Gestione del rischio globale del diabetico tipo 2

un ruolo per i DPP4?

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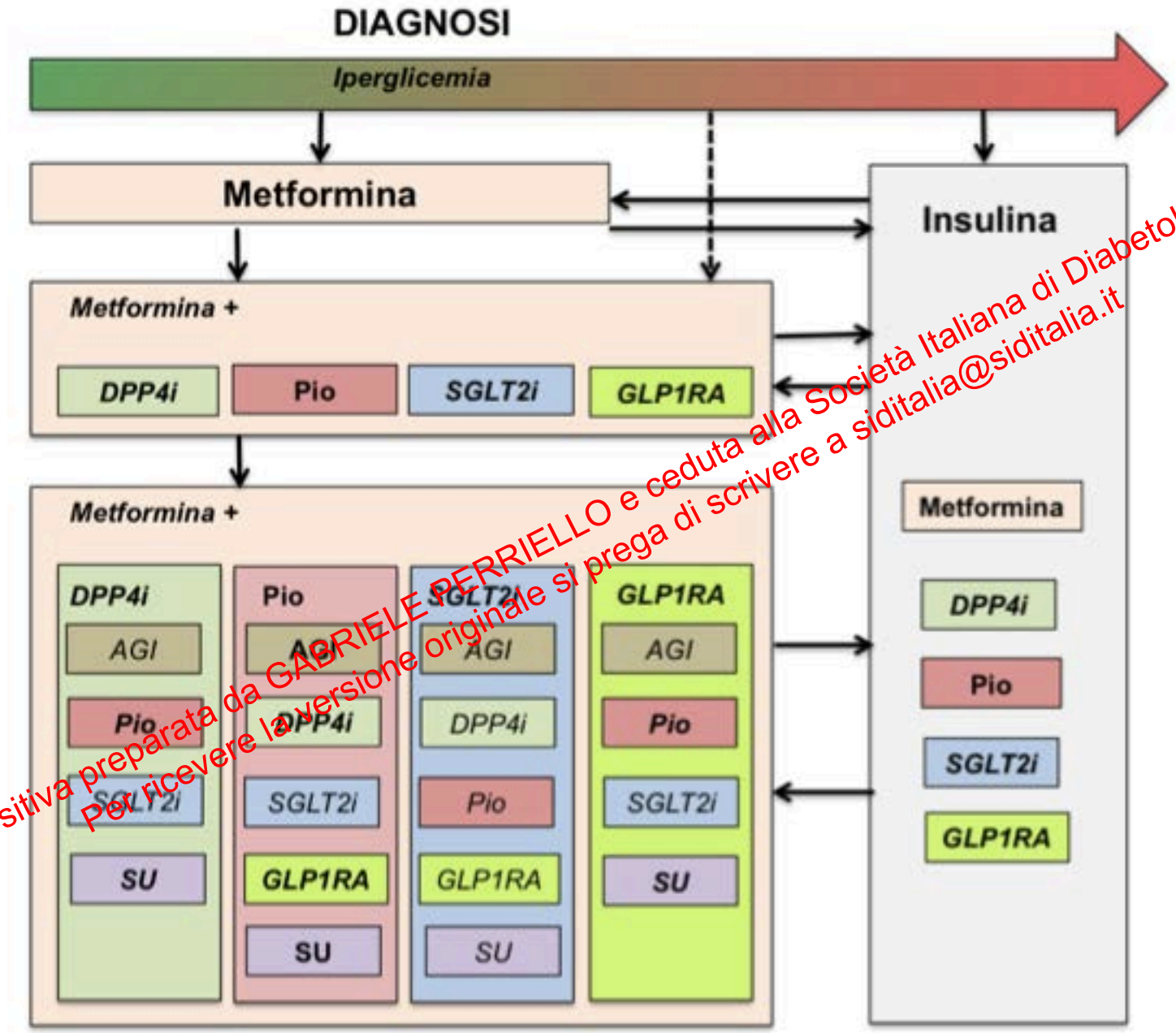
Dopo la metformina (pro e contro rispetto agli altri farmaci)

