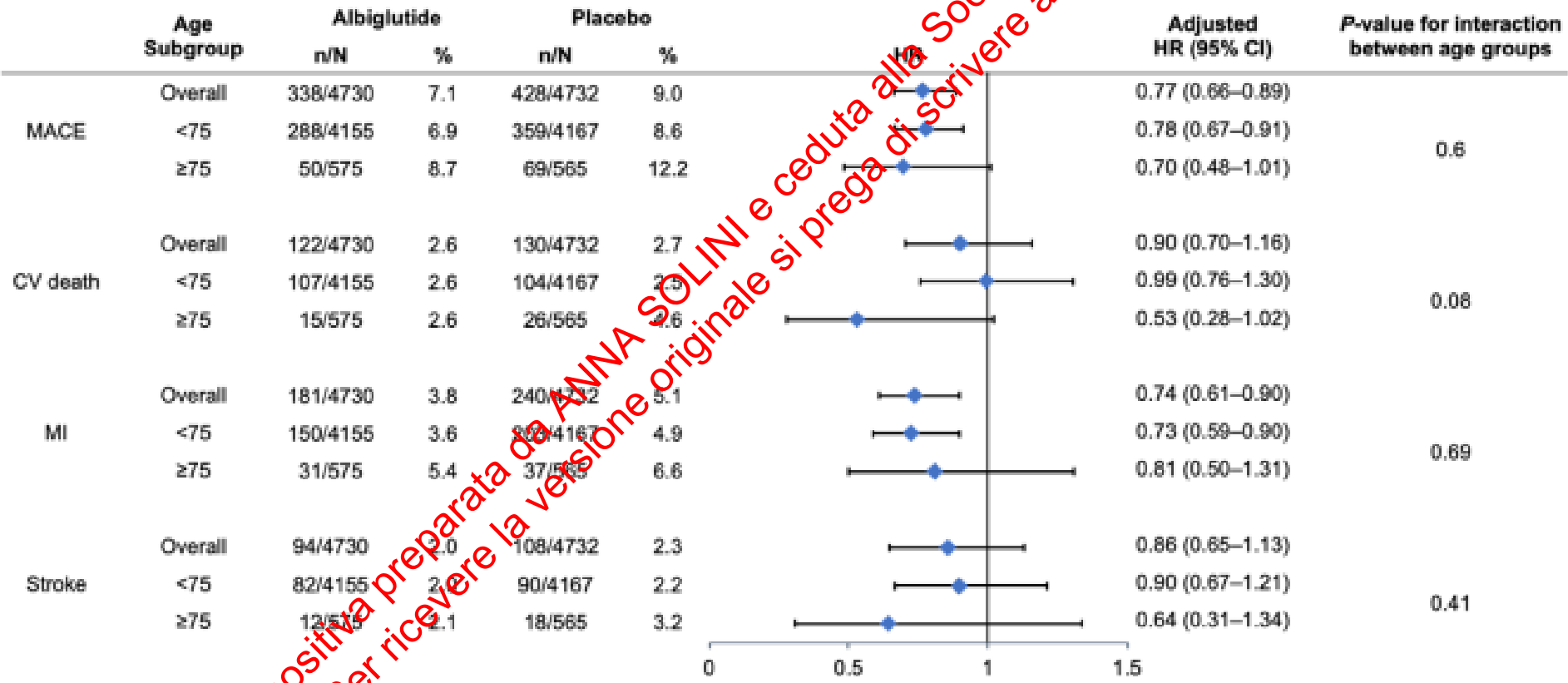
Changes from baseline at week 52



- Empagliflozin significantly improved HbA1c and was well tolerated in elderly patients with type 2 diabetes.
- No new concerns including sarcopenia or muscle weakness were observed for empagliflozin treatment.

