Come è cambiata la terapia del diabete: vantaggi e limiti dei vecchi e dei nuovi farmaci

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Disclosure information

Research support

Astra Zeneca, Novo Nordisk

Advisory Board

Astra Zeneca, Boheringer Ingelheim, Eli Lilly & Co, Merck Sharpe & Dohme, Novo Nordisk, Sanofi

Troppe opzioni terapeutiche?

- Metformina
- Sulfoniluree — glibenclamide, gliclazide, glimepiride, repaglinide
- Glitazoni — pioglitazone
- Inibitori DPP4 — sitagliptin, vildagliptin, linagliptin, saxagliptin, alogliptin
- Agonisti recettori GLP1 — exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide
- Inibitori SGLT2 — empaglifozin, dapaglifozin, canaglifozin
- Insulina basale — lantus, detemir, deglutec, tujeo, abasaglar

Terapia basata sul target di controllo glicemico

Metformina

Se non sufficiente, aggiungere alla metformina un secondo farmaco:

SU/Glinidi | Pioglitazone | Acarbose | DPP4 inibitori | GLP1 agonisti | SGLT2 inibitori | Insulina

Se non sufficiente, aggiungere un terzo farmaco:

SU/Glinidi	Pioglitazone	Acarbose	DPP4 inibitori	GLP1 agonisti	SGLT2 inibitori	Insulina
Pioglitazone	SU/Glinidi	Pioglitazone	Pioglitazone	Pioglitazone	Pioglitazone[1]	Pioglitazone
Acarbose	Acarbose	SU/Glinidi	SU/Glinidi	SU/Glinidi	Acarbose[1]	Acarbose
DPP4 inib.	DPP4 inib.	SGLT2 inib.[1]	SGLT2 inib.[1]	SGLT2 inib.[1]	DPP4 inib.[1]	DPP4 inib.
GLP1 agon.	GLP1 agon.	Insulina	Insulina	Insulina	GLP1 agon.[1]	GLP1 agon.
SGLT2 inib.[1]	SGLT2 inib.[1]				SU/Glinidi[1]	SGLT2 inib.
Insulina	Insulina				Insulina	SU/Glinidi

In caso di scarso controllo con la triplice terapia, iniziare comunque la terapia insulinica, mantenendo la metformina:

Insulina

con l'eventuale aggiunta di:

SU/Glinidi | Pioglitazone | Acarbose | DPP4 inibitori | GLP1 agonisti | SGLT2 inibinitori

Is It Time to Change the Type 2 Diabetes Treatment Paradigm? No! Metformin Should Remain the Foundation Therapy for Type 2 Diabetes

Silvio E. Inzucchi

Diabetes Care 2017;40:1128–1132 | https://doi.org/10.2337/dc16-2372

Table 1—Major proposed mechanisms of action of metformin

- Reduction in HGP
- Enhanced release of GLP-1 and other gut peptides
- Improvement in peripheral insulin sensitivity
- Decrease in gut carbohydrate absorption
- Increase in enteric glucose extraction
- Increased fatty acid oxidation

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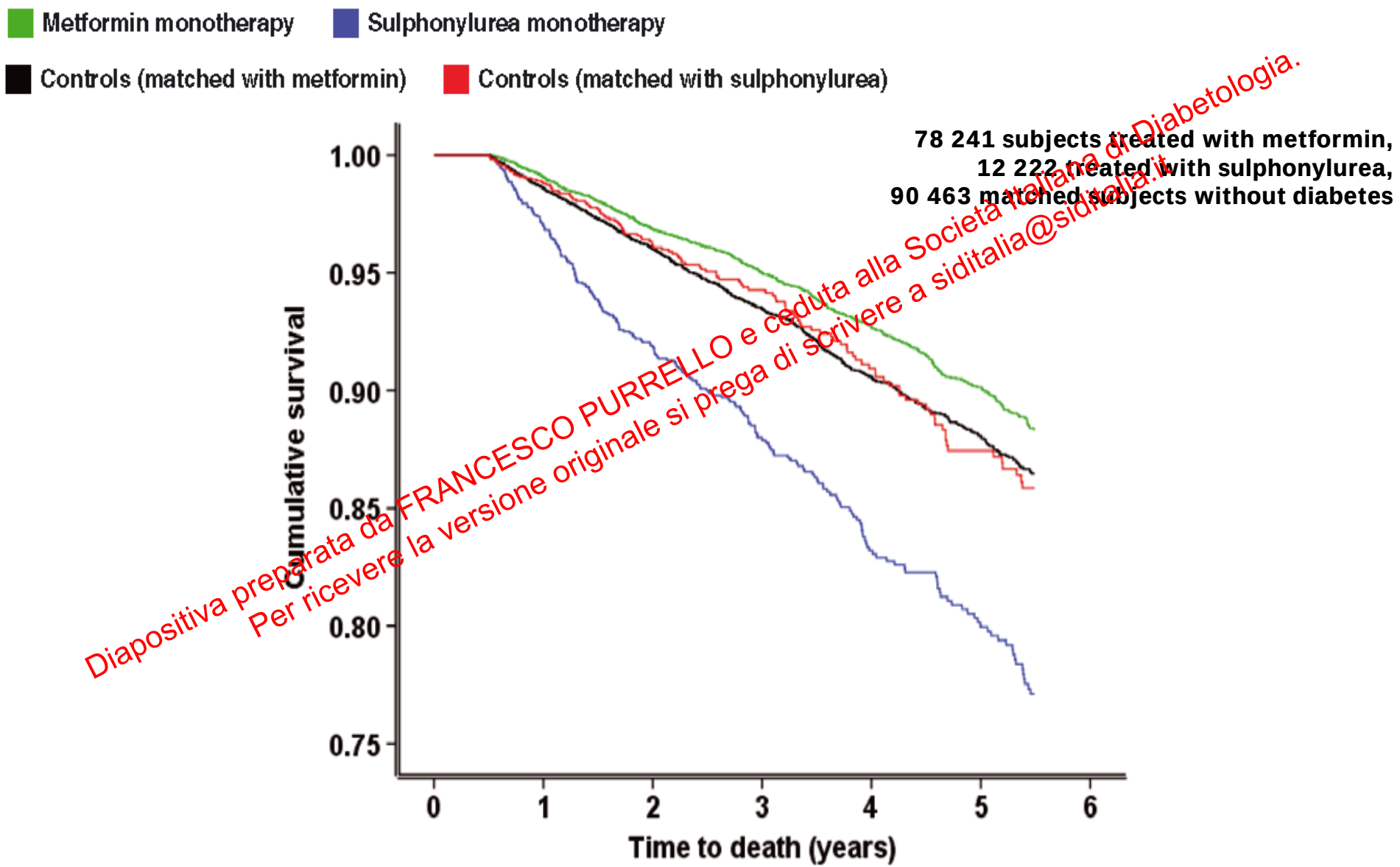
Table 2—Randomized clinical trials involving metformin and CVD outcomes

Trial/year	Comparison	Study population	*N*	Main CVD outcome(s)	HR (95% CI)	*P*
UKPDS 34 (4) (1998)	Metformin vs. diet	Overweight, newly diagnosed	1,704	All-cause mortality	0.64 (0.45, 0.91)	NR
	Metformin vs. SU/insulin	T2D patients		Myocardial infarction	0.61 (0.41, 0.89)	0.010
HOME (6) (2009)	Metformin vs. placebo	T2D patients on insulin	390	Expanded MACE*	0.61 (0.40, 0.94)	0.02
SPREAD-DIMCAD (7) (2013)	Metformin vs. glipizide	T2D patients with CAD	304	Expanded MACE†	0.54 (0.30, 0.90)	0.026

CAD, coronary artery disease; MACE, major adverse cardiovascular events; NR, not reported; SU, sulfonylurea. *Myocardial infarction, acute coronary syndrome, coronary or peripheral revascularization, electrocardiogram changes, heart failure, stroke/transient ischemic attack. †Cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization.

Kaplan–Meier curves comparing metformin or sulphonylurea monotherapy with their matched non-diabetic control group in patients aged 71–75 years at baseline from the UK Clinical Practice Research Datalink (CPRD)



Bannister CA et al Diabetes Obes Metab16: 1165–1173, 2014

Metformin and ageing: improving ageing outcomes beyond glycaemic control

Diabetologia (2017) 60:1630–1638

Willy Marcos Valencia[1,2] · Ana Palacio[1,2,3] · Leonardo Tamariz[1,2,3] · Hermes Florez[1,2,3]

Metformin might inhibit the ageing process Metformin reduces inflammation and ameliorates DNA and cellular damage. Data from definitive large randomised clinical trials in humans are lacking, but observational and pilot data show that metformin may improve clinical outcomes beyond diabetes, including cognition, depression and other ageing outcomes.

Metformin and ageing: improving ageing outcomes beyond glycaemic control

Diabetologia (2017) 60:1630–1638

Willy Marcos Valencia[1,2] · Ana Palacio[1,2,3] · Leonardo Tamariz[1,2,3] · Hermes Florez[1,2,3]

Upcoming clinical trials of metformin

1. VA-IMPACT: Participants with heart disease, without diabetes. Outcomes include time to death from any cause, myocardial infarction, stroke, hospitalisation for unstable angina, or symptom-driven coronary revascularisation.
2. TAME: Participants without diabetes. Outcomes include time to development of age-dependent diseases (e.g. cancer), CVD, dementia and type 2 diabetes.
3. ePREDICE: Participants with prediabetes. Outcomes include microvascular complications and cognitive function.