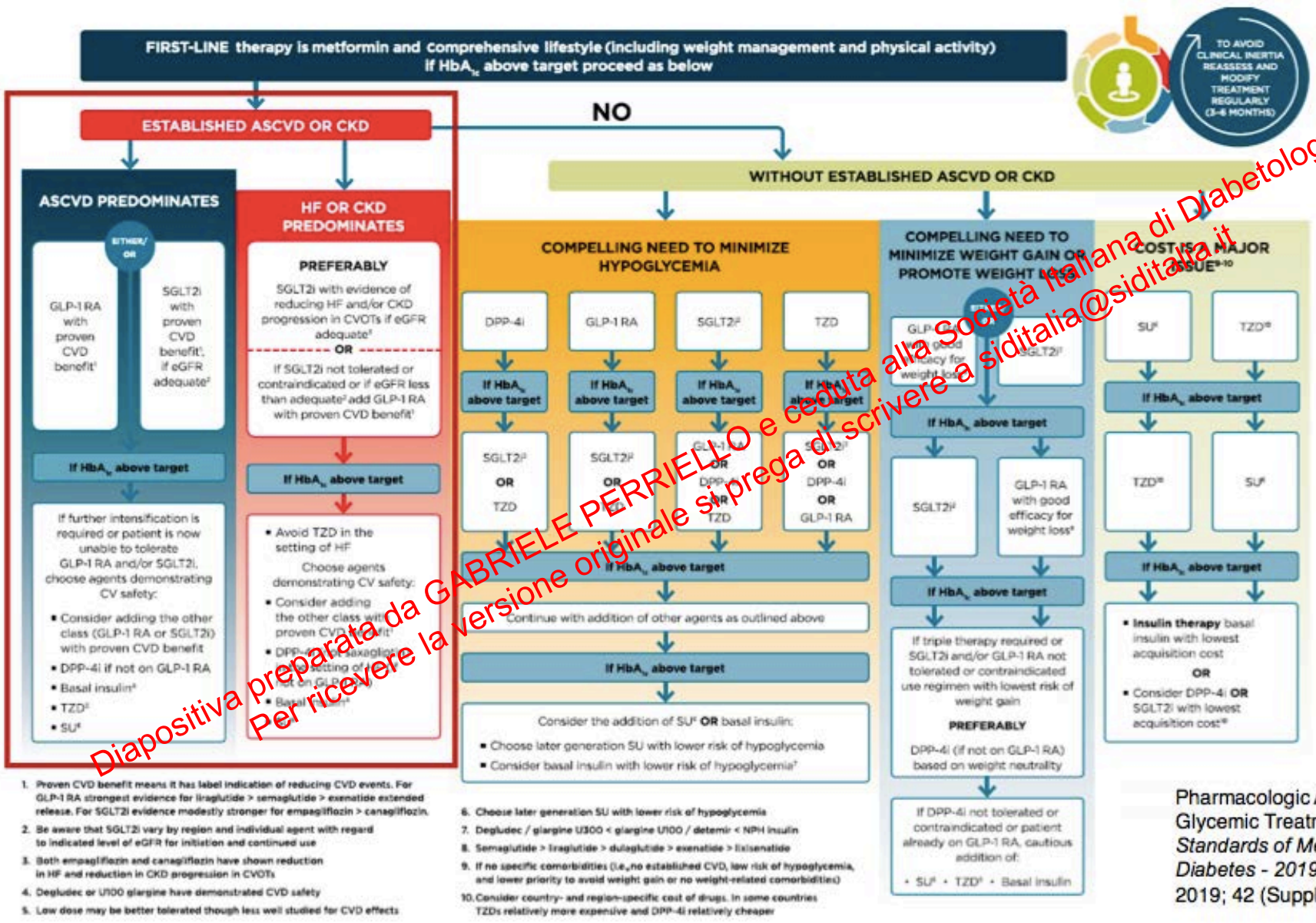
23 novembre 2019

Il sottoscritto dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

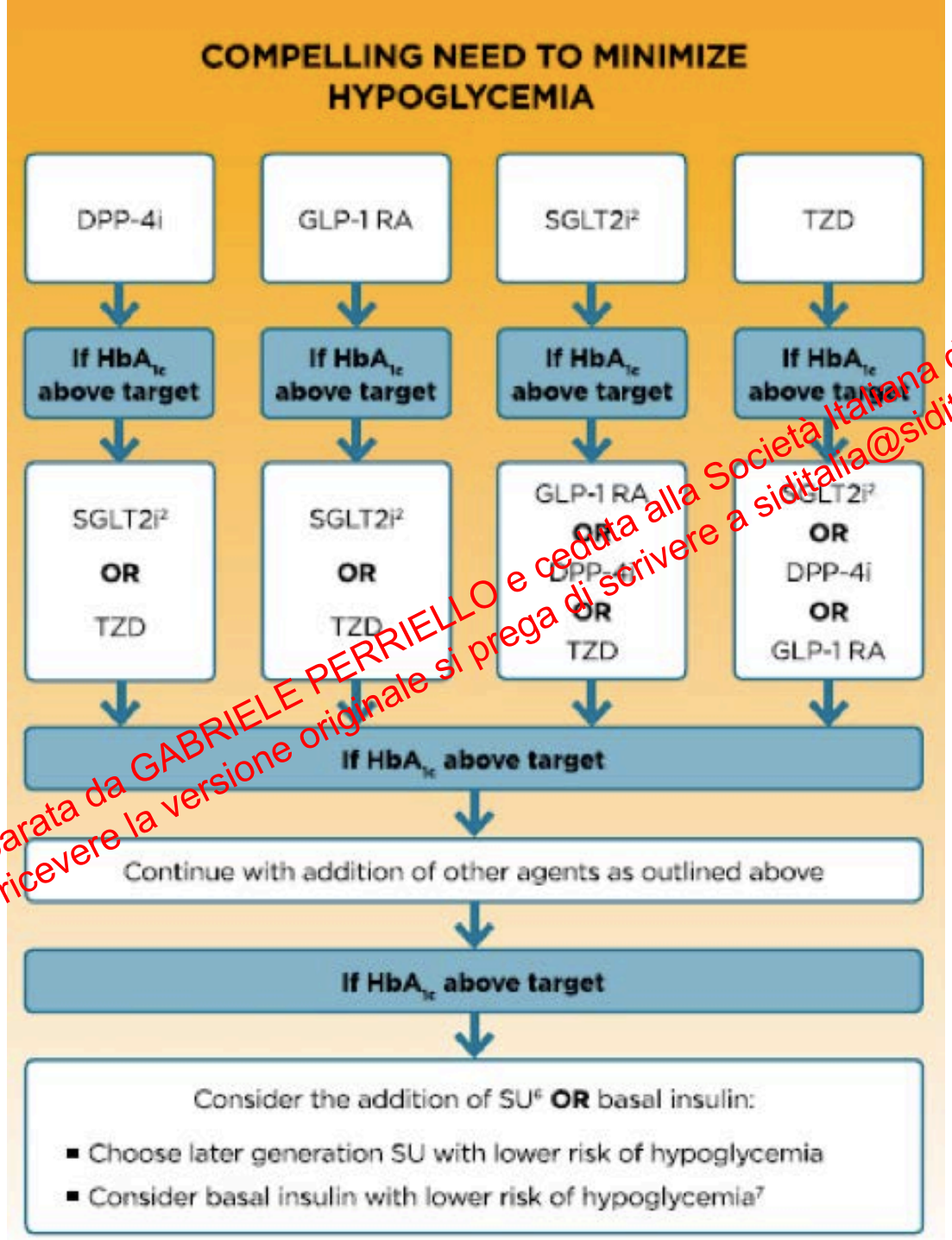


Standard italiani per la cura del diabete mellito 2018

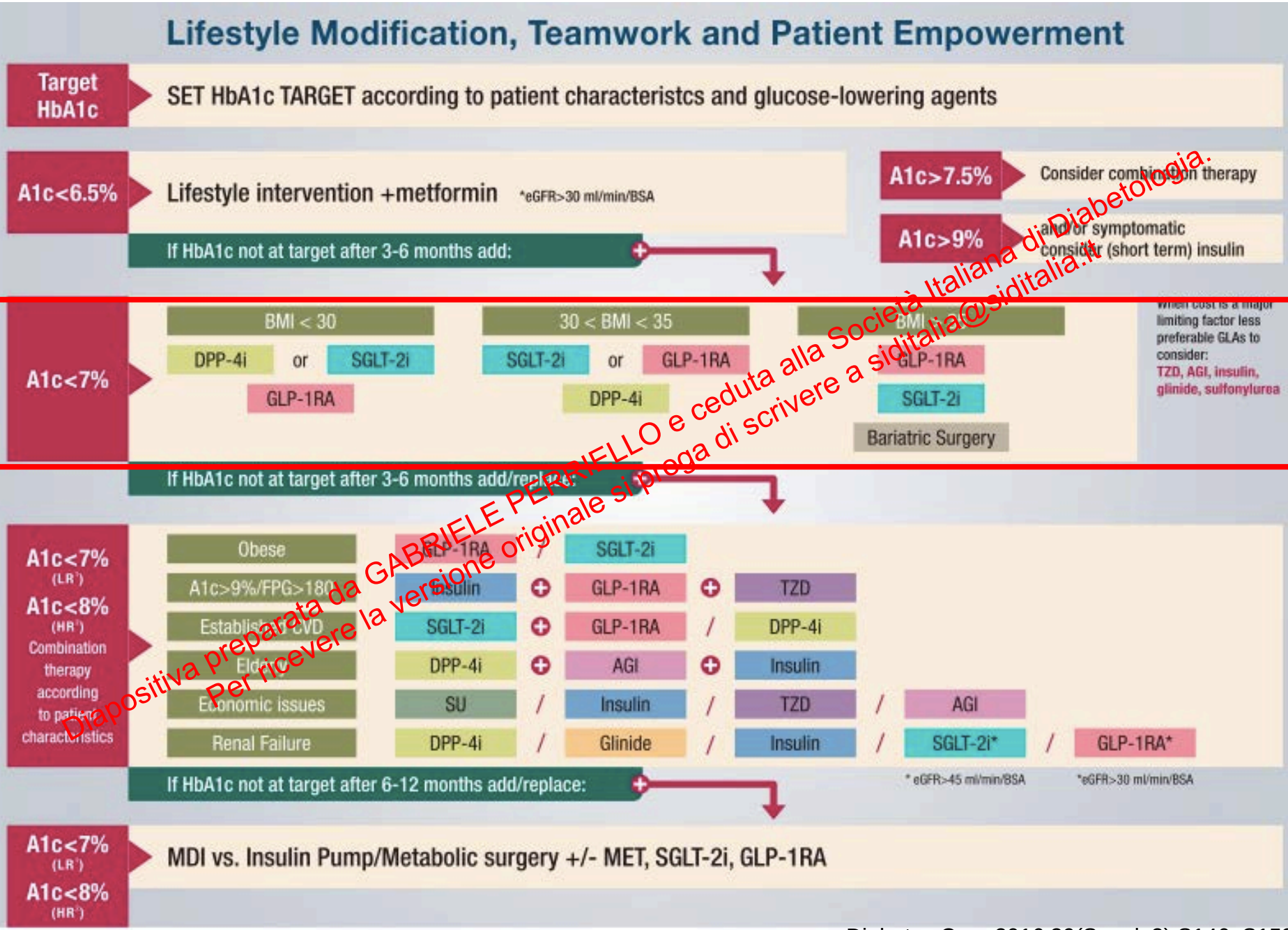


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

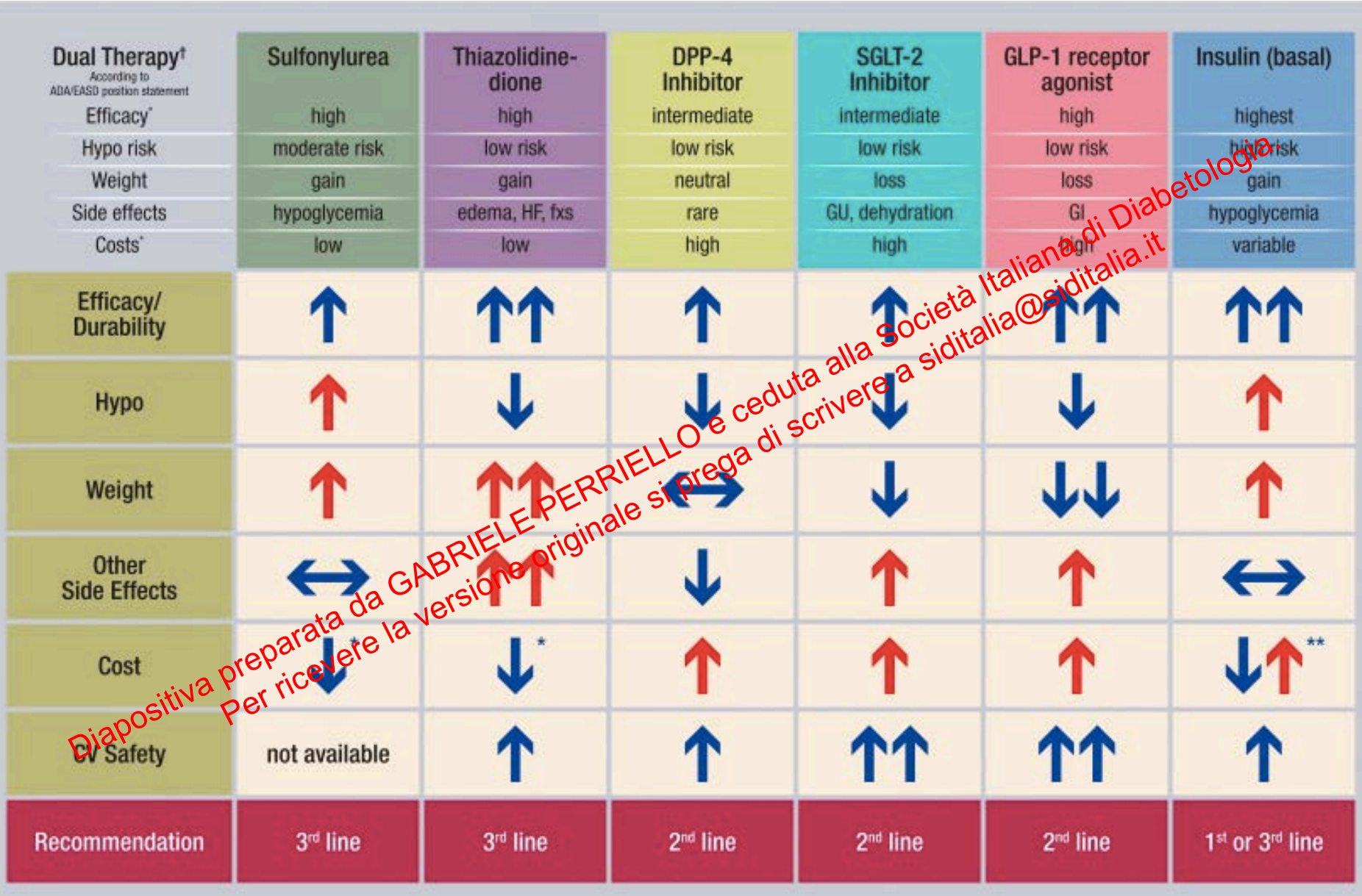
Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes - 2019. Diabetes Care* 2019; 42 (Suppl. 1): S90-S102



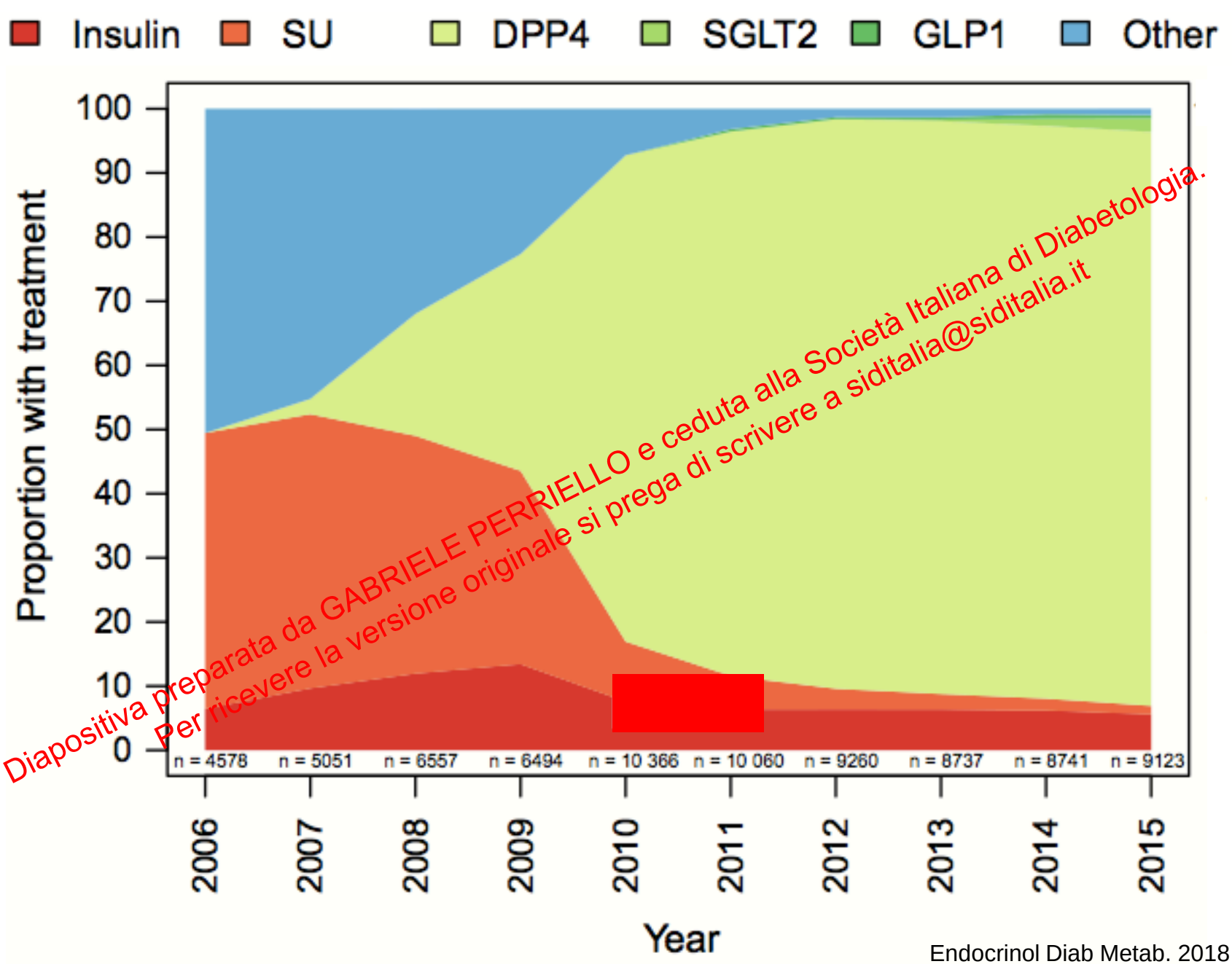
Recommendations of the Israel National Diabetes Council