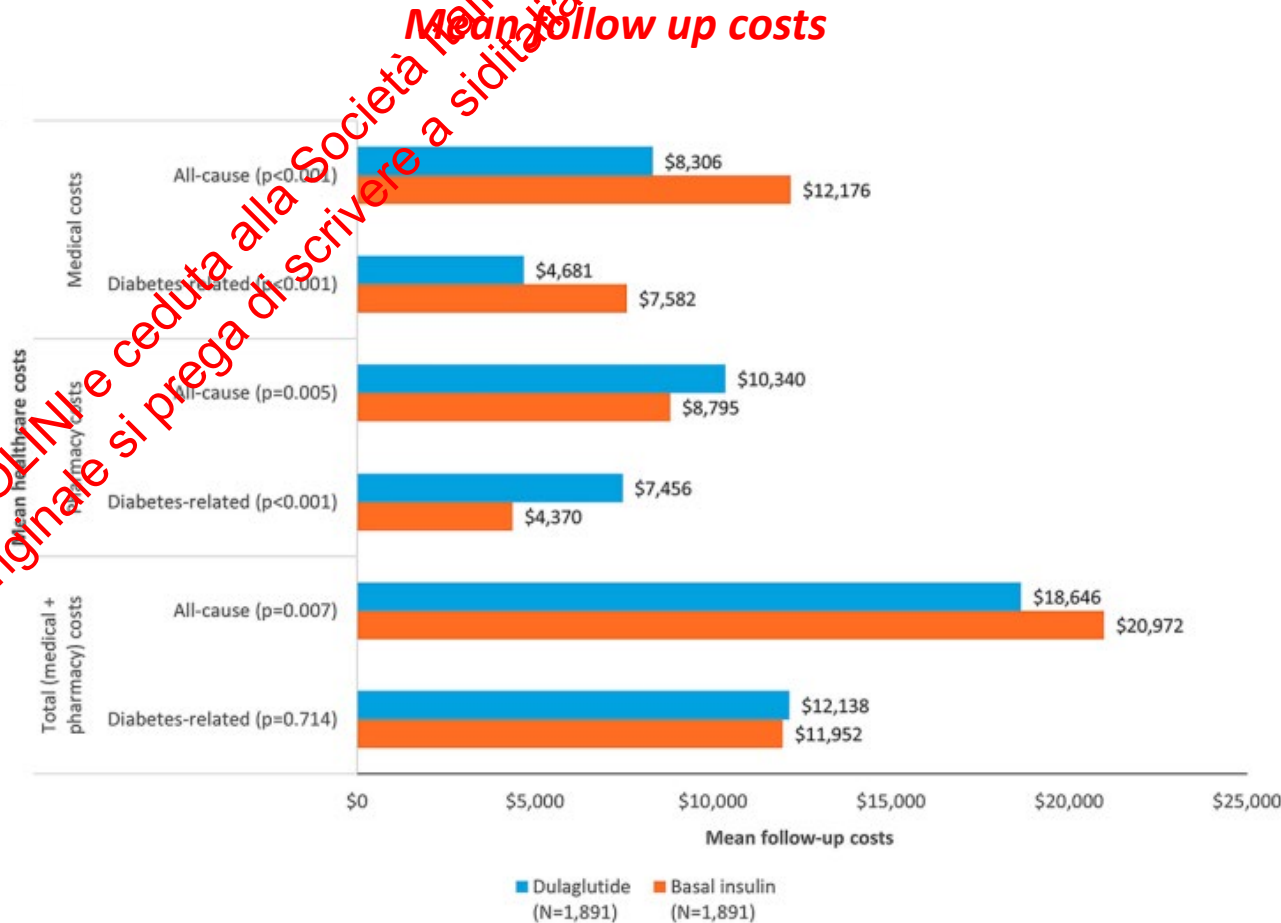
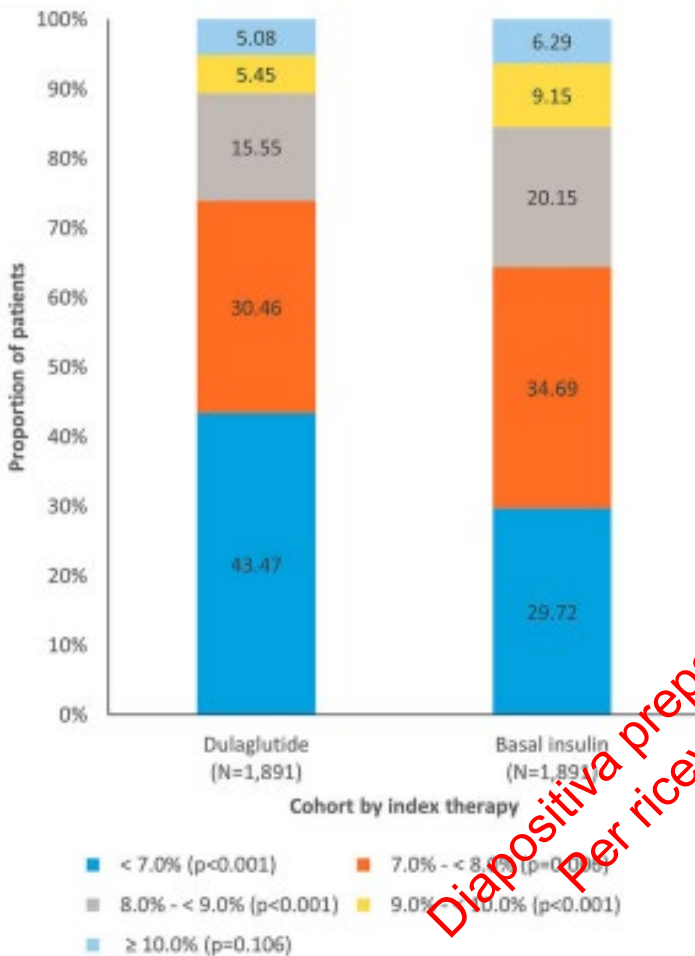
Effect of albiglutide on CV outcomes in older adults: a post hoc analysis of a randomized controlled trial

Adjusted HR in patients aged <75 and ≥75 years



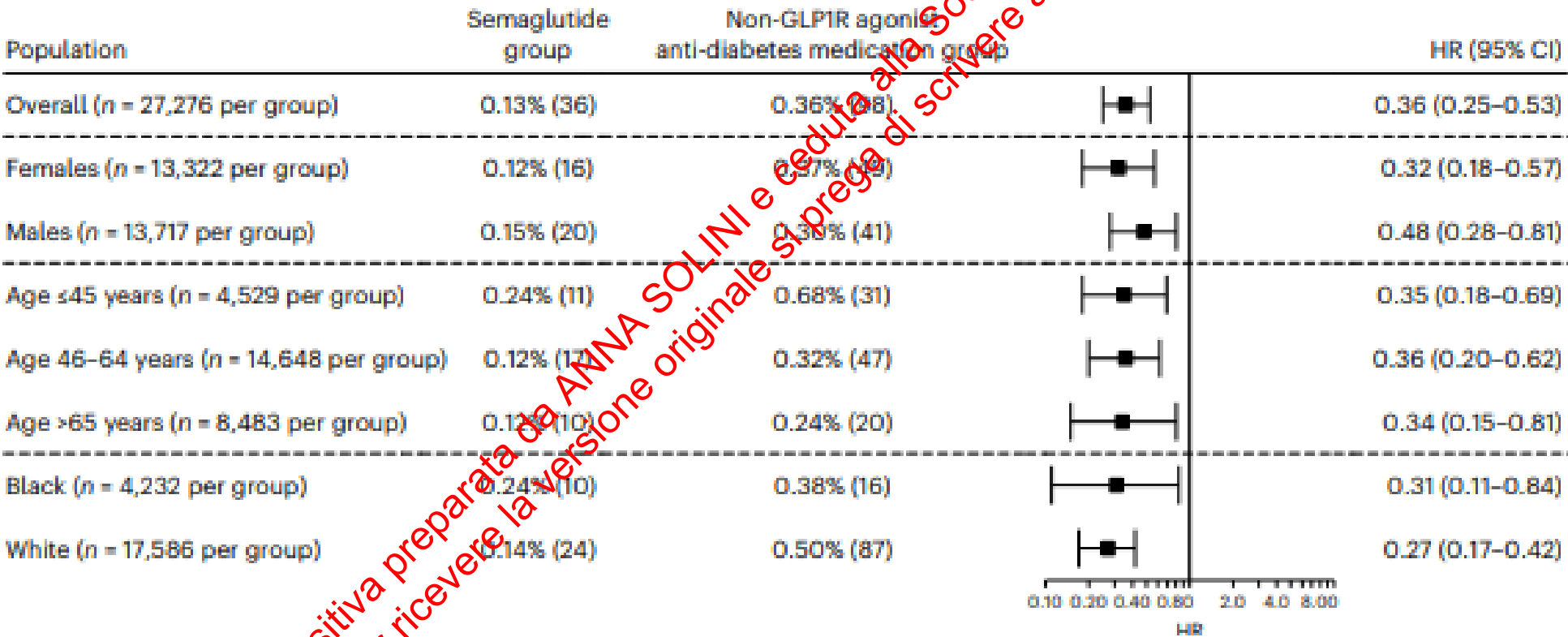
Glycemic and economic outcomes in elderly T2D subjects initiating dulaglutide vs basal insulin in a real-world setting: the DISPEL-Advance Study