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Pioglitazone	SU/Glinidi	Pioglitazone	Pioglitazone	Pioglitazone	Pioglitazone[1]	Pioglitazone
Acarbose	Acarbose	SU/Glinidi	SU/Glinidi	SU/Glinidi	Acarbose[1]	Acarbose
DPP4 inib.	DPP4 inib.	SGLT2 inib.[1]	SGLT2 inib.[1]	SGLT2 inib.[1]	DPP4 inib.[1]	DPP4 inib.
GLP1 agon.	GLP1 agon.	Insulina	Insulina	Insulina	GLP1 agon.[1]	GLP1 agon.
SGLT2 inib.[1]	SGLT2 inib.[1]				SU/Glinidi[1]	SGLT2 inib.
Insulina	Insulina				Insulina	SU/Glinidi

In caso di scarso controllo con la triplice terapia, iniziare comunque la terapia insulinica, mantenendo la metformina:

Insulina

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Terapia "personalizzata"

- in base all'età

- in base al peso corporeo

- in base alle complicanze cardiovascolari

Osservatorio ARNO Diabete

Il profilo assistenziale della popolazione con diabete

Tabella 2

Caratteristiche demografiche delle persone con diabete

Classi di età	Maschi		Femmine		Totale	
	N	%	N	%	N	%
0-19	1.859	0,7	1.755	0,6	3.614	0,7
20-34	3.316	1,2	10.116	3,7	13.432	2,4
35-49	20.075	7,2	25.313	9,4	45.388	8,3
50-64	76.069	27,3	46.536	17,2	122.605	22,3
65-79	126.805	45,5	106.703	39,5	233.508	42,6
>=80	50.590	18,2	79.599	29,5	130.189	23,7
Totale	**278.714**	**100,0**	**270.022**	**100,0**	**548.735**	**100,0**

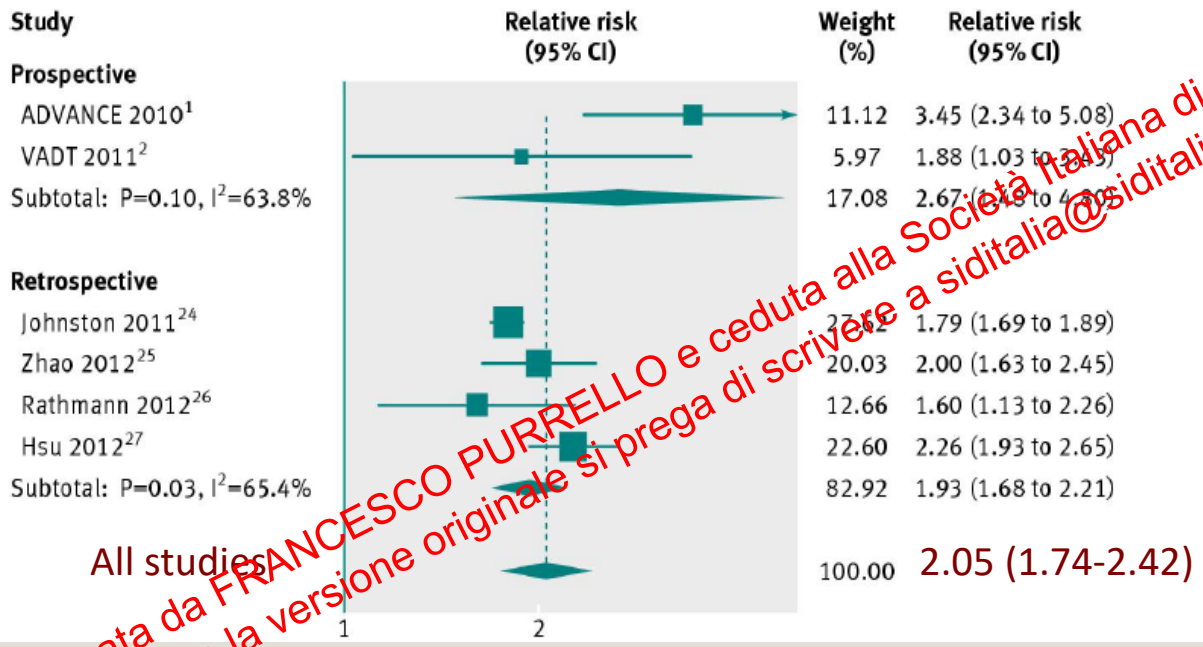
American Diabetes Association

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)

Terapia del diabete nel paziente anziano

- Evitare al paziente complicanze metaboliche acute (ipoglicemia, iperglicemia iperosmolare)
- Prevenire la comparsa e/o la progressione delle complicanze.
- Conservare le funzioni cognitive e la capacità fisica
- Assicurare un'adeguata qualità di vita

Severe hyoglycaemia and CVD



What this study adds

Conventional meta-analysis suggests that severe hypoglycaemia is associated with a higher risk of cardiovascular disease

Furthermore, a bias analysis indicates that comorbid severe illness alone may not entirely explain the positive association between severe hypoglycaemia and risk of cardiovascular disease

Avoiding severe hypoglycaemia may be important to prevent cardiovascular disease in people with type 2 diabetes

Goto A, BMJ 2013

Hypoglycemic Episodes and Risk of Dementia in Older Patients with Type 2 Diabetes Mellitus

Rachel A. Whitmer[1], **Andrew J. Karter**[1], **Kristine Yaffe**[2], **Charles P. Quesenberry Jr.**[1], and **Joseph V. Selby**[1]

JAMA 2009

Frequency of hypoglycemic episodes by dementia status

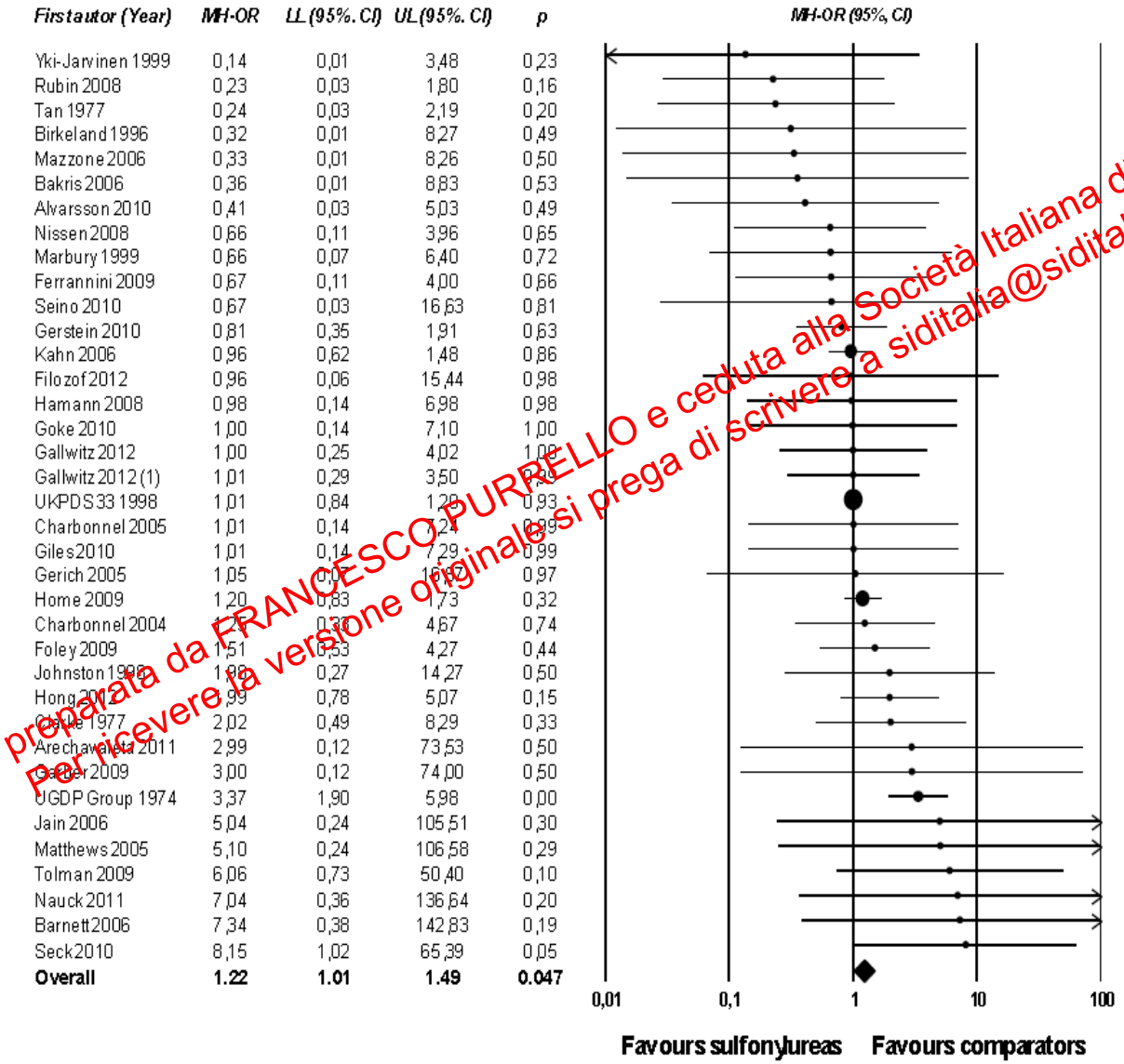
	No. (%)		Age-adjusted incidence rates per 10,000 person-years (95% CI)	Excess attributable risk per year, % (95% CI)[a]
	Dementia (n=1822)	Nondementia (n=14,845)		
Any hypoglycemia				
No	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
Yes	250 (16.95)	1215 (83.05)[b]	566.82 (496.52-637.48)	2.39 (1.72-3.01)
No. of hypoglycemic episodes				
0	1572 (10.34)	13,630 (89.66)	327.60 (311.02-343.18)	
1	150 (14.84	852 (85.16)	491.73 (412.60-570.80)	1.64 (0.91-2.36)
2	57 (22.26)	201 (77.74)	761.75 (561.24-962.27)	4.34 (2.36-6.32)
3 or more	43 (20.40)	162 (79.60)[b]	755.46 (526.46-984.46)	4.28 (2.10-6.44)