Diabetes Care 2016;39(Suppl. 2):S146–S153

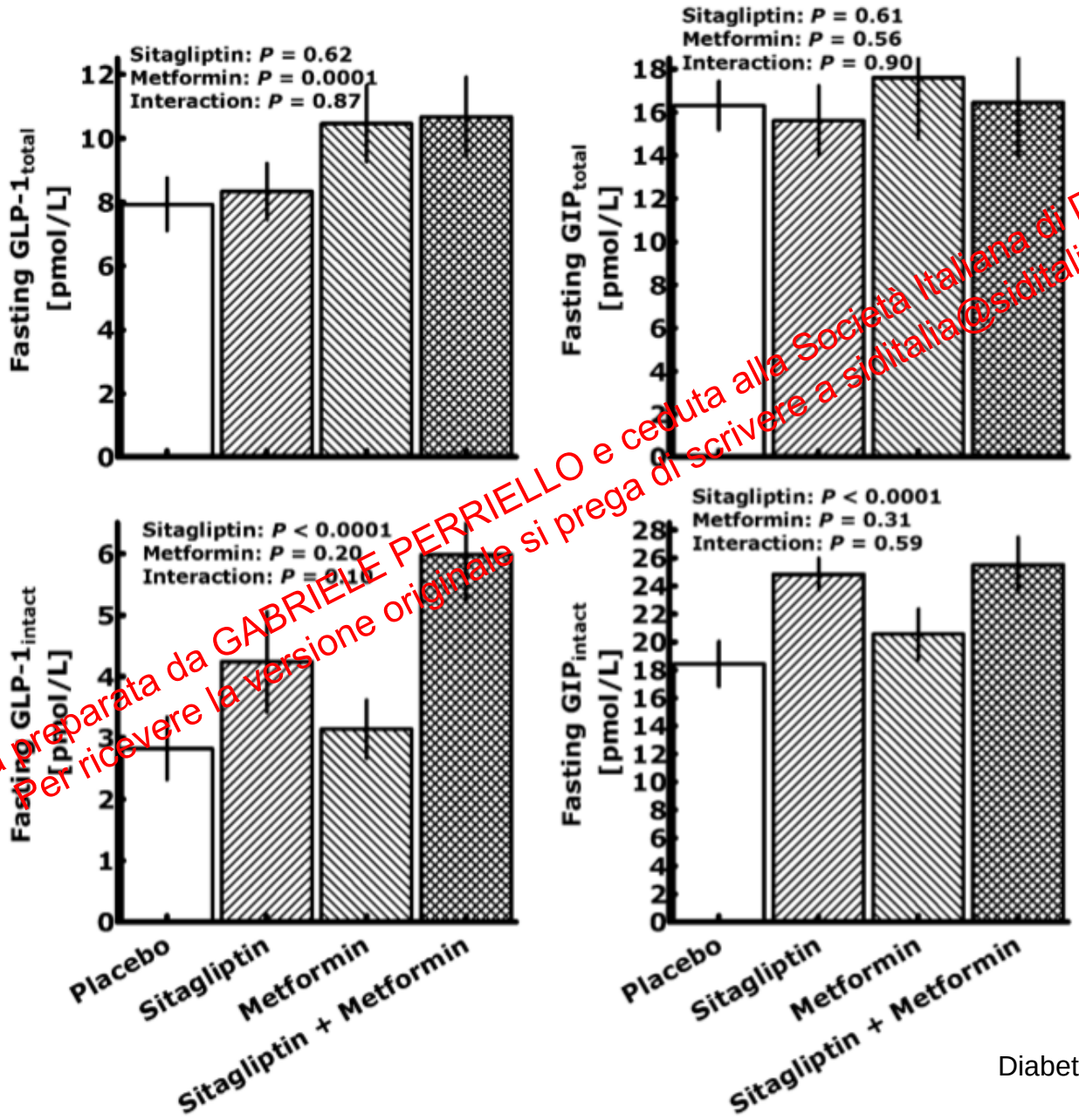


Dual Therapy† According to ADA/EASD position statement	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist
Efficacy*	intermediate	intermediate	high
Hypo risk	low risk	low risk	low risk
Weight	neutral	loss	loss
Side effects	rare	GU, dehydration	GI
Costs^	high	high	high
Efficacy/ Durability	↑	↑	↑↑
Hypo	↓	↓	↓
Weight	↔	↓	↓↓
Other Side Effects	↓	↑	↑
Cost	↑	↑	↑
CV Safety	↑	↑↑	↑↑
Recommendation	2nd line	2nd line	2nd line



Endocrinol Diab Metab. 2018

Synergistic effect of association sitagliptin/metformin on active GLP-1 production/secretion



Diabetes 2014;63:663–674

Glycemic effect of various agents as add-on therapy to metformin

Drug	*Decrease in A1c (%) when used as add-on therapy to metformin*
DPP4 inhibitors	-0.5-0.8
SGLT2 inhibitors	-0.5-0.9
TZDs	-1.0-1.2
GLP-1 Ras	-0.9-1.5
Sulfonylureas	-0.5-1.3

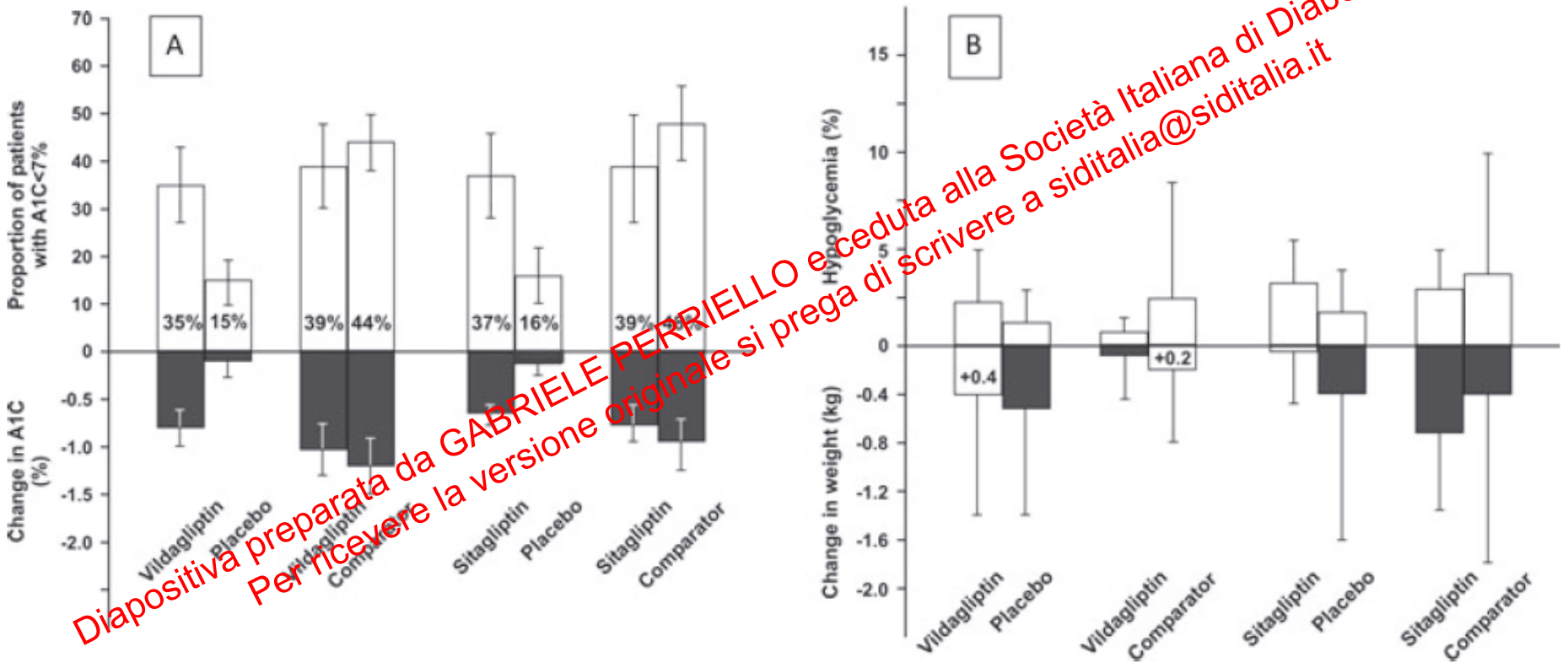
	Fasting Glucose	Post-meal glucose
Metformin	↓↓	↓
GLP-1 RA	↓ To ↓↓	↓↓ To ↓↓↓
SGLT-2I	↓↓	↓
DPP-4I	↓	↓
TZD	↓↓	↓
AGI	-	↓↓
Colesevalem	↓	↓
BCR-QR	-	↓
SFU	↓↓	↓↓
Glinide	↓	↓↓
Basal Insulin	↓↓ To ↓↓↓	-
Prandial Insulin	-	↓↓ To ↓↓↓
Pramlintide	↓	↓↓ To ↓↓↓

Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.2017 Mar 31.