Patients reaching the target



Association of semaglutide with risk of suicidal ideation in a real-world cohort

Incident suicidal ideations in the study population with T2DM



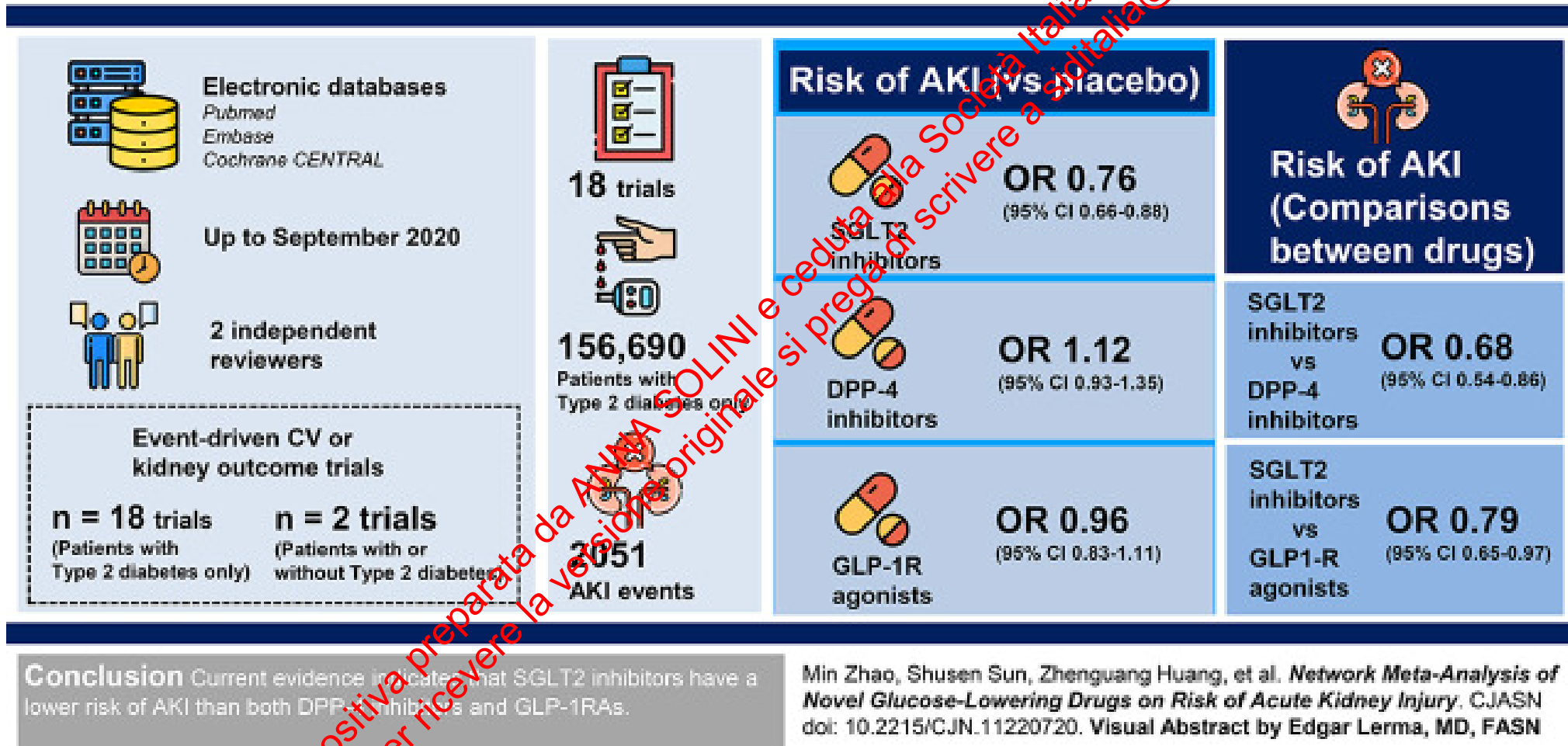
The frail, elderly subject might take multiple advantages from the use of innovative drugs

✓ Efficacy

✓ AKI

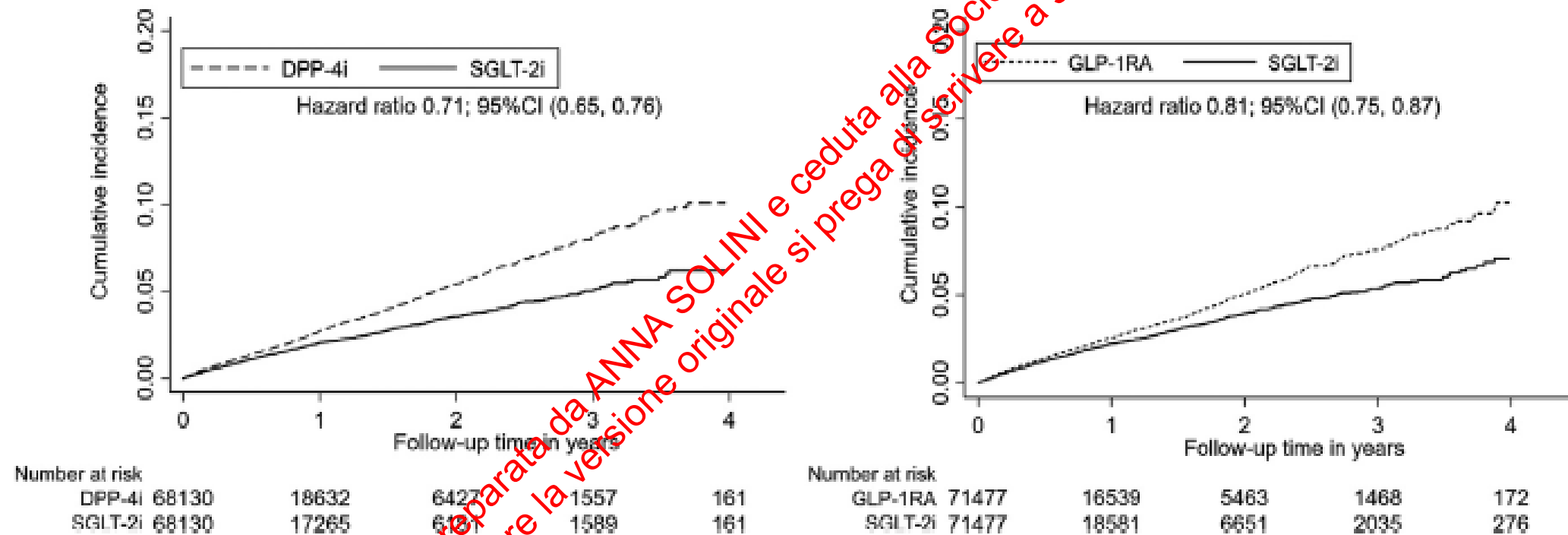
Diapositiva preparata da ANNA SOLINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Comparison of three classes of glucose-lowering drugs on AKI risk in patients with or without T2DM