Association of Depression With Increased Risk of Severe Hypoglycemic Episodes in Patients With Diabetes

Table 2. Hazard Ratios for Major Depression for Time to an Hypoglycemic Event or for Relative Risk for Number of Hypoglycemic Events (N = 4,117)

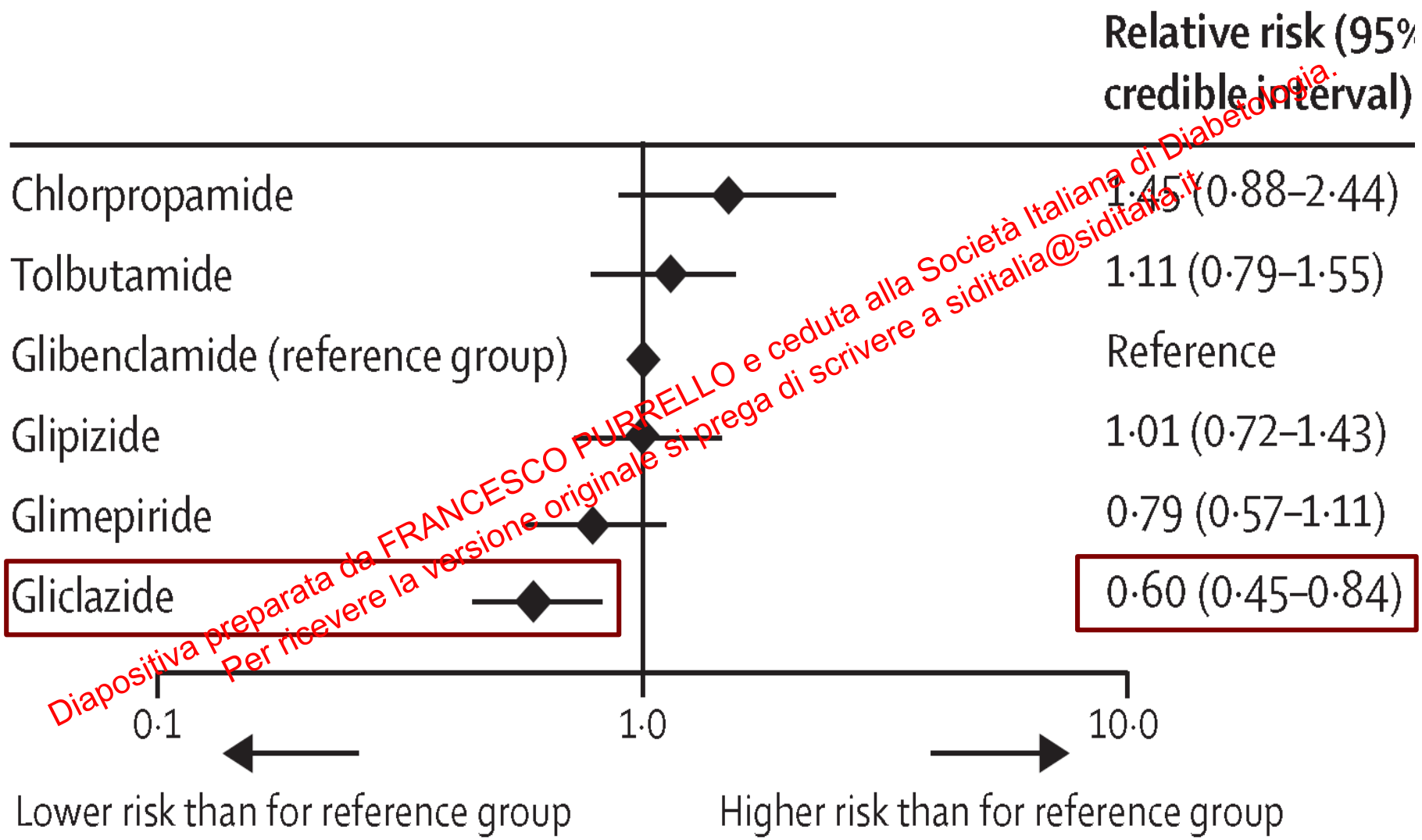
Covariate Adjustment	Time to Hypoglycemic Event HR (95% CI)	Number of Hypoglycemic Events RR (95% CI)
Unadjusted	1.89 (1.39-2.56)	1.91 (1.49-2.43)
Adjusted		
Prior hypogycemic event[a]	1.65 (1.21-2.25)	1.69 (1.32-2.17)
Prior hypogycemic event[a] and demographic characteristics[b]	1.78 (1.30-2.44)	1.76 (1.37-2.26)
Prior hypogycemic event[a] and demographic[b] and clinical[c] characteristics	1.41 (1.03-1.94)	1.39 (1.08-1.80)
Prior hypogycemic event[a] and demographic,[b] clinical,[c] and health risk behavior[d] characteristics	1.42 (1.03-1.96)	1.34 (1.03-1.74)

A significant increase in mortality observed with sulfonylureas (MHOR: 1.22 [1.01–1.49], P=0.047): a meta-analysis of randomized clinical trials



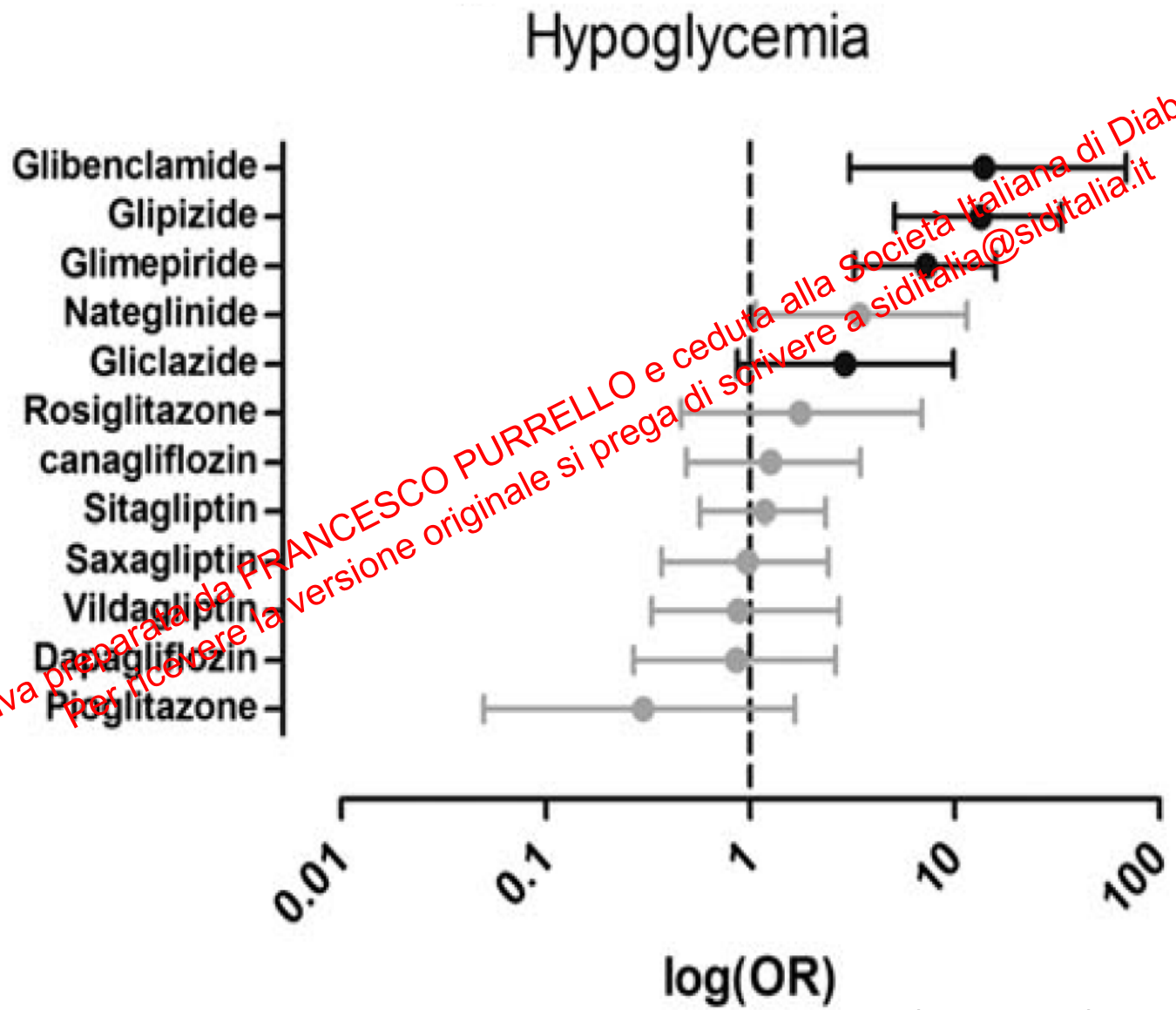
Monami M. . et al. Diabetes Obes Metab 15: 938–953, 2013