Glucose Control With DPP-4 Inhibitors

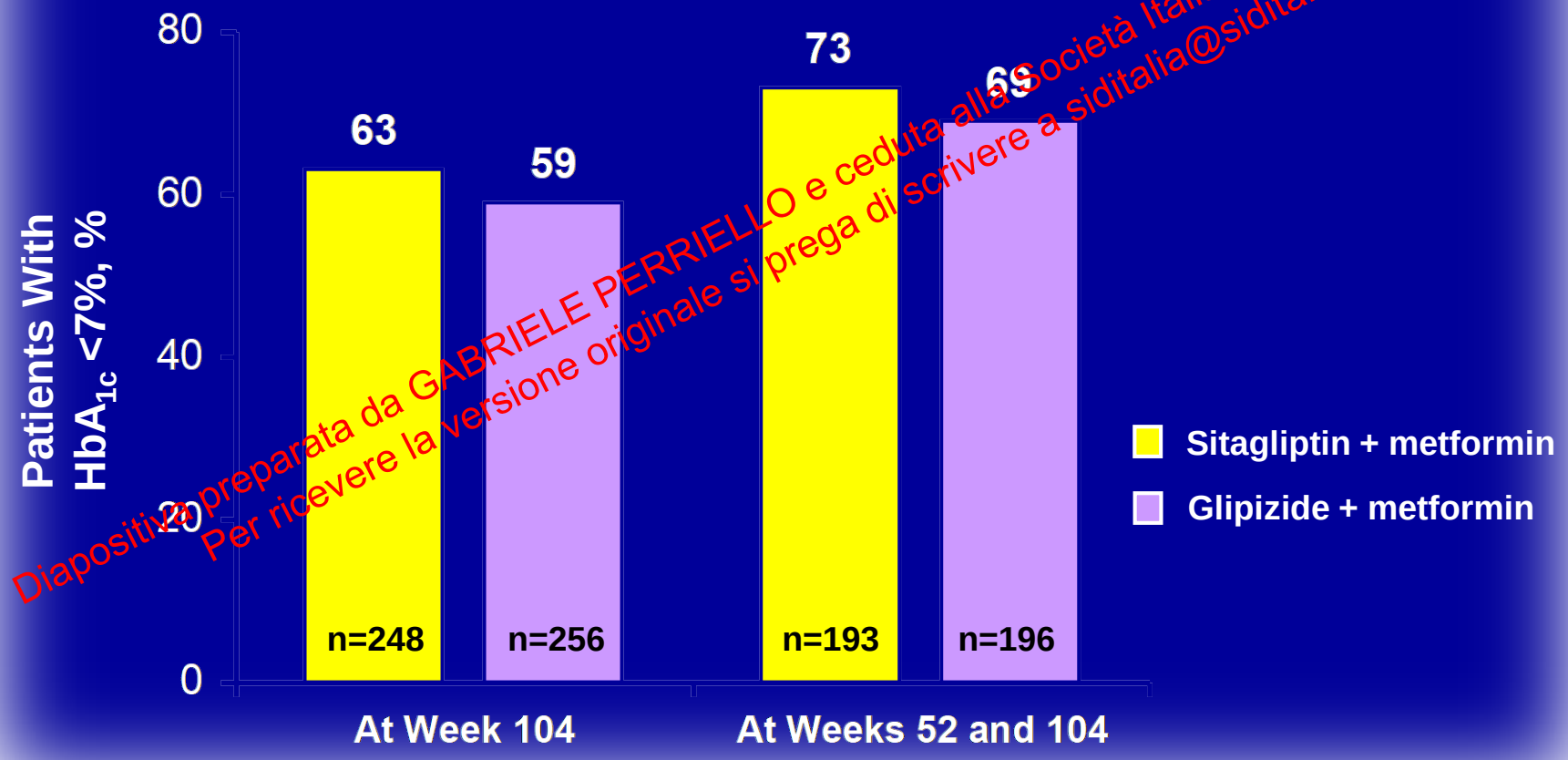
Placebo-Adjusted Change in A1c (%) from Baseline (Not Head-to-Head Trials)

Proportion of patients with Hba1c <7%, hypoglycemia and change in weight



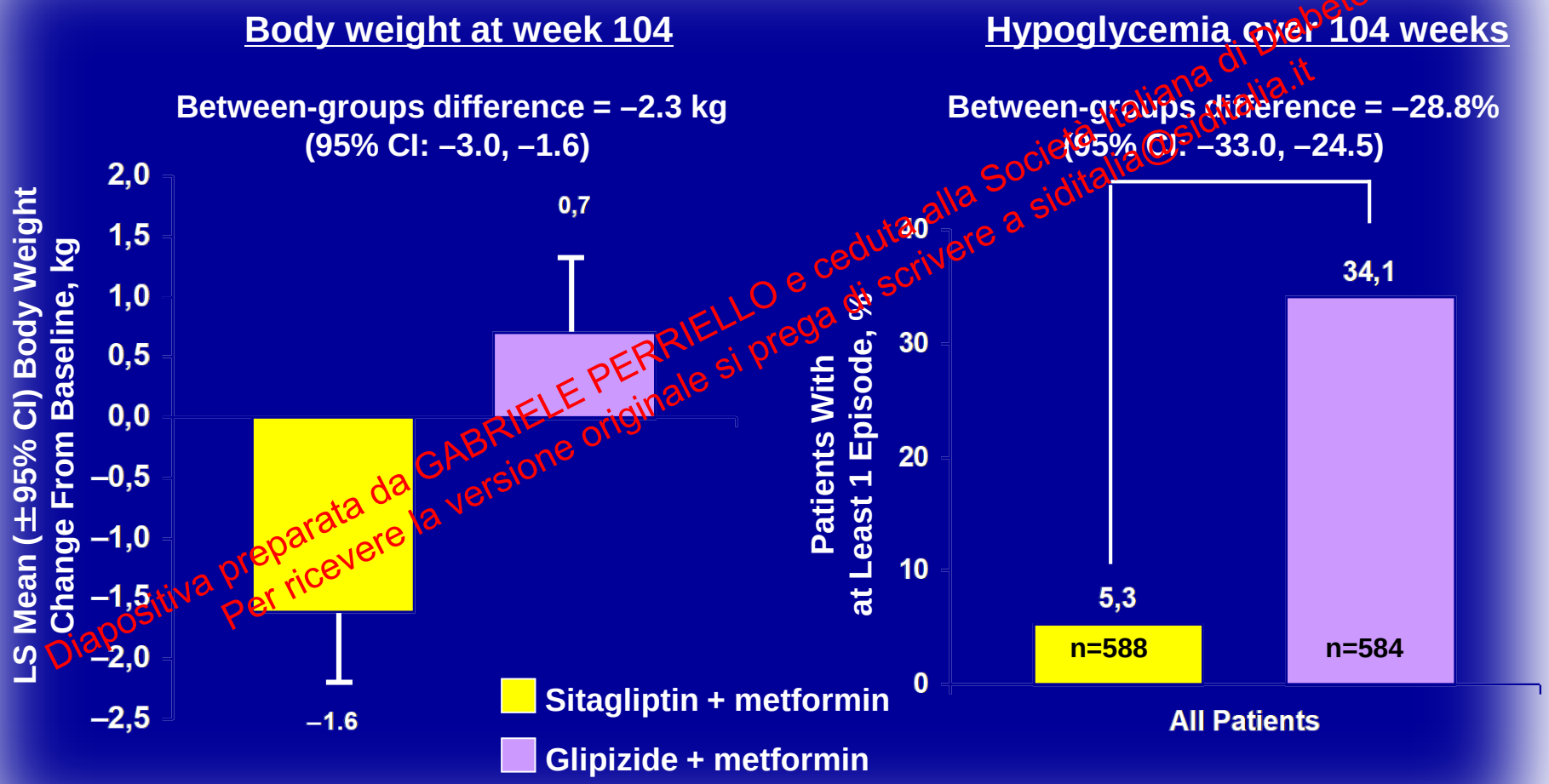
Diabetes, Obesity and Metabolism 13: 594–603, 2011.

Similar Proportions of Patients Receiving Sitagliptin or Glipizide Achieved HbA1c Levels <7.0% at 104 Weeks



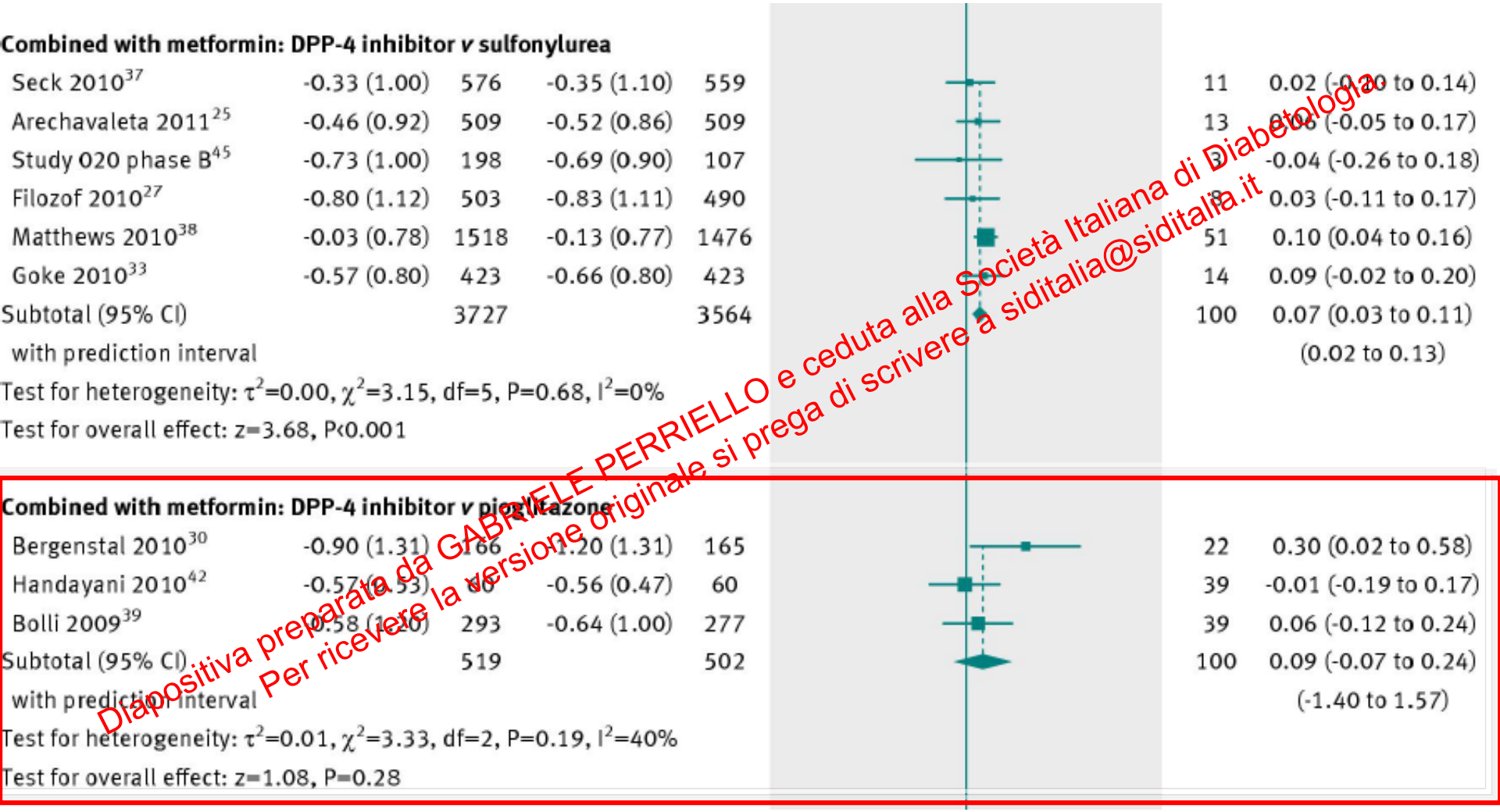
Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.