SGLT2 Inhibitors and the risk of AKI in older adults with T2D

68,130 and 71,477 new users of SGLT2i were matched to new users of DPP-4i or GLP-1RAs, respectively
Mean age 72 years

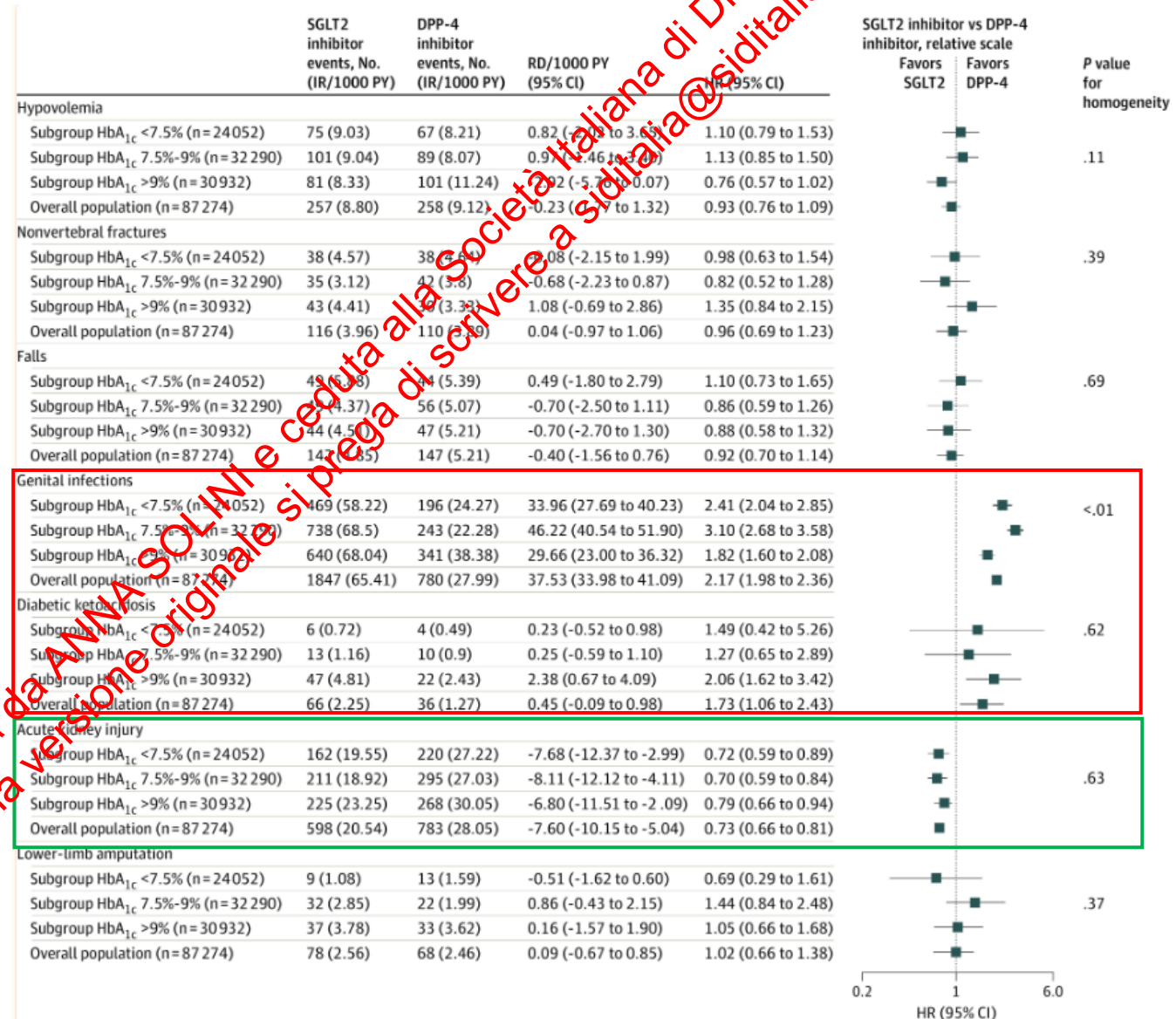


Diapositiva preparata da ANNA SOLINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Safety of SGLT2i vs DPP-4i in varying baseline HbA_{1c} levels

Safety Outcomes in 1:1 Propensity Score-matched patients initiating SGLT2 inhibitor vs DPP-4 inhibitor

87,274 adults with T2D



The frail, elderly subject might take multiple advantages from the use of innovative drugs