Comparison of cardiovascular-related mortality between sulfonylureas by network meta-analysis using direct and indirect evidence from 13 studies



Simpson SH et al. Lancet Diabetes Endocrinol 3:43-51, 2015

Network meta-analysis of RCTs lasting 12–52 weeks and evaluating SUs added to inadequate metformin monotherapy (≥1000 mg/day) in type 2 diabetes



Andersen SE et al. Br J Clin Pharmacol 2016

2015 American Geriatrics Society beers criteria for potentially inappropriate medication use in older adults

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting; refers to sole use of short- or rapid-acting insulins to manage or avoid hyperglycemia in absence of basal or long-acting insulin; does not apply to titration of basal insulin or use of additional short- or rapid-acting insulin in conjunction with scheduled insulin (i.e., correction insulin)	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long-duration Chlorpropamide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion	Avoid	High	Strong
Glyburide	Glyburide: higher risk of severe prolonged hypoglycemia in older adults			

J Am Geriatr Soc 63:2227–2246, 2015

Sitagliptin Safety Profile

% of patients	Placebo (n=125)	5 mg BID (n=124)	12.5 mg BID (n=123)	25 mg BID (n=123)	50 mg BID (n=122)	**Glipizide** 5–20 mg QD (n=123)
Treatment-related adverse events	10	9	16	14	12	28
Serious adverse events	3	3	2	1	3	5
Discontinuation	0	1	2	1	2	3
Hypoglycemia	2	0	4	4	2	17

Tolerability and efficacy of glycemic control with saxagliptin in older patients (aged ≥ 65 years) with inadequately controlled type 2 diabetes mellitus

Table 1 Pivotal phase III Studies (24 Weeks) of saxagliptin in patients with type 2 diabetes mellitus

Study	Entry conditions	Number of patients aged ≥ 65 years	Number of patients aged < 65 years	Treatment groups	
				Saxagliptin	Comparator
SAXA vs PBO as monotherapy in drug-naïve patients					
NCT00121641[18]	HbA_{1c} 7%–10% (n = 401)[a]	63	338	2.5, 5, or 10 mg QD	PBO
				2.5 mg QD	PBO
NCT00316082[24]	HbA_{1c} 7%–10% (n = 365)	64	301	2.5/5 mg QD[b]	PBO
				5 mg QD	PBO
SAXA vs PBO as add-on to continuing therapy with another oral antidiabetic drug					
NCT00121667[20]	MET (1500–2550 mg/d ≥ 8 wk)	77	626	2.5, 5, or 10 mg	PBO + MET
(add-on to MET)	HbA_{1c} 7%–10% (n = 743)			QD + MET	
NCT00295633[19]	TZD (stable dose)[c] ≥ 12 wk	87	478	2.5 or 5 mg	PBO + TZD[c]
(add-on to TZD)	HbA_{1c} 7%–10.5% (n = 565)			QD + TZD[c]	
NCT00313313[21]	SU (submaximal)[d] ≥2 mo	137	631	2.5 or 5 mg	PBO + SU[d]
(add-on to SU)	HbA_{1c} 7.5%–10.0% (n = 768)			QD + SU[d]	
SAXA as initial combination therapy with MET vs MET monotherapy in drug-naïve patients					
NCT00327015[22]	HbA_{1c} 8.0%–12.0% (n = 1306)	166	1140	10 mg QD	PBO + MET[e]
				5 or 10 mg QD + MET[e]	

Tolerability and efficacy of glycemic control with saxagliptin in older patients (aged ≥ 65 years) with inadequately controlled type 2 diabetes mellitus

Table 4A Adverse events in older and younger patients with type 2 diabetes mellitus from five pooled studies of saxagliptin vs placebo as monotherapy and as add-on therapy[18-21,24]

	Age ≥ 65 years			Age < 65 years		
	SAXA 2.5 mg	SAXA 5 mg	PBO	SAXA 2.5 mg	SAXA 5 mg	PBO
	n = 149	n = 142	n = 137	n = 733	n = 740	n = 662
Hypoglycemia, n (%)						
Reported[b]	14 (9.4)	9 (6.3)	11 (8.0)	53 (7.2)	60 (8.1)	43 (6.5)
Confirmed[c]	1 (0.7)	0	1 (0.7)	6 (0.8)	4 (0.5)	2 (0.3)
Hypoglycemia excluding study of saxagliptin add-on to glyburide, n (%)	n = 106	n = 100	n = 85	n = 528	n = 529	n = 447
Reported[b]	8 (7.5)	4 (4.0)	5 (5.9)	23 (4.4)	26 (4.9)	17 (3.8)
Confirmed[c]	0	0	0	2 (0.4)	0	1 (0.2)

Experience with Vildagliptin in Patients ≥75 Years with Type 2 Diabetes and Moderate or Severe Renal Impairment

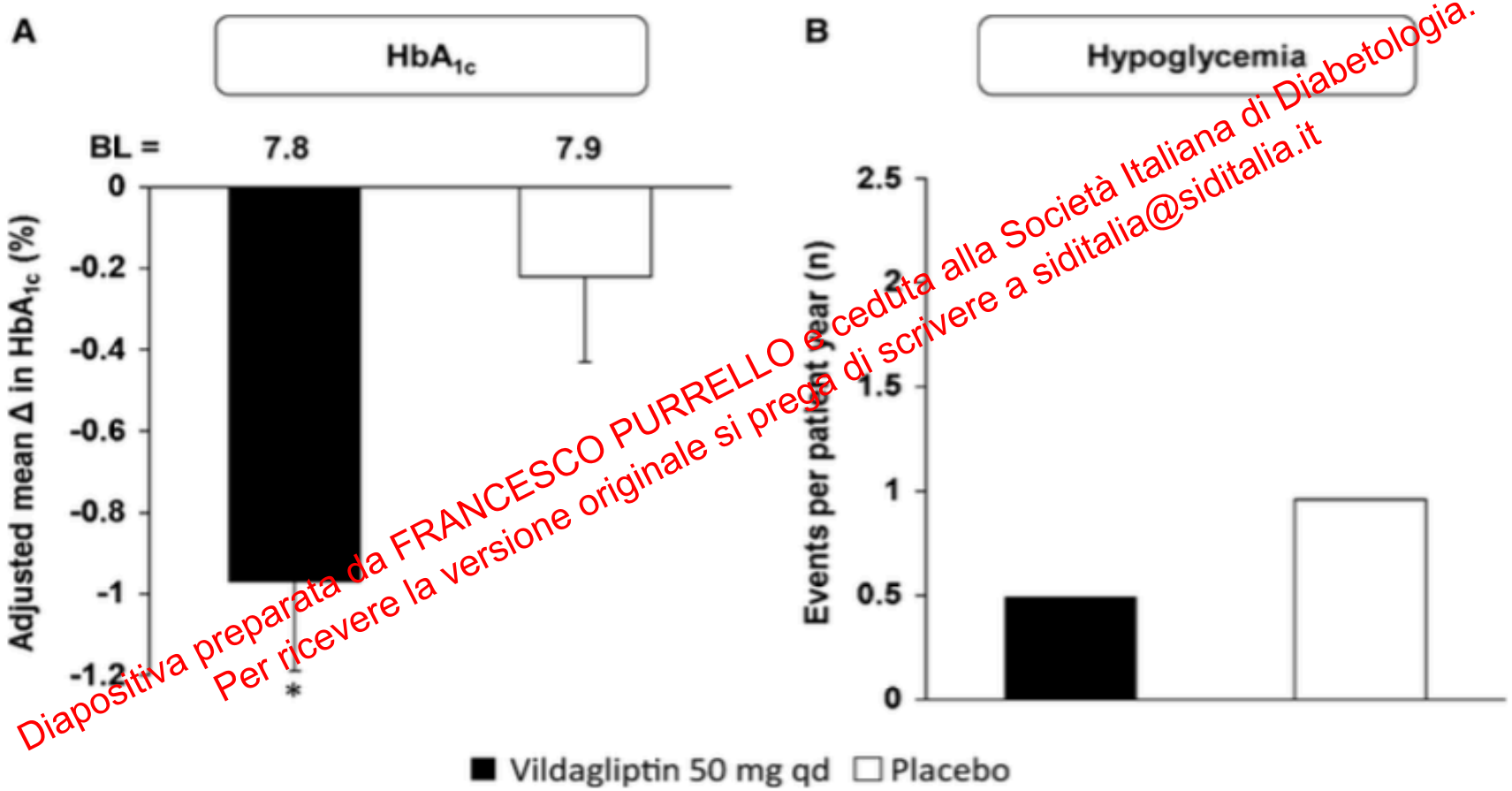


Fig. 1 **a** Adjusted mean (±SEM) change from baseline to week 24 endpoint in HbA_{1c} in patients adding vildagliptin 50 mg qd ($n = 49$) or placebo ($n = 55$) to their ongoing background therapy; *$p < 0.001$ (between-group difference). An ANCOVA model with baseline value, background therapy, pooled center and treatment as covariates was used. **b** Events per patient-year of hypoglycemia during 24-week treatment with vildagliptin 50 mg qd ($n = 50$) or placebo ($n = 55$) added to their ongoing background therapy; $p = 0.970$ (between-group difference). *BL* baseline