Sitagliptin vs Glipizide: Weight Change and Incidence of Hypoglycemia



Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.

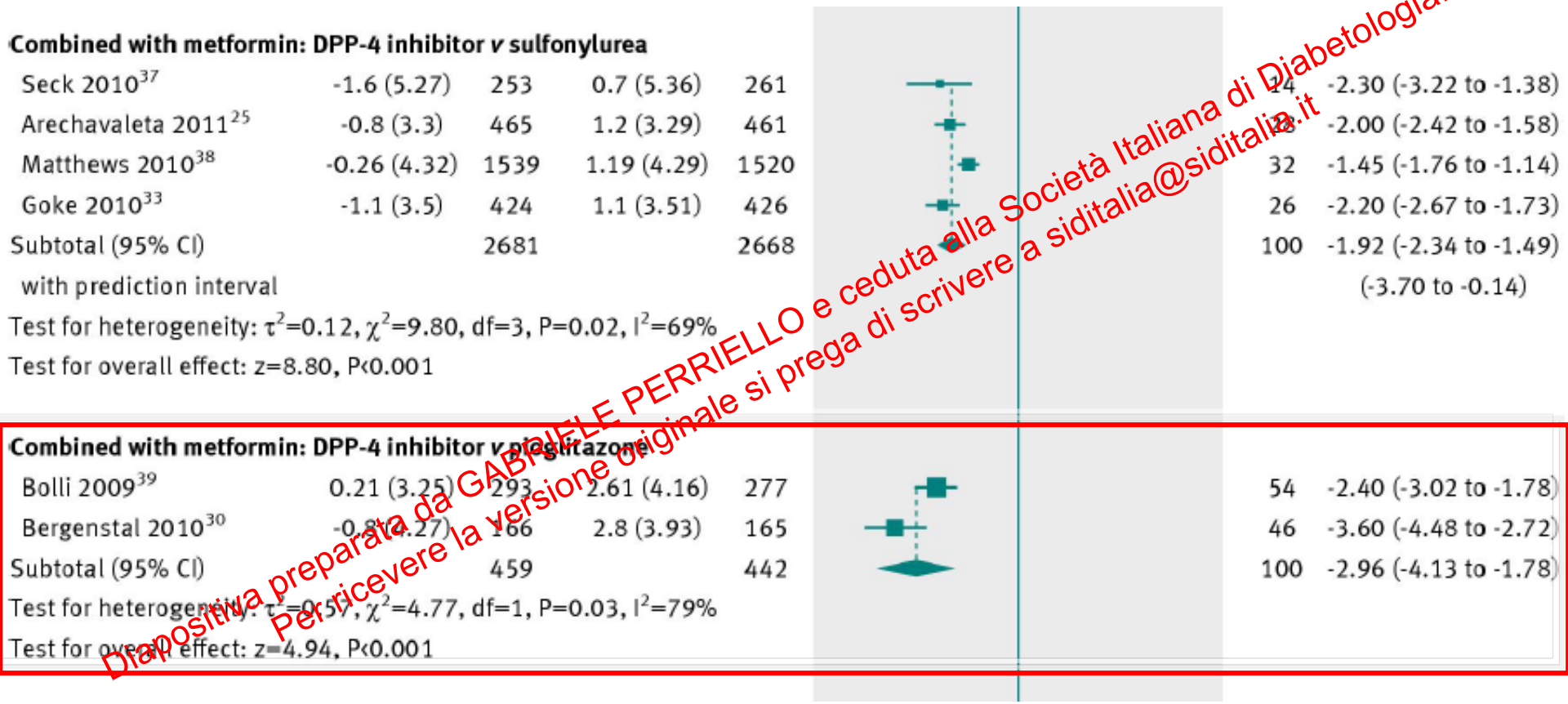
Weighted mean difference in change in HbA_{1c} (%) from baseline



Combined with metformin: DPP-4 inhibitor *v* sulfonylurea						
Seck 2010[37]	-0.33 (1.00)	576	-0.35 (1.10)	559	11	0.02 (-0.10 to 0.14)
Arechavaleta 2011[25]	-0.46 (0.92)	509	-0.52 (0.86)	509	13	0.06 (-0.05 to 0.17)
Study 020 phase B[45]	-0.73 (1.00)	198	-0.69 (0.90)	107	3	-0.04 (-0.26 to 0.18)
Filozof 2010[27]	-0.80 (1.12)	503	-0.83 (1.11)	490	8	0.03 (-0.11 to 0.17)
Matthews 2010[38]	-0.03 (0.78)	1518	-0.13 (0.77)	1476	51	0.10 (0.04 to 0.16)
Goke 2010[33]	-0.57 (0.80)	423	-0.66 (0.80)	423	14	0.09 (-0.02 to 0.20)
Subtotal (95% CI)		3727		3564	100	0.07 (0.03 to 0.11)
with prediction interval						(0.02 to 0.13)
Test for heterogeneity: τ^2=0.00, χ^2=3.15, df=5, P=0.68, I^2=0%						
Test for overall effect: z=3.68, P<0.001						
Combined with metformin: DPP-4 inhibitor *v* pioglitazone						
Bergenstal 2010[30]	-0.90 (1.31)	166	-1.20 (1.31)	165	22	0.30 (0.02 to 0.58)
Handayani 2010[42]	-0.57 (0.53)	60	-0.56 (0.47)	60	39	-0.01 (-0.19 to 0.17)
Bolli 2009[39]	-0.58 (1.20)	293	-0.64 (1.00)	277	39	0.06 (-0.12 to 0.24)
Subtotal (95% CI)		519		502	100	0.09 (-0.07 to 0.24)
with prediction interval						(-1.40 to 1.57)
Test for heterogeneity: τ^2=0.01, χ^2=3.33, df=2, P=0.19, I^2=40%						
Test for overall effect: z=1.08, P=0.28						

BMJ 2012:344:1369

Weighted mean difference in change in body weight (kg) from baseline



Combined with metformin: DPP-4 inhibitor *v* sulfonylurea

Seck 2010[37]	-1.6 (5.27)	253	0.7 (5.36)	261	14	-2.30 (-3.22 to -1.38)
Arechavaleta 2011[25]	-0.8 (3.3)	465	1.2 (3.29)	461	28	-2.00 (-2.42 to -1.58)
Matthews 2010[38]	-0.26 (4.32)	1539	1.19 (4.29)	1520	32	-1.45 (-1.76 to -1.14)
Goke 2010[33]	-1.1 (3.5)	424	1.1 (3.51)	426	26	-2.20 (-2.67 to -1.73)
Subtotal (95% CI)		2681		2668	100	-1.92 (-2.34 to -1.49)
with prediction interval						(-3.70 to -0.14)

Test for heterogeneity: τ^2=0.12, χ^2=9.80, df=3, P=0.02, I^2=69%

Test for overall effect: z=8.80, P<0.001

Combined with metformin: DPP-4 inhibitor *v* pioglitazone

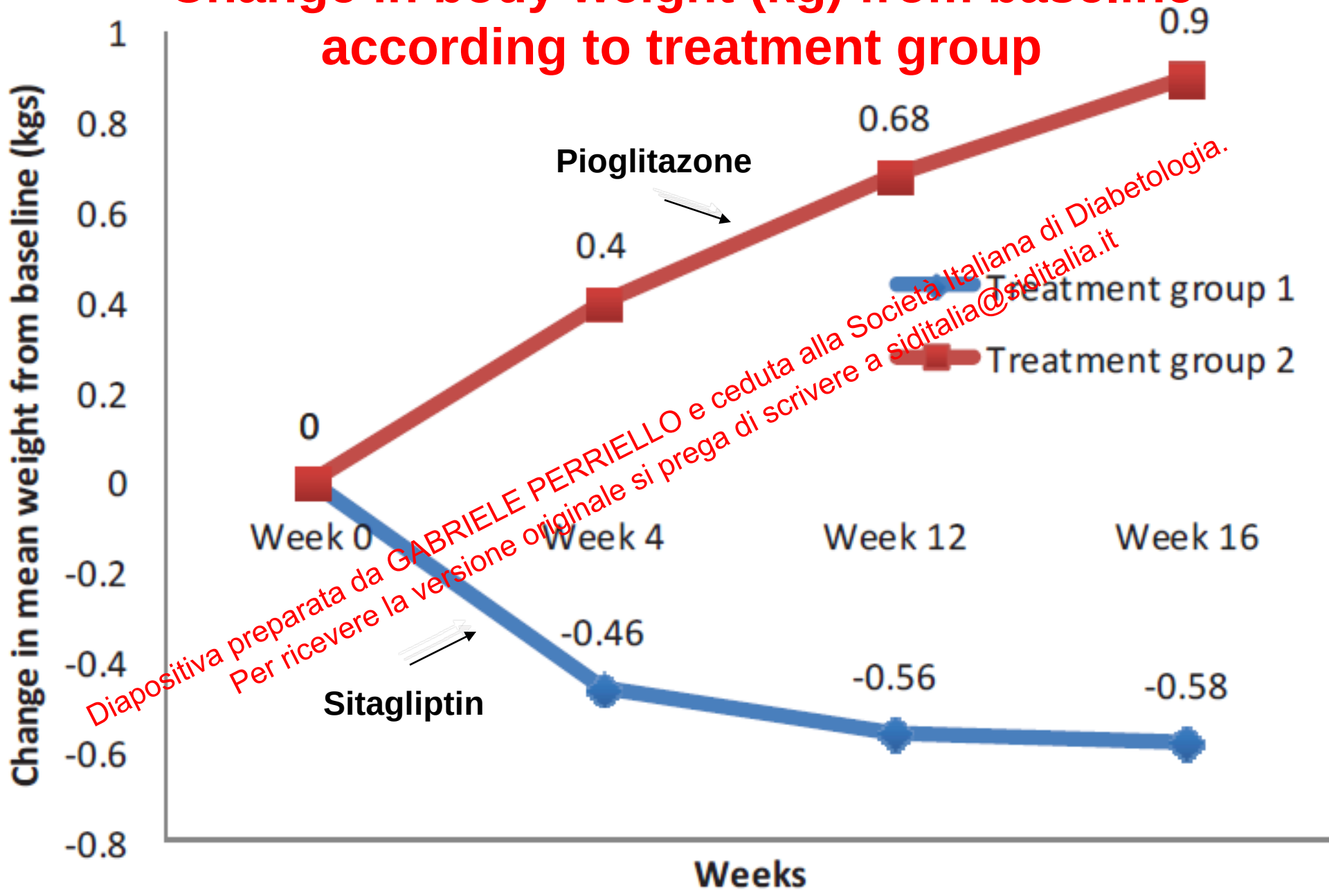
Bolli 2009[39]	0.21 (3.25)	293	2.61 (4.16)	277	54	-2.40 (-3.02 to -1.78)
Bergenstal 2010[30]	-0.8 (4.27)	166	2.8 (3.93)	165	46	-3.60 (-4.48 to -2.72)
Subtotal (95% CI)		459		442	100	-2.96 (-4.13 to -1.78)