✓ Efficacy

✓ AKI

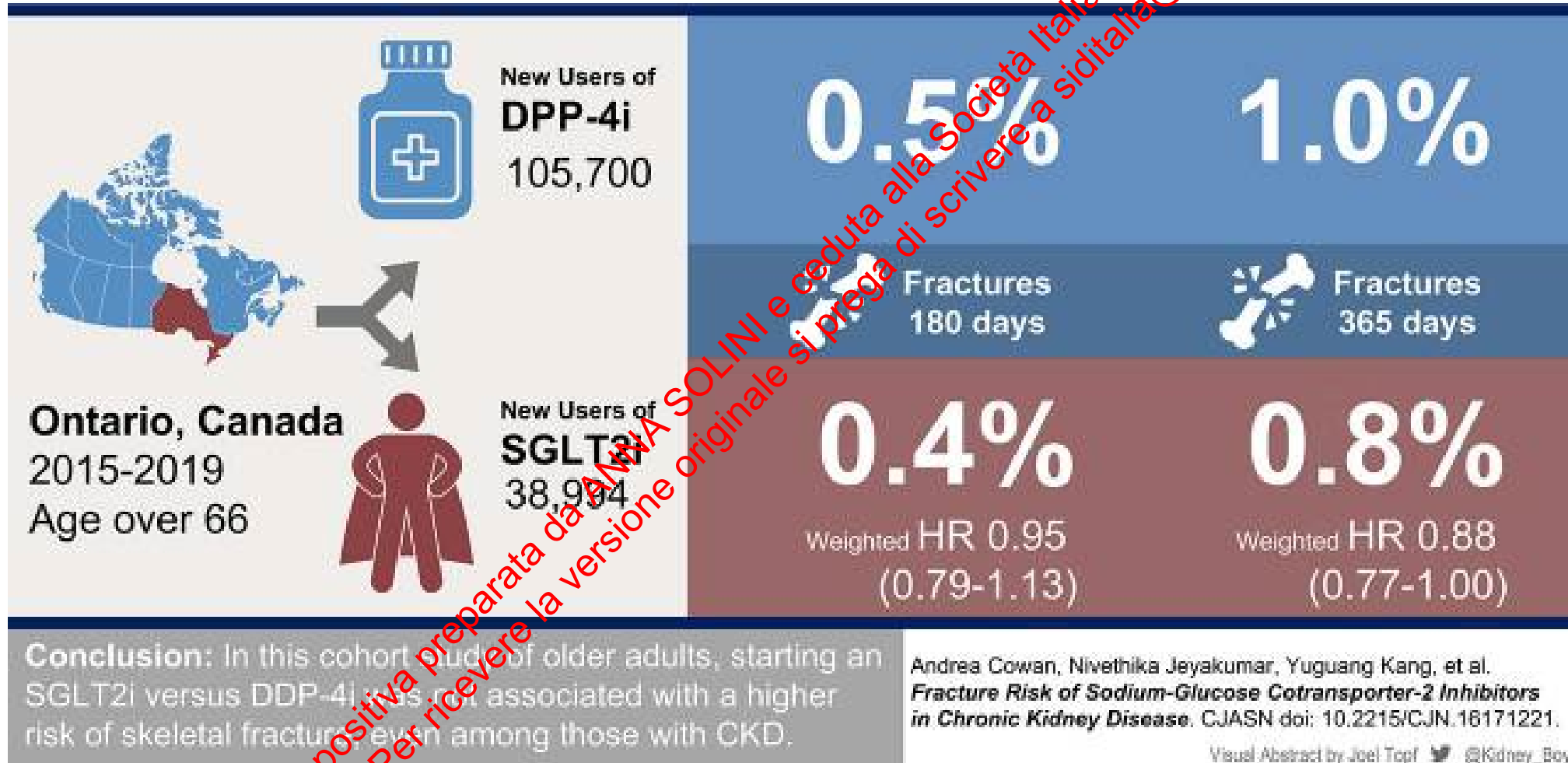
✓ Falls

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

Fracture risk of SGLT2i in subjects with and without CKD

Are SGLT2i associated with fractures?

CJASN
Clinical Journal of the American Society of Nephrology



Association of SGLT2i vs DPP-4i as add-on to metformin with fracture risk in patients with T2D

Risk of any fracture in SGLT2i vs DPP-4i users, stratified by sex and age group

	Number of patients	Number of fractures	IR/1000 PY	aHR (95% CI)
Age 60-69 years, any fracture				
DPP-4 inhibitor use	3520	59	9.4 (7.3-12.1)	Reference
SGLT2 inhibitor use	3520	40	8.7 (6.4-11.8)	0.93 (0.65-1.34)
Age > 70 years, any fracture				
DPP-4 inhibitor use	1258	41	19.0 (14.1-25.8)	Reference
SGLT2 inhibitor use	1258	26	17.6 (12.0-25.8)	0.93 (0.60-1.44)
Age 60-69 years, any fracture				
DPP-4 inhibitor use	1562	21	9.1 (5.9-14.0)	Reference
SGLT2 inhibitor use	1562	20	10.8 (7.0-16.7)	1.23 (0.70-2.17)
Age > 70 years, any fracture				
DPP-4 inhibitor use	622	12	13.9 (8.0-24.2)	Reference
SGLT2 inhibitor use	622	4	6.0 (2.3-16.1)	0.49 (0.17-1.45)

13,807 SGLT2i users
vs 28,524 DPP-4i users

SGLT2i and the reporting of falls and fractures: an european pharmacovigilance analysis

Reporting probabilities of fall (A) and fractures (B) between SGLT2i and DPP4i for sex and age (<65 and >65 yrs)

653 events

A Fall

Comparison	ROR	95% CI	p-value
SGLT2 inhibitors vs DPP4 inhibitors in male	0.67	0.53-0.86	0.001
SGLT2 inhibitors vs DPP4 inhibitors in female	0.66	0.54-0.81	<0.001
SGLT2 inhibitors vs DPP4 inhibitors in ≥ 65 years	0.81	0.66-1.00	0.047
SGLT2 inhibitors vs DPP4 inhibitors in < 65 years	0.43	0.31-0.60	<0.001

B Fractures

Comparison	ROR	95% CI	p-value
SGLT2 inhibitors vs DPP4 inhibitors in male	0.92	0.67-1.24	0.581
SGLT2 inhibitors vs DPP4 inhibitors in female	1.13	0.90-1.41	0.301
SGLT2 inhibitors vs DPP4 inhibitors in ≥ 65 years	1.06	0.82-1.36	0.664
SGLT2 inhibitors vs DPP4 inhibitors in < 65 years	1.24	0.81-1.88	0.317

Diuretics, SGLT2 inhibitors and falls in older heart failure patients: to prescribe or to deprescribe?