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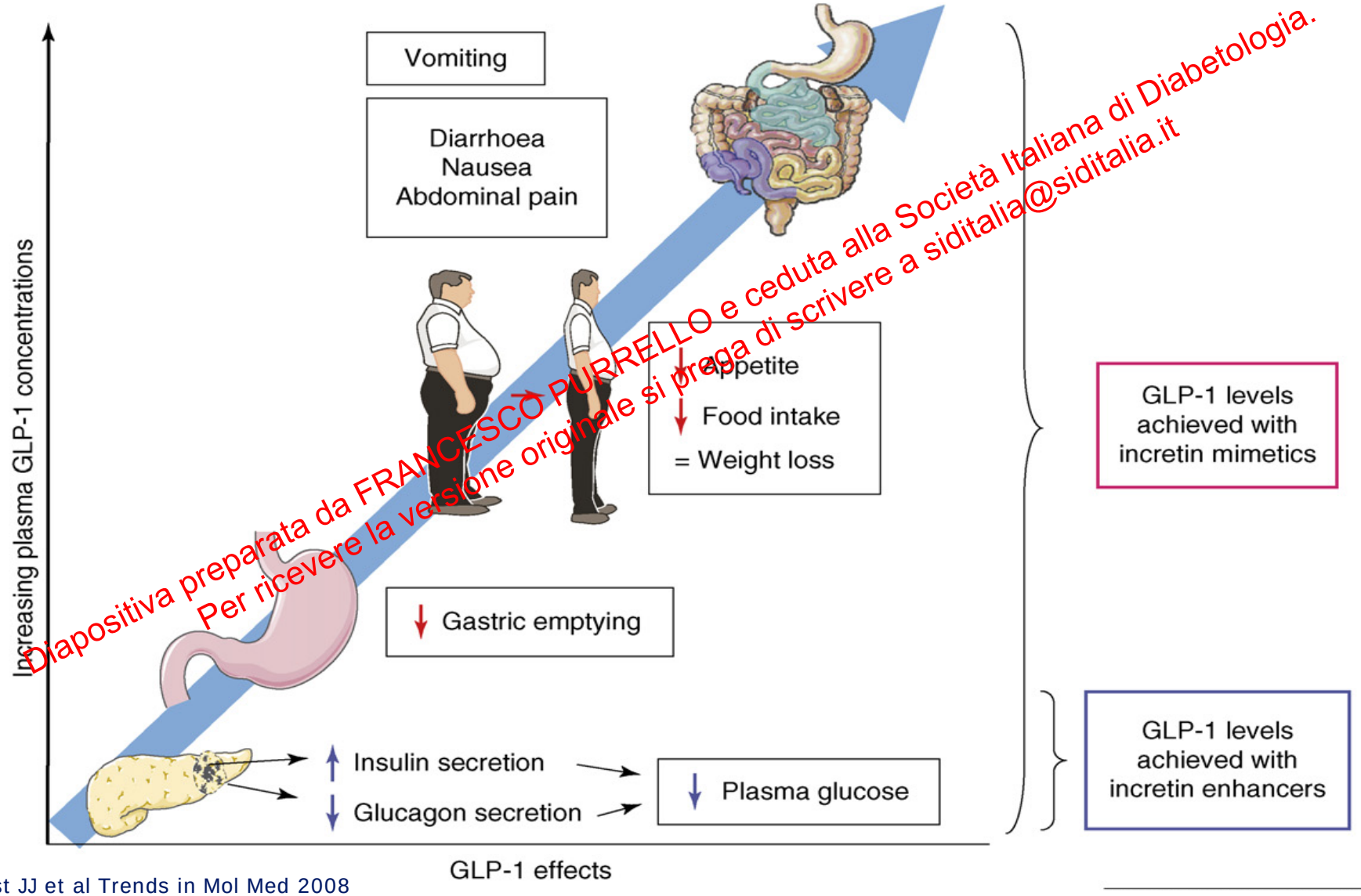
- **in base alle complicanze cardiovascolari**

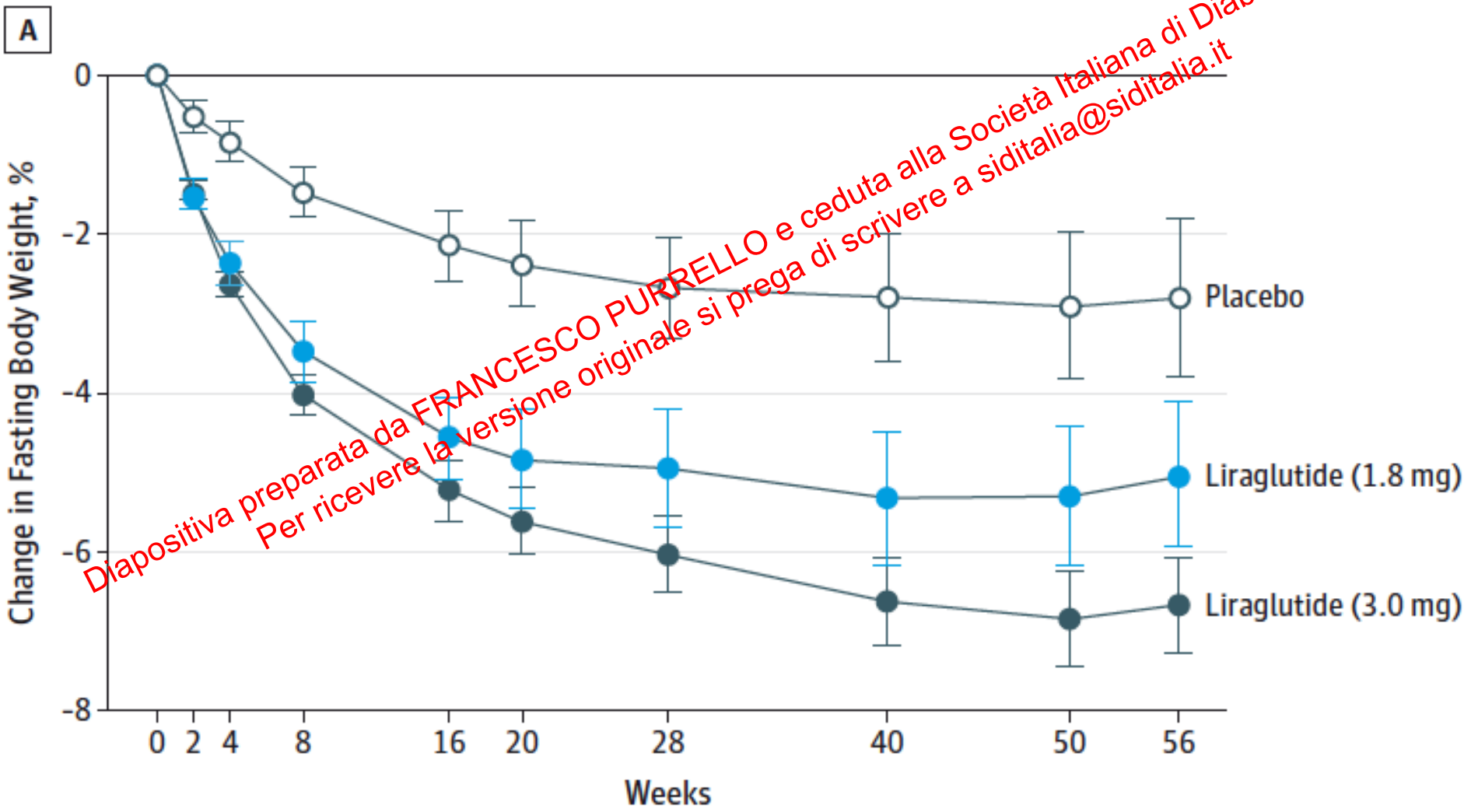
Relazione dose-risposta per gli effetti del GLP-1



Holst JJ et al Trends in Mol Med 2008

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial



Efficacia di analoghi del GLP-1 o Inibitori di DPP-4 su parametri di controllo glicemico

	DPP-4 inhibitors	GLP-1R agonists	
		Short-acting	Continuous
Mechanism of action in the fasting state			
Enhance insulin secretion	+	+/Neutral	++
Suppress glucagon secretion	+	+/Neutral	++
Mechanism of action in the postprandial state			
Enhance insulin secretion	+	+++*	++
Suppress glucagon secretion	+	+++*	++
Slow gastric emptying	Neutral	+++	+
Reduce food intake	Neutral	++	++
Clinical effects			
Reduce FPG†	++	+	+++
Reduce PPG increment‡	+	+++	++
Reduce bodyweight	Neutral	+	+