Test for heterogeneity: τ^2=0.57, χ^2=4.77, df=1, P=0.03, I^2=79%

Test for overall effect: z=4.94, P<0.001

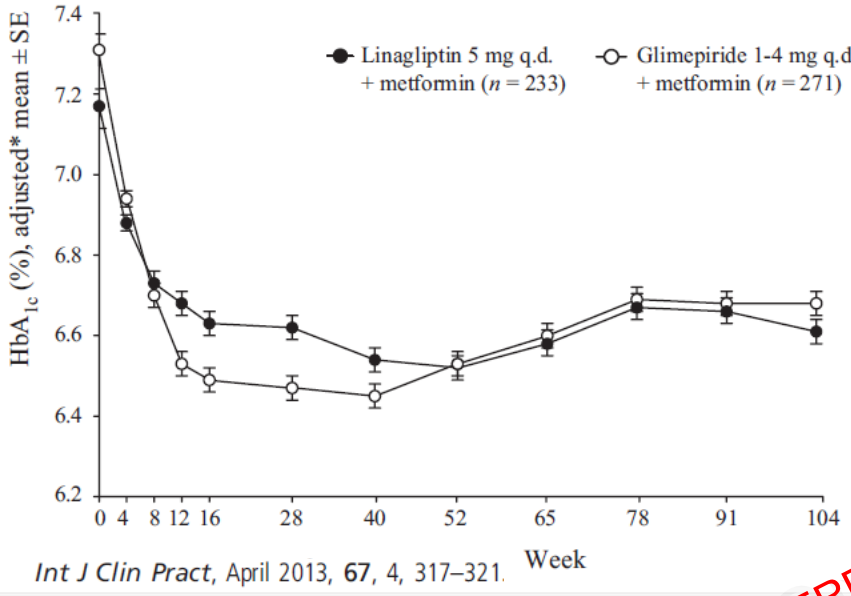
BMJ 2012:344:1369

Change in body weight (kg) from baseline according to treatment group

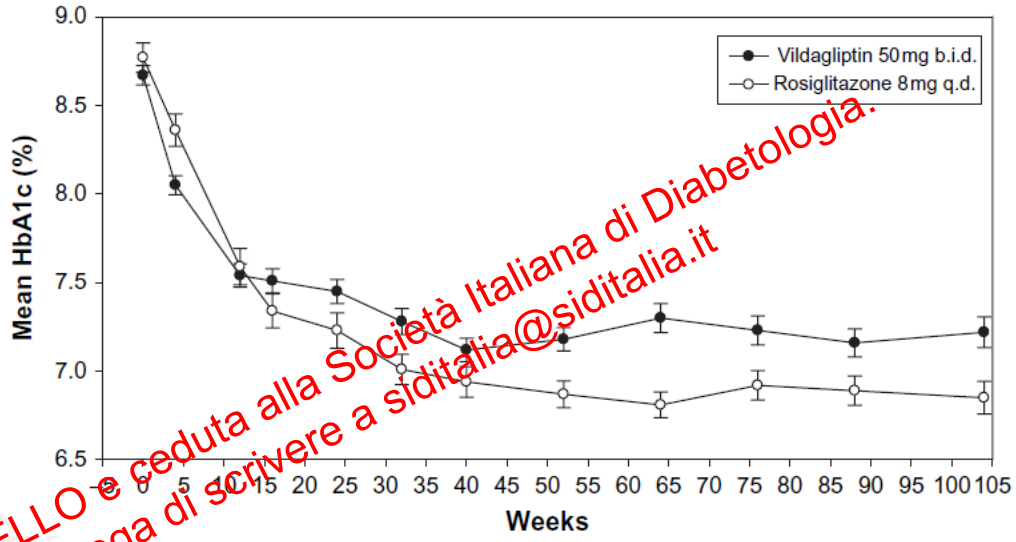


J Pharmacol Pharmather 2013: 4: 27-32

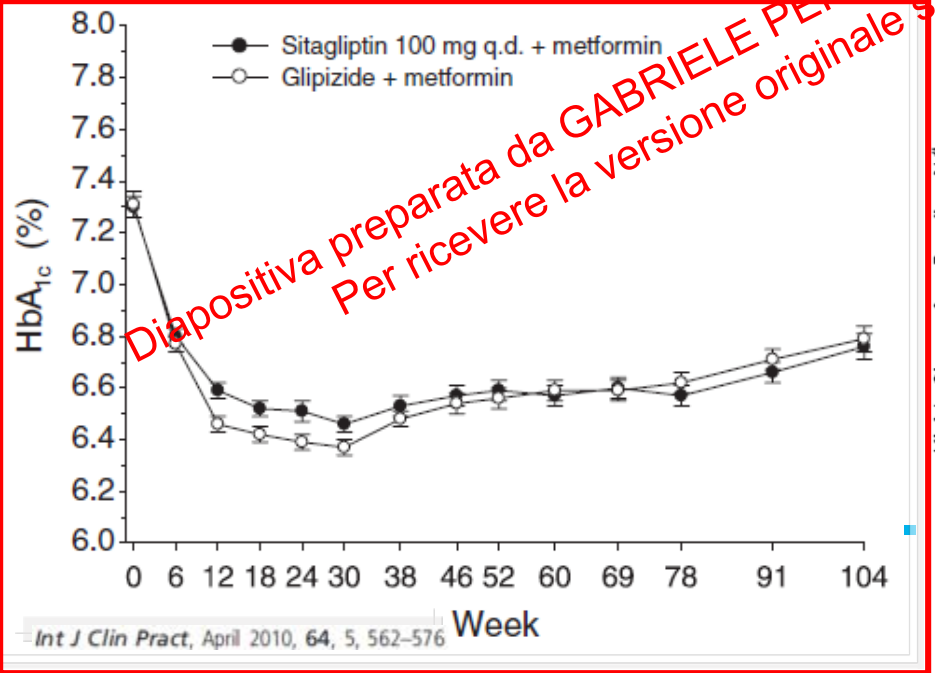
Durability of Efficacy of DPP-4 Inhibitors



Int J Clin Pract, April 2013, **67**, 4, 317–321.



Diabetes, Obesity and Metabolism, **11**, 2009, 571–578



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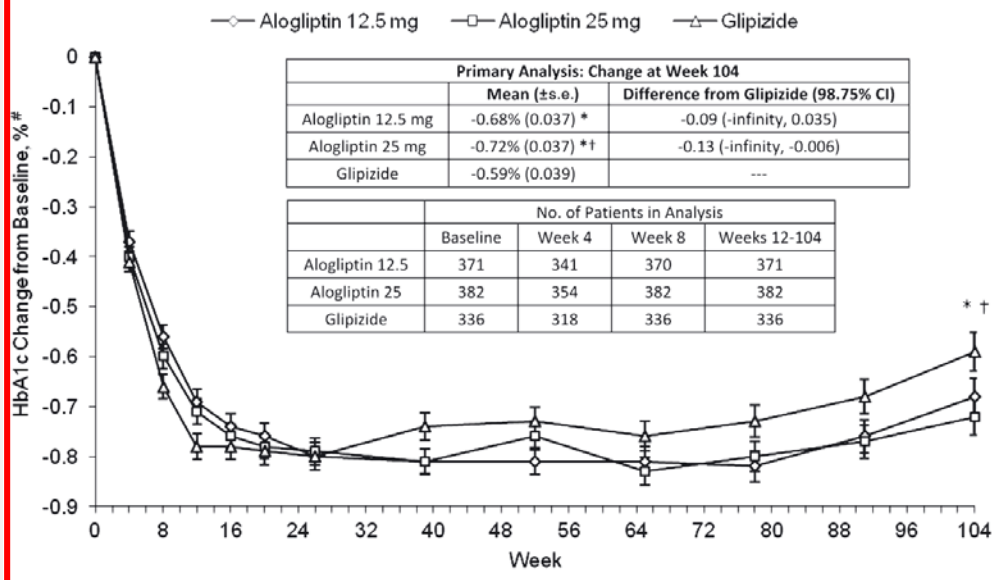
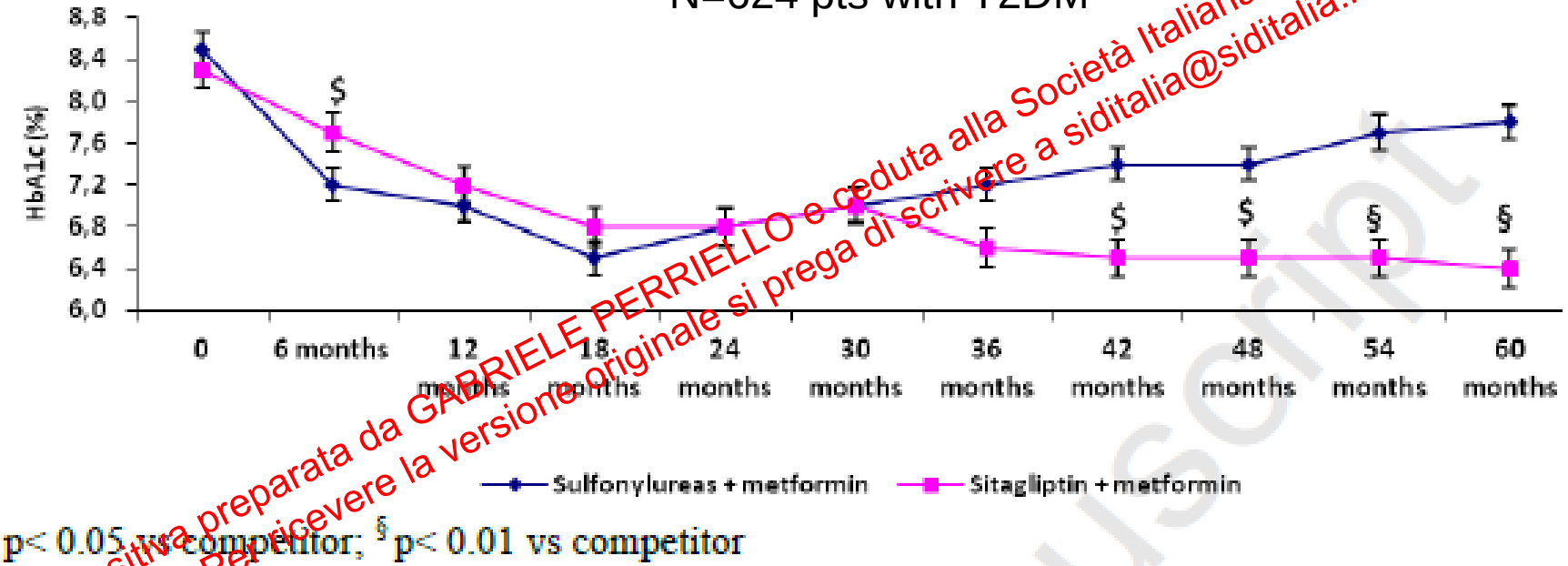


Primary Analysis: Change at Week 104		
	Mean (±s.e.)	Difference from Glipizide (98.75% CI)
Alogliptin 12.5 mg	-0.68% (0.037) *	-0.09 (-infinity, 0.035)
Alogliptin 25 mg	-0.72% (0.037) *†	-0.13 (-infinity, -0.006)
Glipizide	-0.59% (0.039)	---

	No. of Patients in Analysis			
	Baseline	Week 4	Week 8	Weeks 12-104
Alogliptin 12.5	371	341	370	371
Alogliptin 25	382	354	382	382
Glipizide	336	318	336	336

Diabetes, Obesity and Metabolism 2014.