Prevalence of fall-related side effects of diuretics and SGLT2 inhibitors

	(Orthostatic) Hypotension	Dizziness	Hypokalemia	Hyponatremia	Volume depletion	Sedation	Syncope
Loop diuretics							
Bumetanide (C03CA02)	++	+++	+++	+++	++	+++	++
Furosemide (C03CA01)	++	Not known	Not known	Not known	++	Not known	Not known
Torsemide (C03CA04)	Not known	+++	Not known	+++	+++	Not known	Not known
Thiazide(like) diuretics							
Hydrochlorothiazide (C03AA03)	+++	+	++++	++++	Not known	Not known	Not known
Indapamide (C03BA11)	+	+	Not known	Not known	Not known	Not known	Not known
Aldosterone receptor antagonists							
Eplerenone (C03DA04)	+++	++	Not known	++	++	Not known	++
Spironolactone (C03DA01)	Not known	++	Not known	Not known	Not known	++	Not known
SGLT2 inhibitors							
Canagliflozin (A10BK02)	++	++	Not known	Not known	++	Not known	++
Dapagliflozin (A10BK01)	+	+++	Not known	Not known	++	Not known	Not known
Empagliflozin (A10BK03)	+	++	Not known	Not known	++	Not known	++
Ertugliflozin (A10BK04)*	+++	+++	Not known	Not known	+++	Not known	+++

+ : Seldom (< 1/1000)

++ : Sometimes (1/100-2/1000)

+++ : Often (1/10-1/100)

++++ : Very often (> 1/10)

*Both SGLT2 and SGLT1 inhibitor

Source: Diuretic and SGLT2 SmPCs

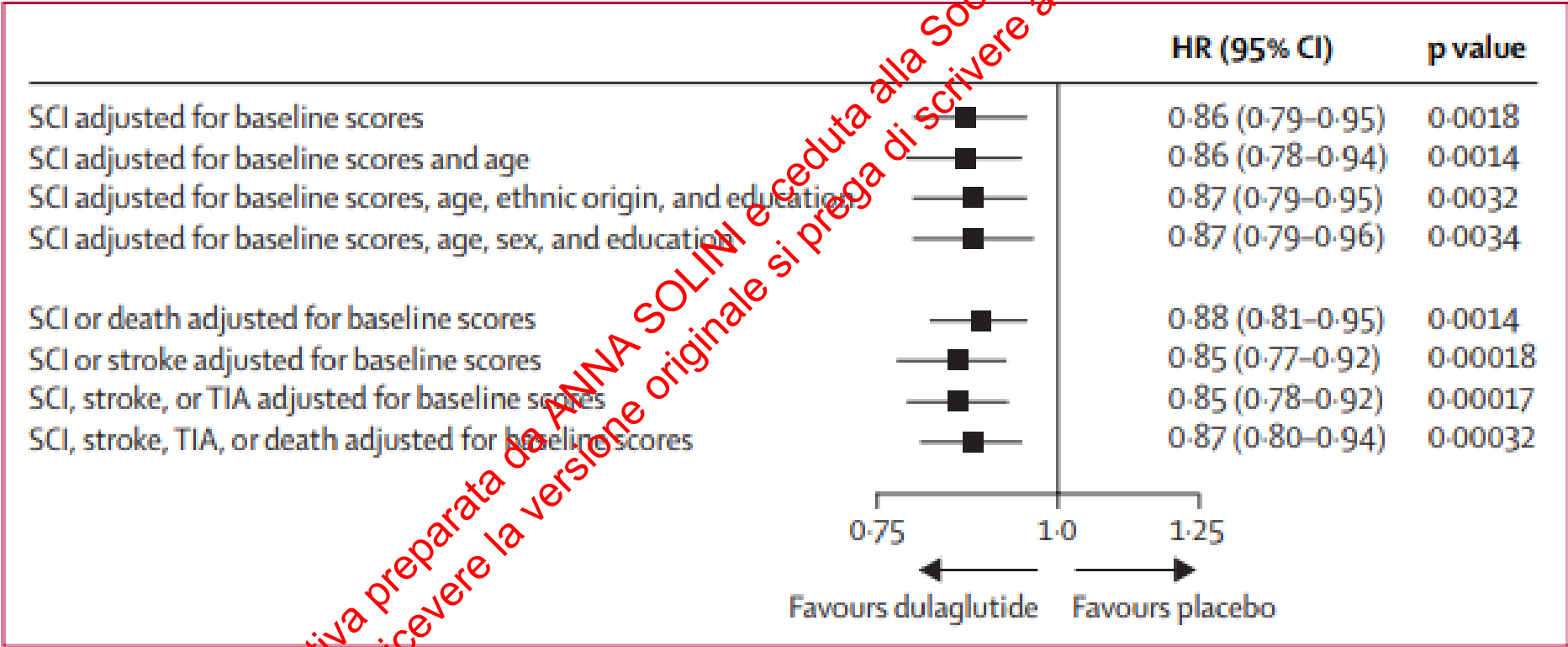
The frail, elderly subject might take multiple advantages from the use of innovative drugs

- ✓ Efficacy
- ✓ AKI
- ✓ Falls
- ✓ Cognitive impairment

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

Effect of dulaglutide on cognitive impairment in T2D: an exploratory analysis of the REWIND trial