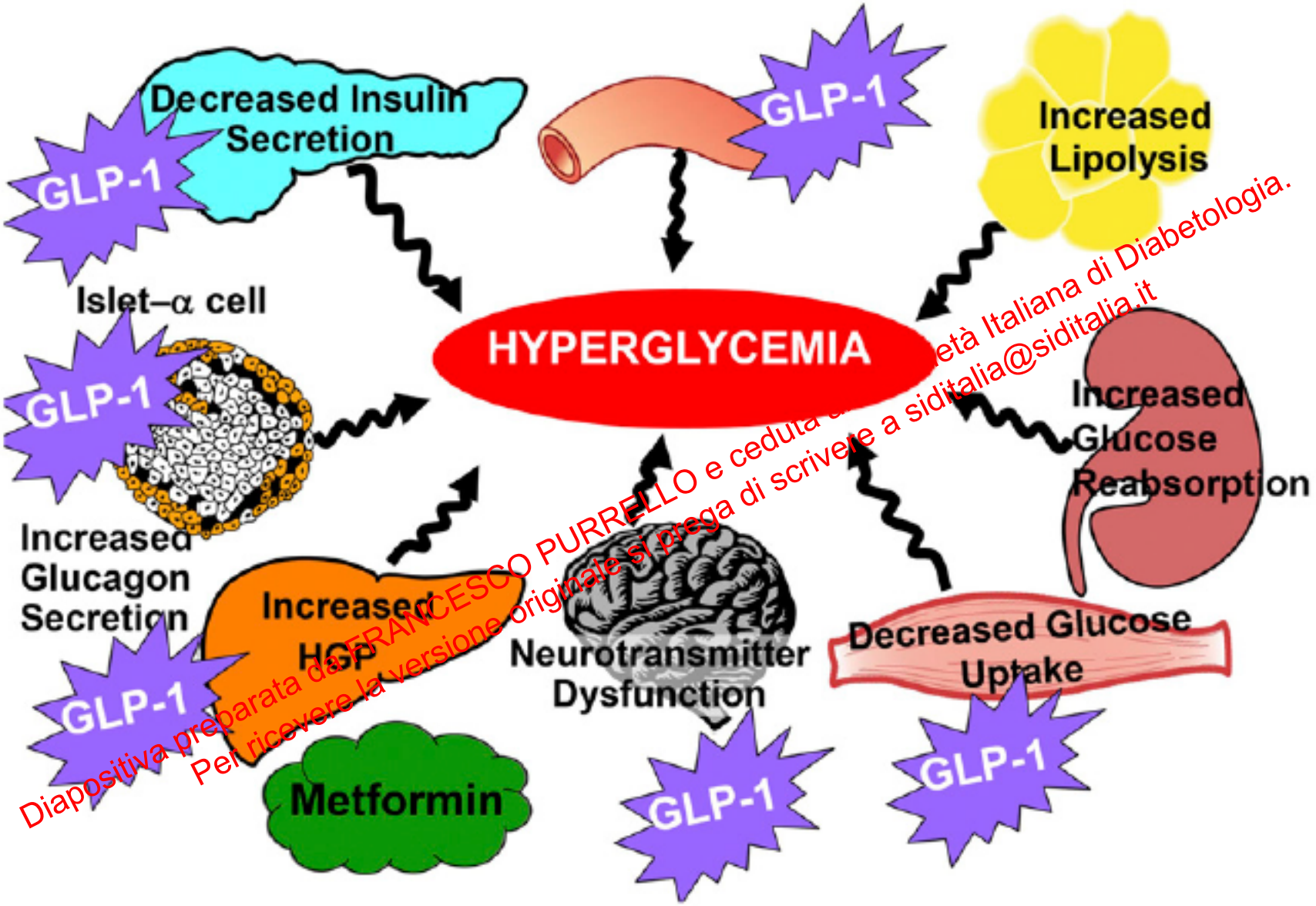


Figure 1—GLP-1 RAs correct six components of the Ominous Octet, whereas metformin corrects only one component.

Is It Time to Change the Type 2 Diabetes Treatment Paradigm? Yes! GLP-1 RAs Should Replace Metformin in the Type 2 Diabetes Algorithm

Muhammad Abdul-Ghani[1,2] and Ralph A. DeFronzo[1]

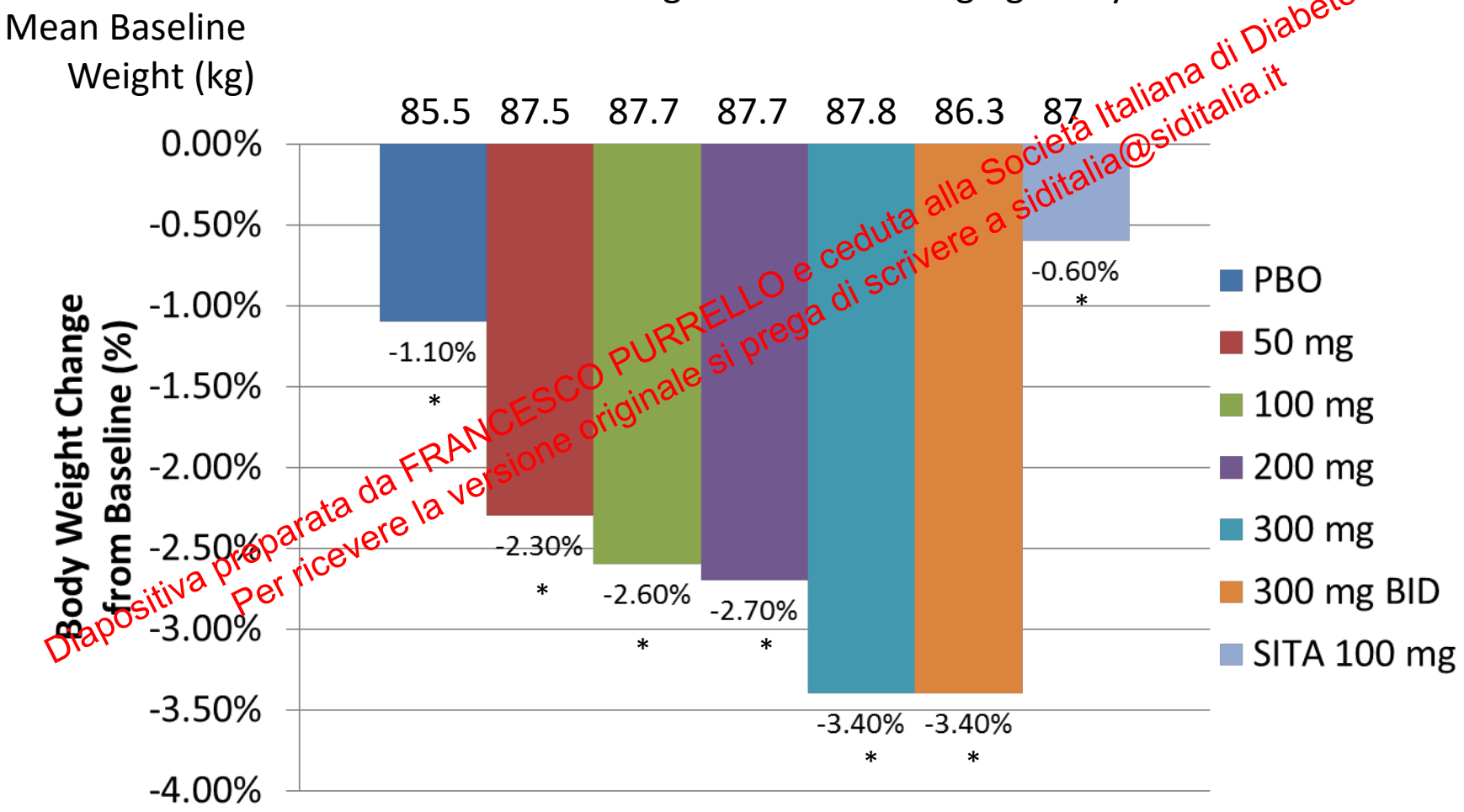
Diabetes Care 2017;40:1121–1127 | https://doi.org/10.2337/dc16-2368

Table 2—Benefits of GLP-1 RAs far outweigh those of metformin

	GLP-1 RAs	Metformin
Pathophysiological defects in T2D (see Fig. 1)	Corrects six of the defects	Corrects only one of the defects
Glucose-lowering efficacy	Strong	Strong
Durability of HbA_{1c} reduction	Strong	None
Weight loss	3–4 kg	1–2 kg
Blood pressure	~2–3 mmHg reduction	Neutral
Lipid profile	Lowers triglycerides, increases HDL cholesterol	Neutral
Cardiovascular protection (MACE)	Reduction by 13–26%	Neutral
Renal protection	Reduction by 22%	Neutral
Tolerability	~10–15% GI side effects	~10–15% GI side effects
Dosing	Weekly subcutaneous injection	Once to twice daily oral administration
Cost	High	Low