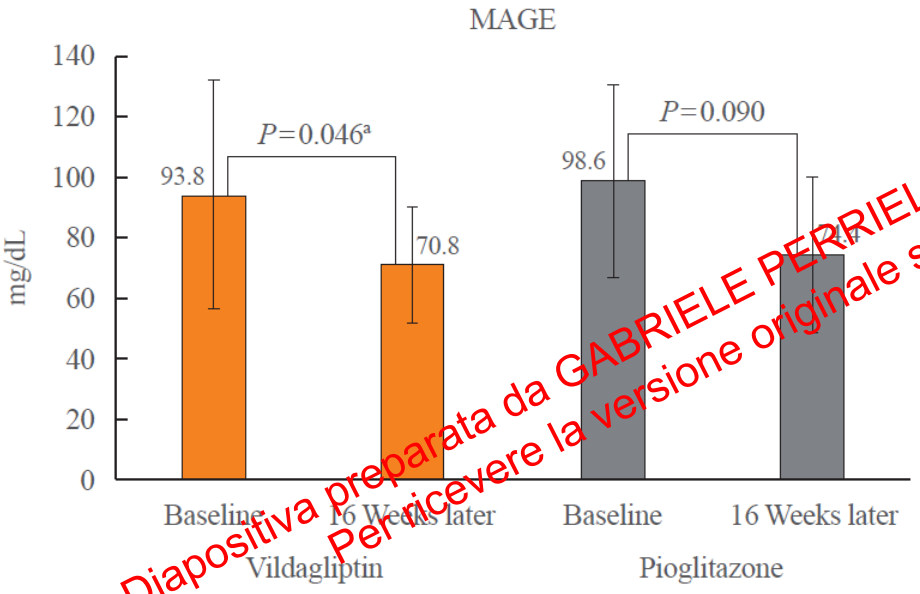
Hypoglycemic efficacy of DPP4-I over 5 years

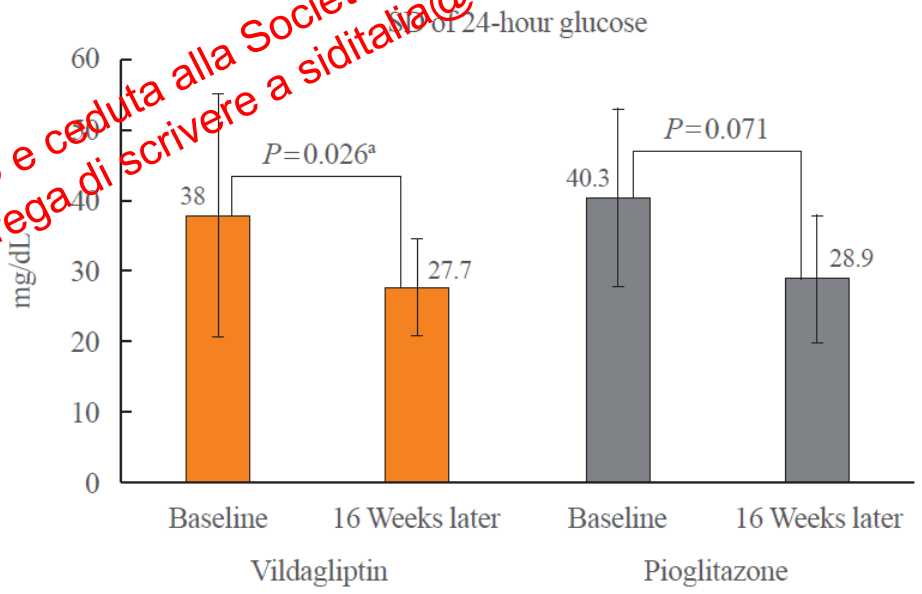


$ p< 0.05 vs competitor; § p< 0.01 vs competitor

Derosa et al. *Pharmacol Res. 2015*;100:127-34

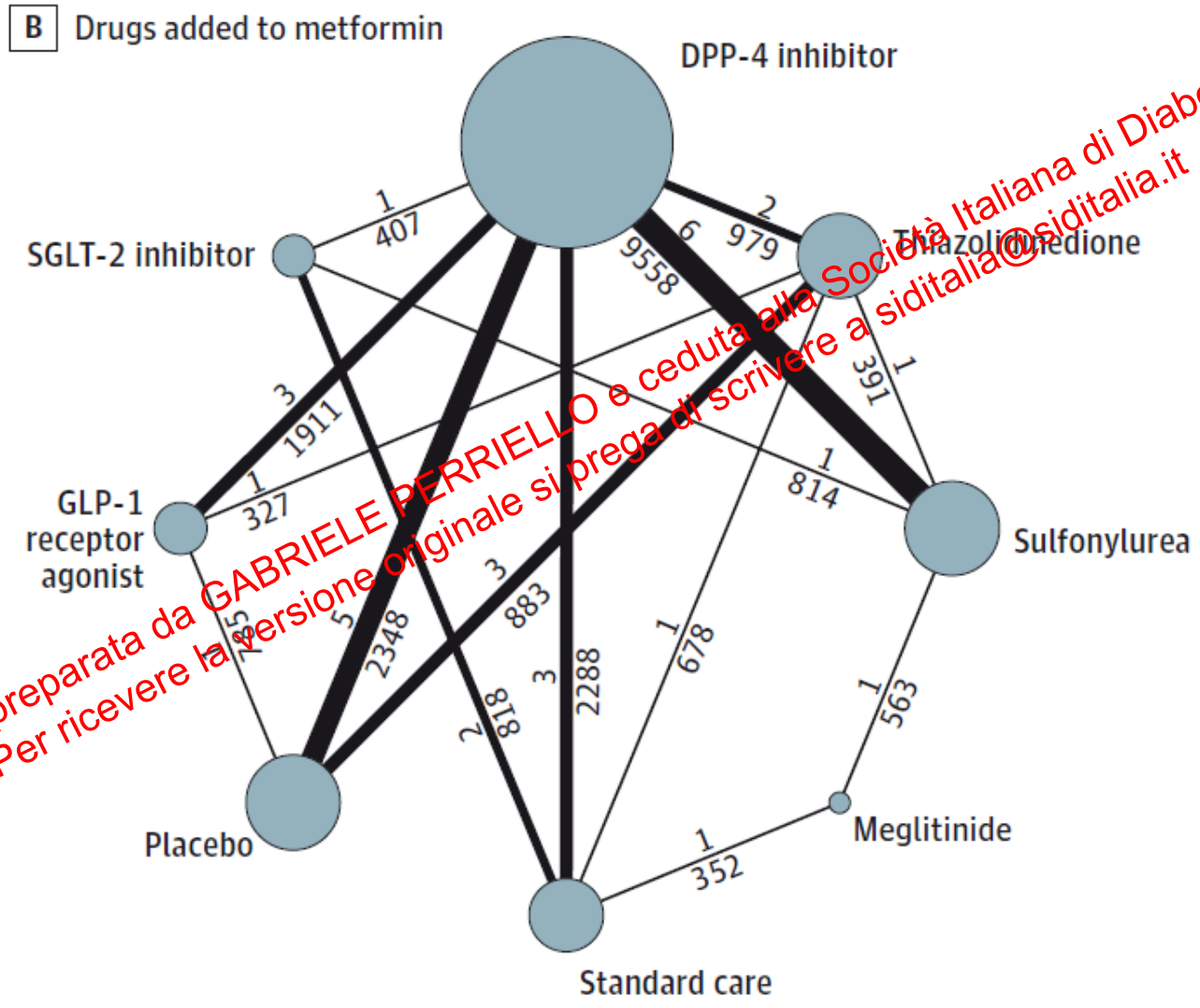
Effects of DPP4-i on glucose variability in patients with T2DM





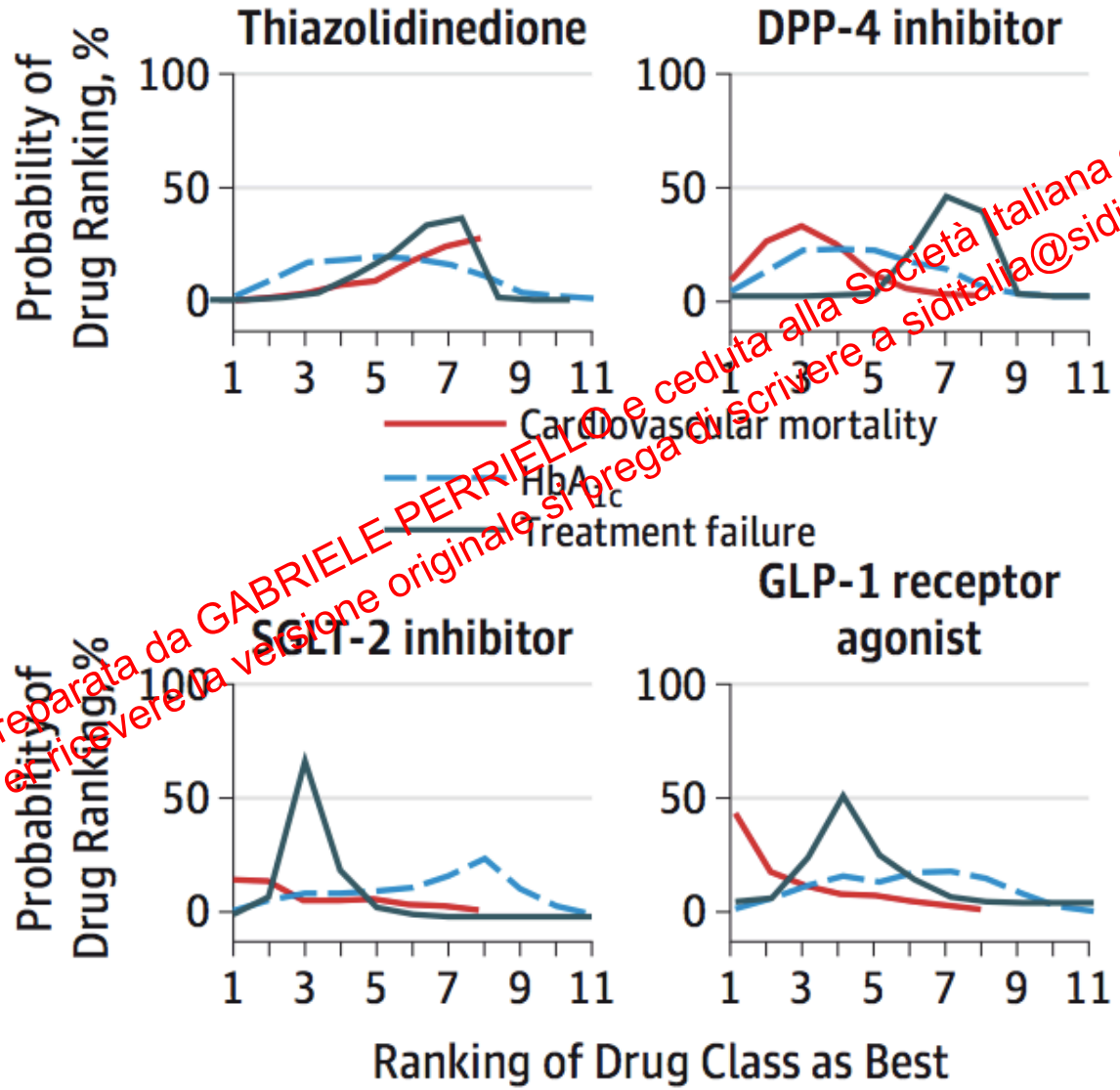
Endocrinol Metab 2017;32:241-47

Network Meta-Analysis (NMA) for indirect comparisons between OHAs in T2DM



Efficacy rankings for add-on to metformin of different OHA classes in Type 2 Diabetes