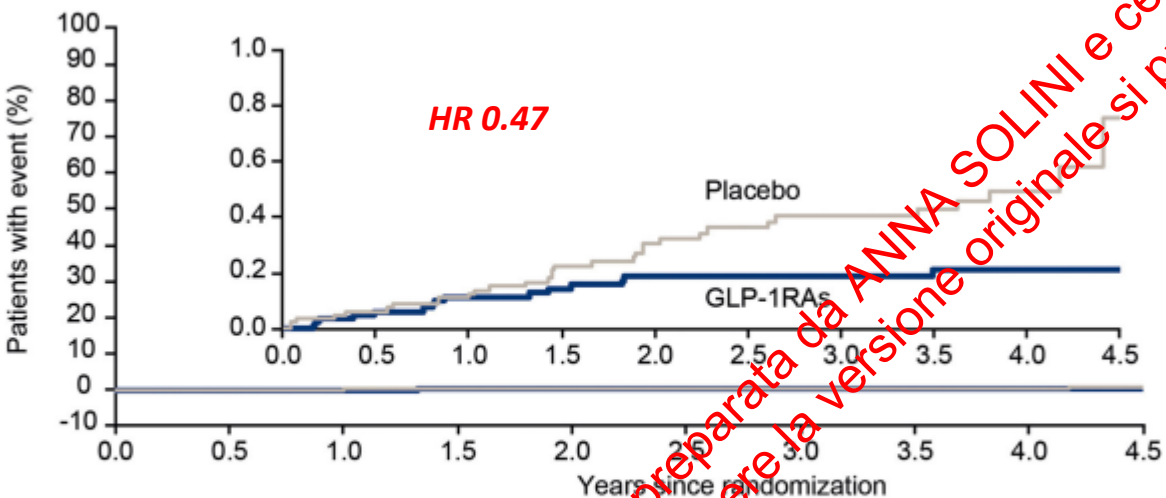
Risk of SCI, adjusted for baseline standardized MoCA and DSST scores



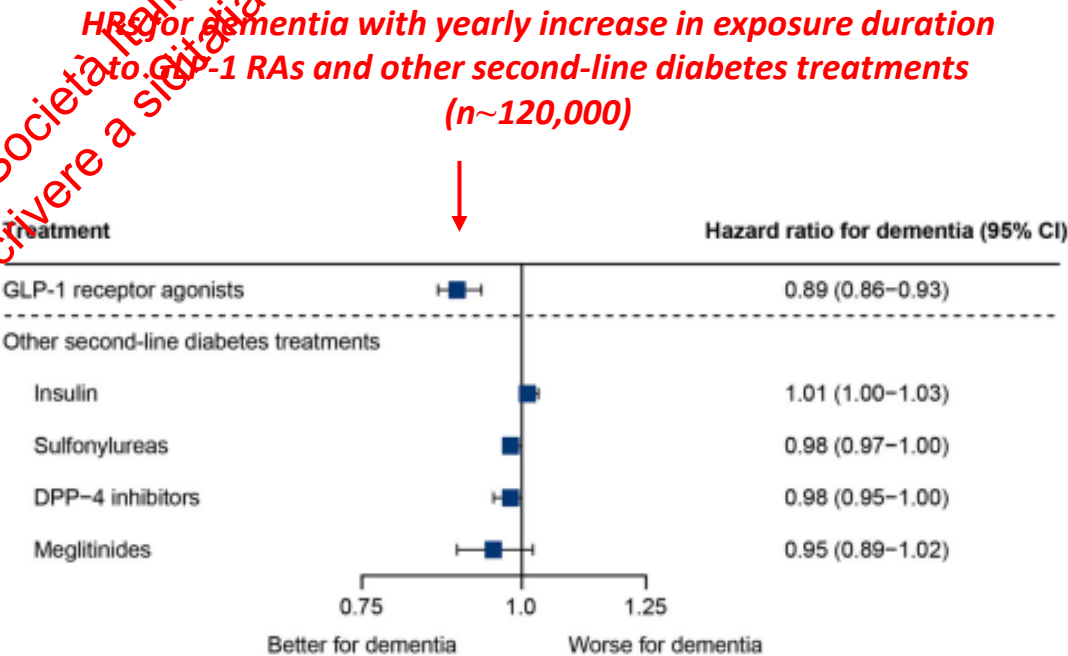
Diapositiva preparata da ANNA SOLINI e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Treatment with GLP-1 RA and incidence of dementia: Data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers

Time to dementia with GLP-1 RAs vs placebo in pooled RCTs
(n~16,000)

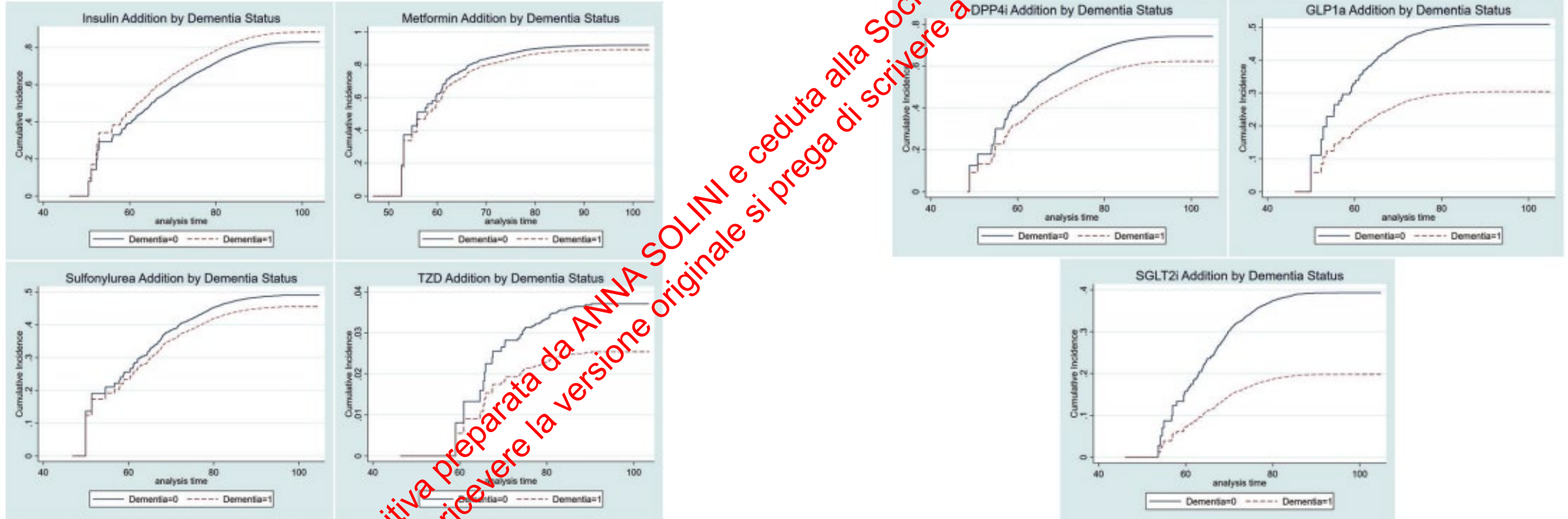


No. at risk										
GLP-1 RA	7907	7852	7763	6479	6004	4441	4373	4312	1716	483
Placebo	7913	7843	7740	6438	6016	4394	4321	4251	1700	460