Canagliflozin

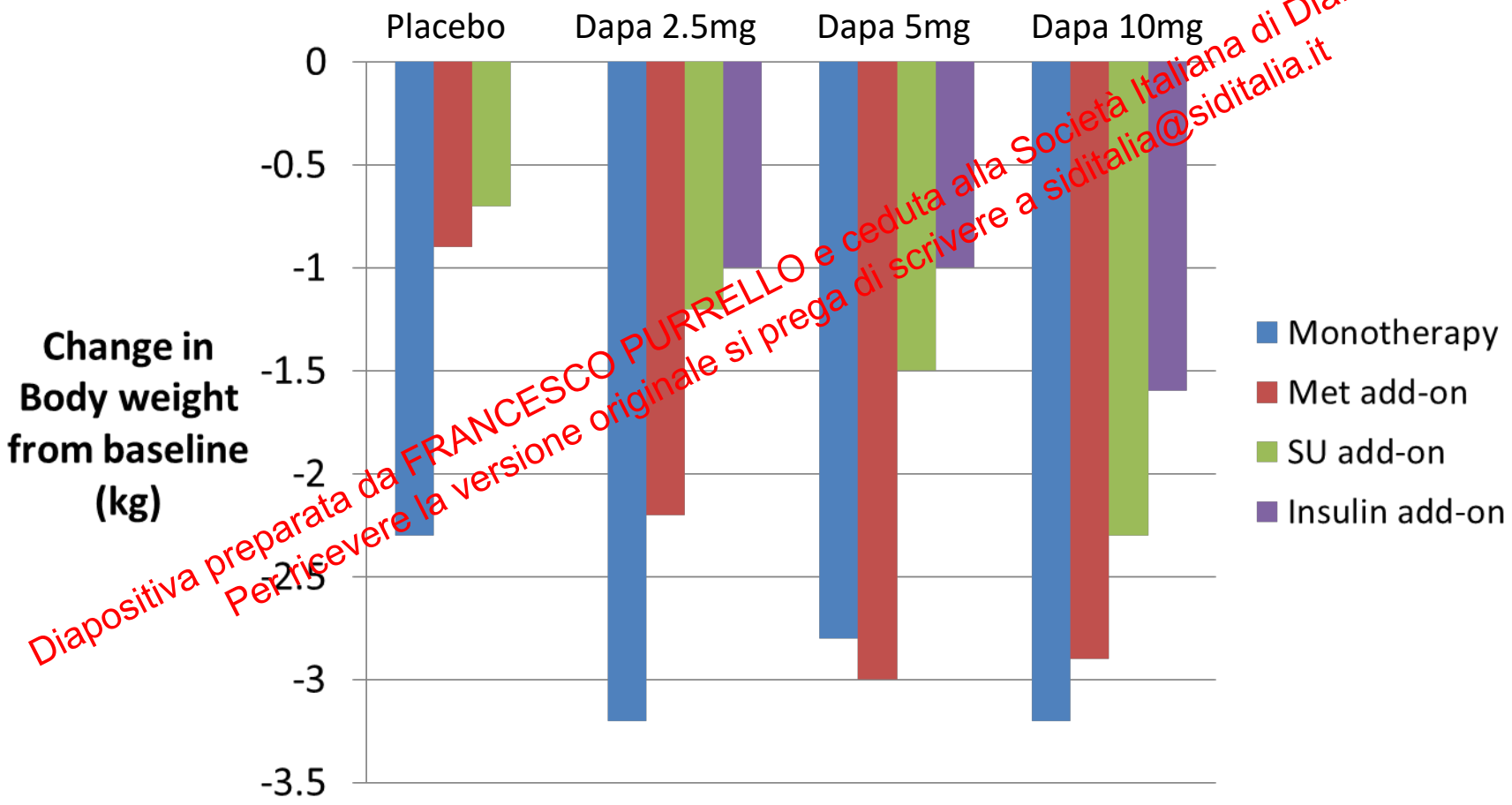
SGLT2 Inhibition for Type 2 Diabetes:
Metformin + Canagliflozin Dose-Ranging Study



Rosenstock J, et al. Abstract 77-OR. ADA 2010.

*P<.001 vs. placebo calculated using LS means

Changes from Baseline in Body Weight in Phase 3 Dapagliflozin Studies



Wilding JPH, et al. Abstract 78-OR. ADA 2010; Strojek K, et al. Abstract 870. EASD 2010; Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224; Bailey CJ, et al. *Lancet.* 2010;375(9733):2223-2233.

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ORIGINAL ARTICLE

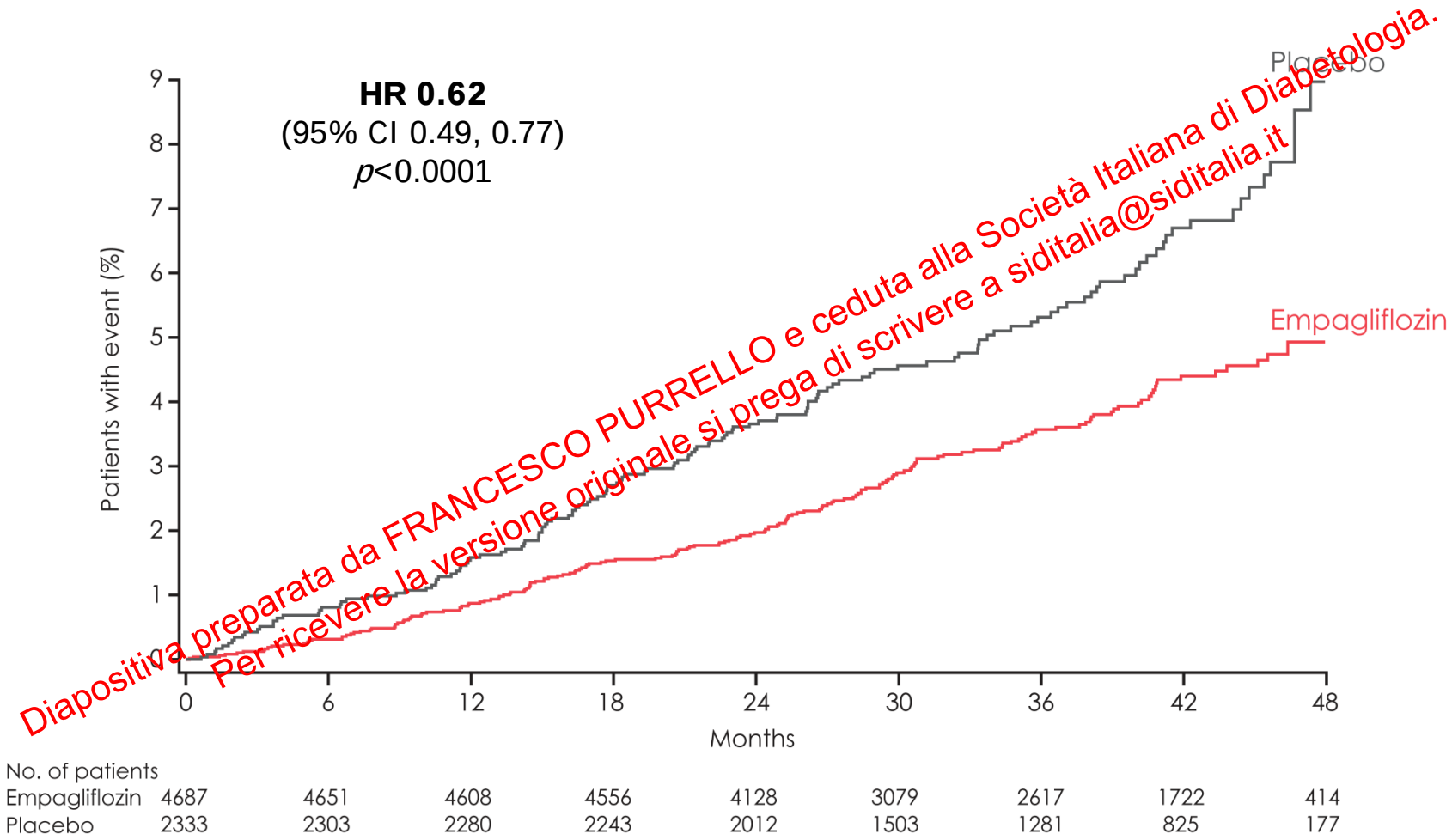
Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