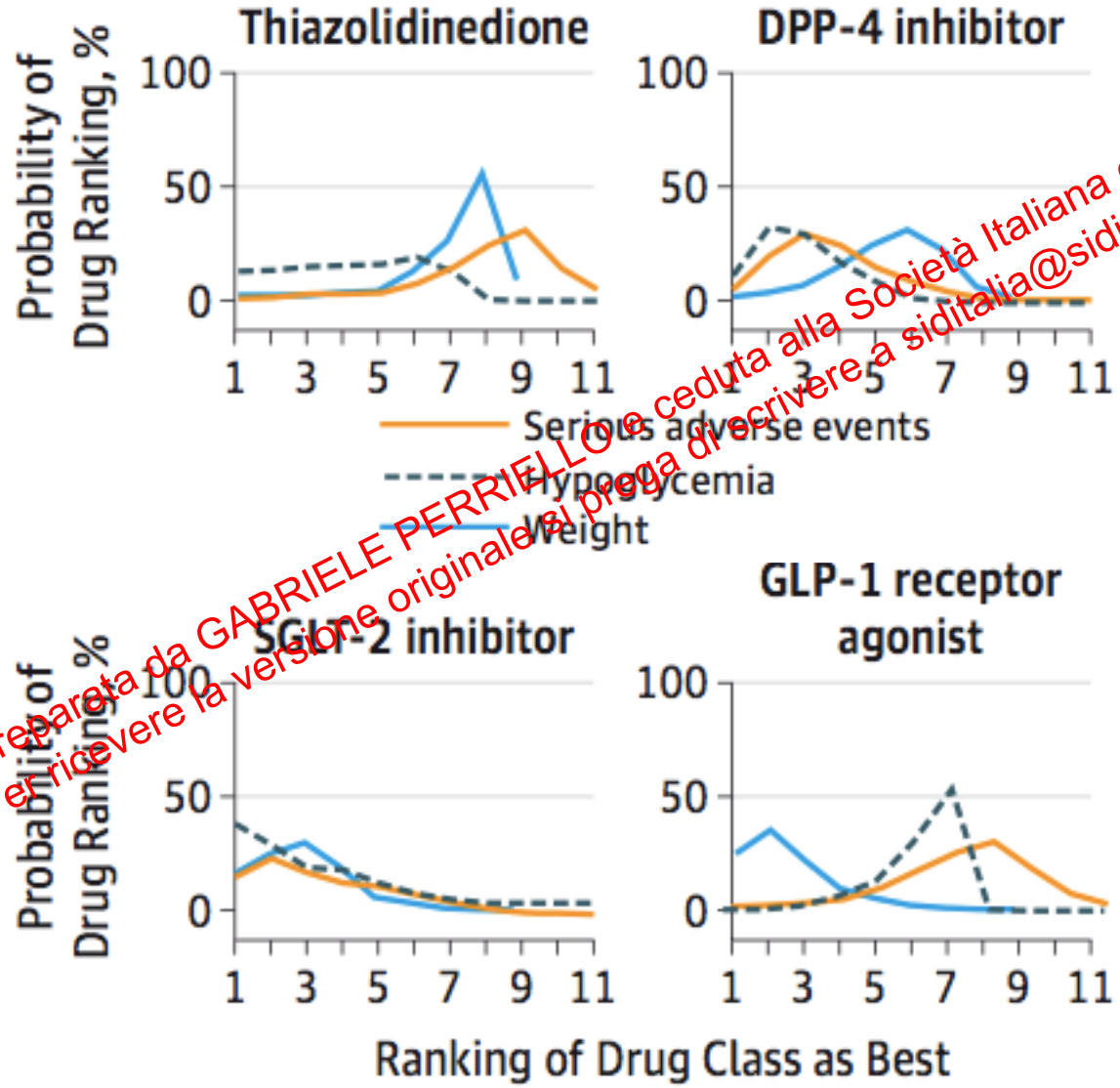
26 RCT trials; n= 20690 patients



JAMA. 2016;316(3):313-324

Adverse event rankings for add-on to metformin of different OHA classes in Type 2 Diabetes

26 RCT trials; n= 20690 patients



JAMA. 2016;316(3):313-324

DPP-4 Inhibitors vs GLP-1 receptor agonists

Properties/Effects	DPP-4 Inhibitors	GLP-1 Analogues
↑ Glucose-dependent insulin secretion	Yes	Yes
↓ Glucagon secretion	Yes	Yes
Effect on incretins	Endogenous incretins enhanced to physiological levels	Exogenous GLP-1: Possible Immune response (antibody formation)
Effect on body weight	Weight neutral	Body weight decreased
Inhibition of gastric emptying	Marginal	Yes
Hypoglycaemia	No	No
Side Effects	No nausea, vomiting	Reported nausea, vomiting
Administration	Oral	Subcutaneous

Barnett A Clinical Endocrinology 2009; 70: 343–53

DIAGNOSIS OF TYPE 2 DIABETES IN OLDER ADULTS

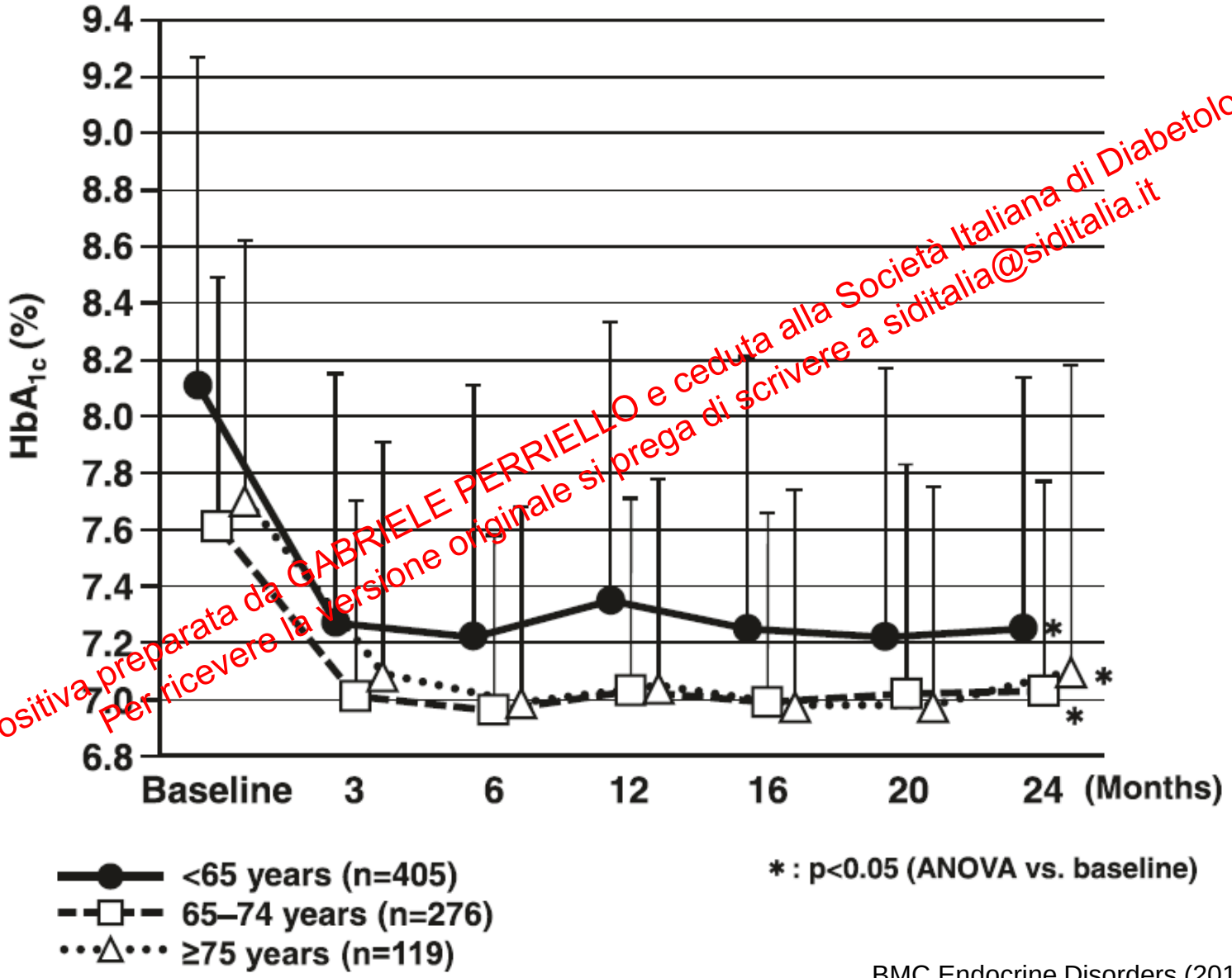
↓

Personalized antihyperglycemic therapy
according to patient characteristics

↓

Class/drug	Risk of Hypoglycemia	Notes	Contraindications, major side effects and warnings
DPP-4 inhibitors	No	- No interactions - No HF risk with sitagliptin	- Increased level of hepatic enzymes (linagliptin) - Potential risk of pancreatitis (saxagliptin) - Potential slight increased risk for heart failure with saxagliptin and alogliptin;

Two-year assessment of the efficacy of sitagliptin in elderly patients with type 2 diabetes



BMC Endocrine Disorders (2015) 15:34

Why prefer DPP4-i in add-on to metformin

- Synergistic effects on GLP-1 activity
- As effective as all other OHAs
- Greater effects on PPG vs SGLT2i/TZD
- Long-term efficacy
- No hypos & weight neutral (vs SU/TZD)
- Cardiovascular safety (neutral)
- Better tolerability/compliance vs GLP1-Ras
- First choice (sitagliptin) in elderly patients

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Direttore ff Endocrinologia e Malattie del Metabolismo

Azienda Ospedaliera di Perugia

Grazie per la vostra attenzione

23 novembre 2019