Dementia diagnosis and changes in antidiabetic drug prescription: an open-cohort study of ~130,000 Swedish subjects over 14 years

Cumulative incidence functions of antidiabetic drug dispensation in new users by dementia status



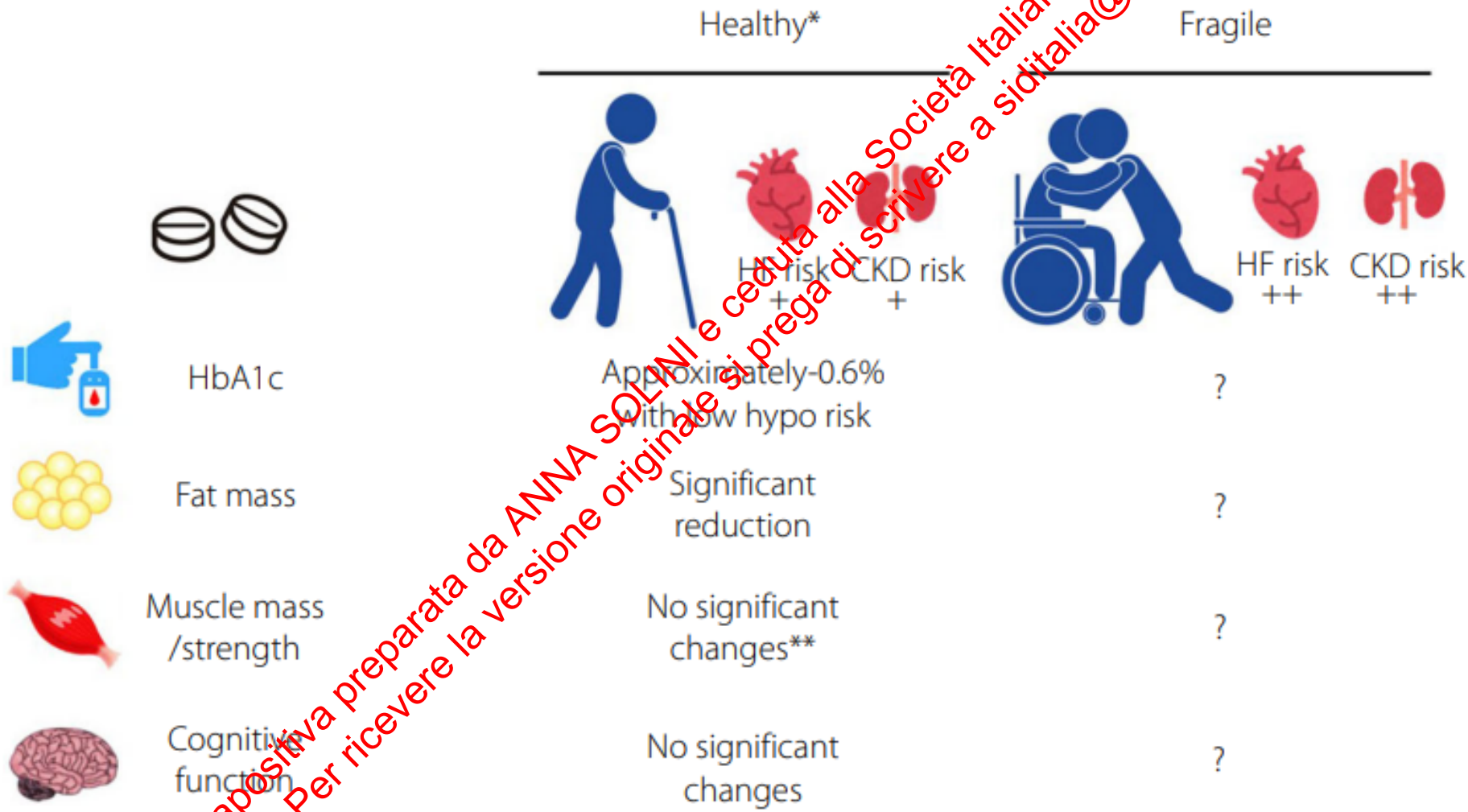
Diapositiva preparata da ANNA SOLINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it.

Clinical characteristics and healthcare utilisation associated with undiagnosed cognitive impairment in elderly patients with diabetes in a primary care setting: a population-based cohort study

They were less likely to be treated with GLP-1 agonists, DPP-4 inhibitors, or SGLT2 inhibitors and more likely to receive insulin or sulfonylurea

	Total	MoCA ≥26	MoCA 19–26	MoCA<19	P value†
n (%)	350	130 (37.1)	152 (43.4)	68 (19.4)	
Age	73.8±5.8	73.7±5.5	74±6.0	73.3±5.7	0.745
Medications (%)					
GLP-1 agonists	77 (22.0)	36 (27.7)	31 (20.4)	10 (14.7)	0.048
SGLT-2 inhibitors	11 (3.1)	51 (39.2)	47 (30.9)	12 (17.7)	0.049
DPP-4 inhibitors	13 (3.7)	31 (23.9)	34 (22.4)	8 (11.7)	0.002
Acarbose	4 (1.1)	1 (0.8)	2 (1.3)	1 (1.5)	†
Sulfonylureas	74 (21.1)	12 (9.2)	36 (23.7)	23 (33.8)	0.001
Meglitinides	42 (12.0)	8 (6.2)	23 (15.1)	11 (16.2)	0.001
Metformin	212 (60.6)	100 (76.9)	84 (55.3)	28 (41.2)	0.024
TZD	37 (10.6)	7 (5.4)	12 (7.9)	18 (26.5)	0.001
Insulin	142 (40.6)	46 (35.4)	65 (41.5)	33 (48.5)	0.0513

Long-term SGLT2i use in older individuals with T2D



My final considerations

- ✓ A multidisciplinary approach is crucial in the decision-making process for managing older individuals or people with frailty with T2D to effectively integrate SGLT2i and GLP-1 RA into treatment pathways, thus reducing their hospitalization
- ✓ Co-morbidities, disability, frailty, anticipated life expectancy, patient preferences and therapeutic goals should all be considered while developing a treatment plan for this population

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