Primary outcome:3-point MACE

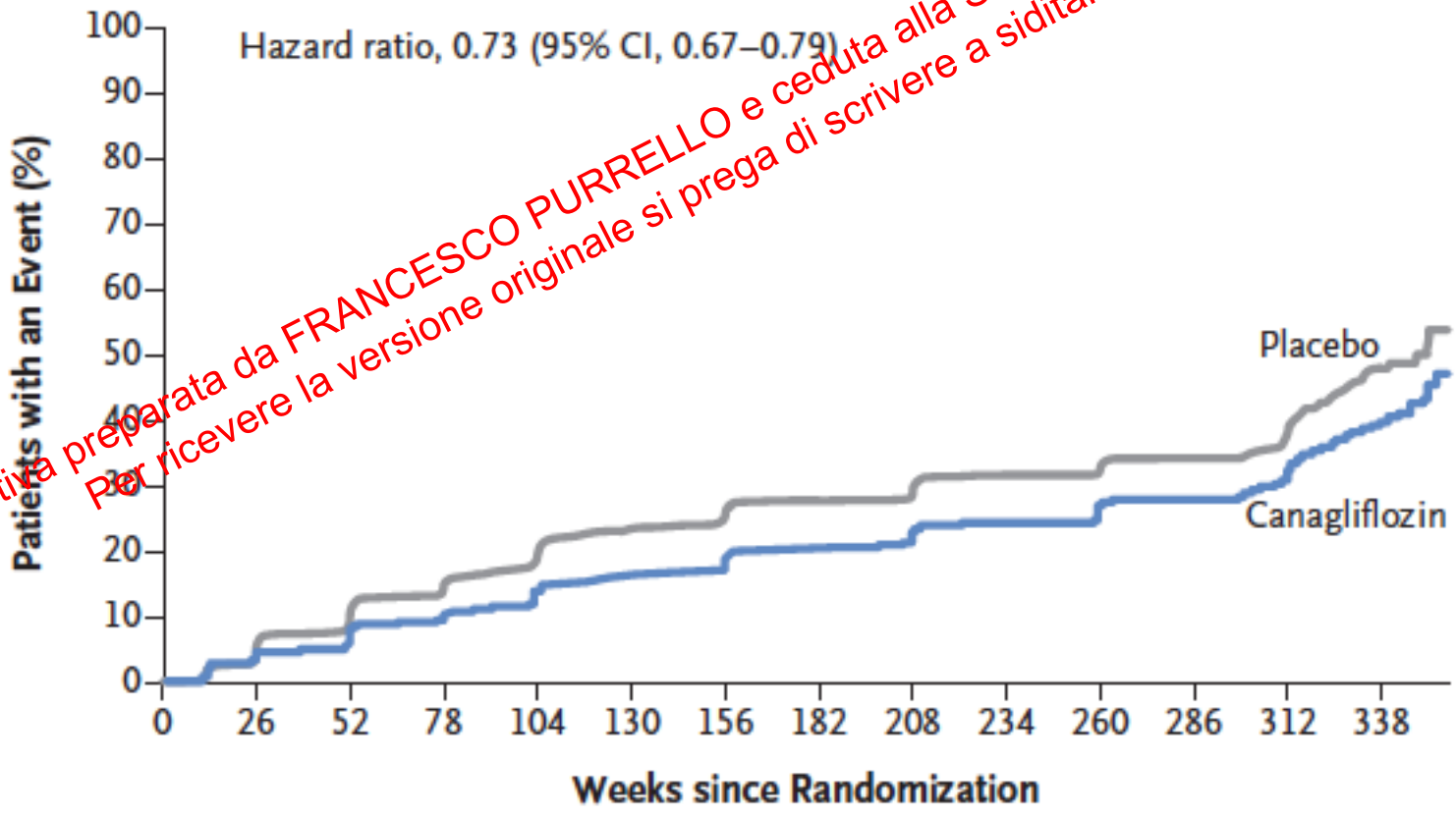
CV death



Cumulative incidence function. HR, hazard ratio

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

C Progression of Albuminuria



ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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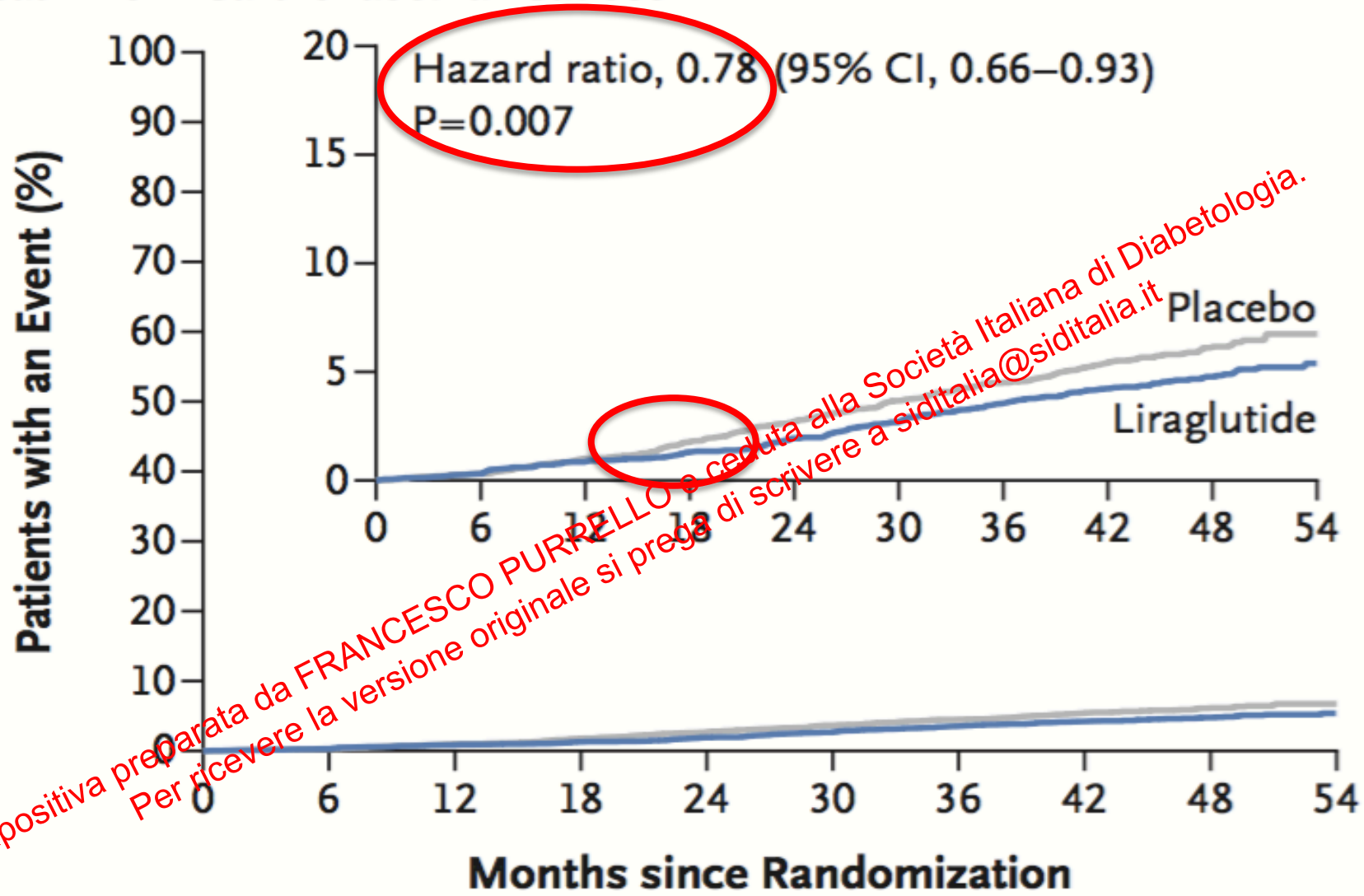
RESULTS

A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of

B Death from Cardiovascular Causes

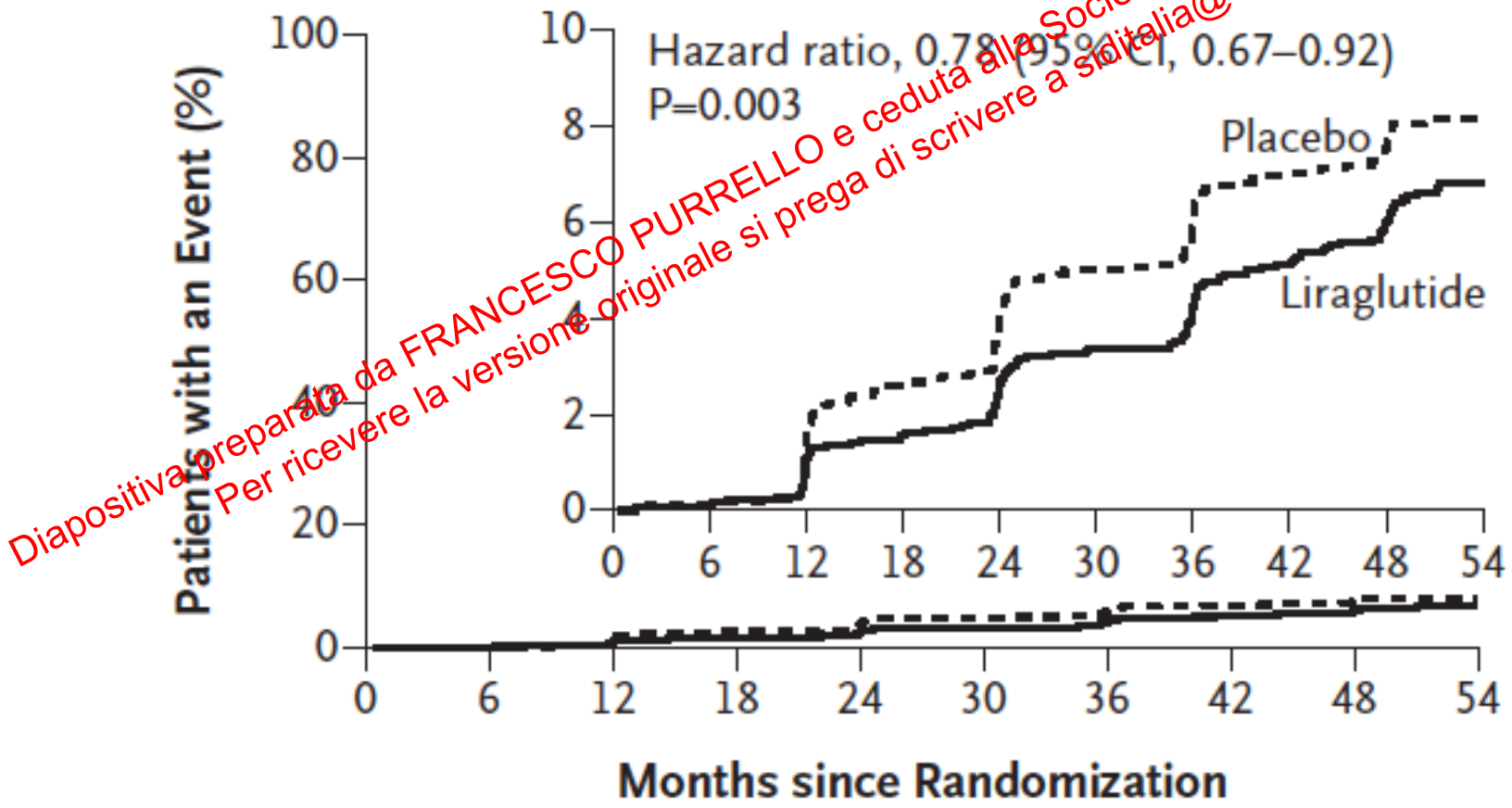


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Liraglutide and Renal Outcomes in Type 2 Diabetes

NEJM 2017



Come è cambiata e come sta cambiando la terapia del diabete?

Terapia basata sul target di controllo glicemico uguale per tutti.

Terapia "personalizzata", almeno in parte sganciata dal compenso glicemico e legata ad effetti dei farmaci sulle complicanze croniche della malattia