Sulfoniluree e glinidi: pro e contro

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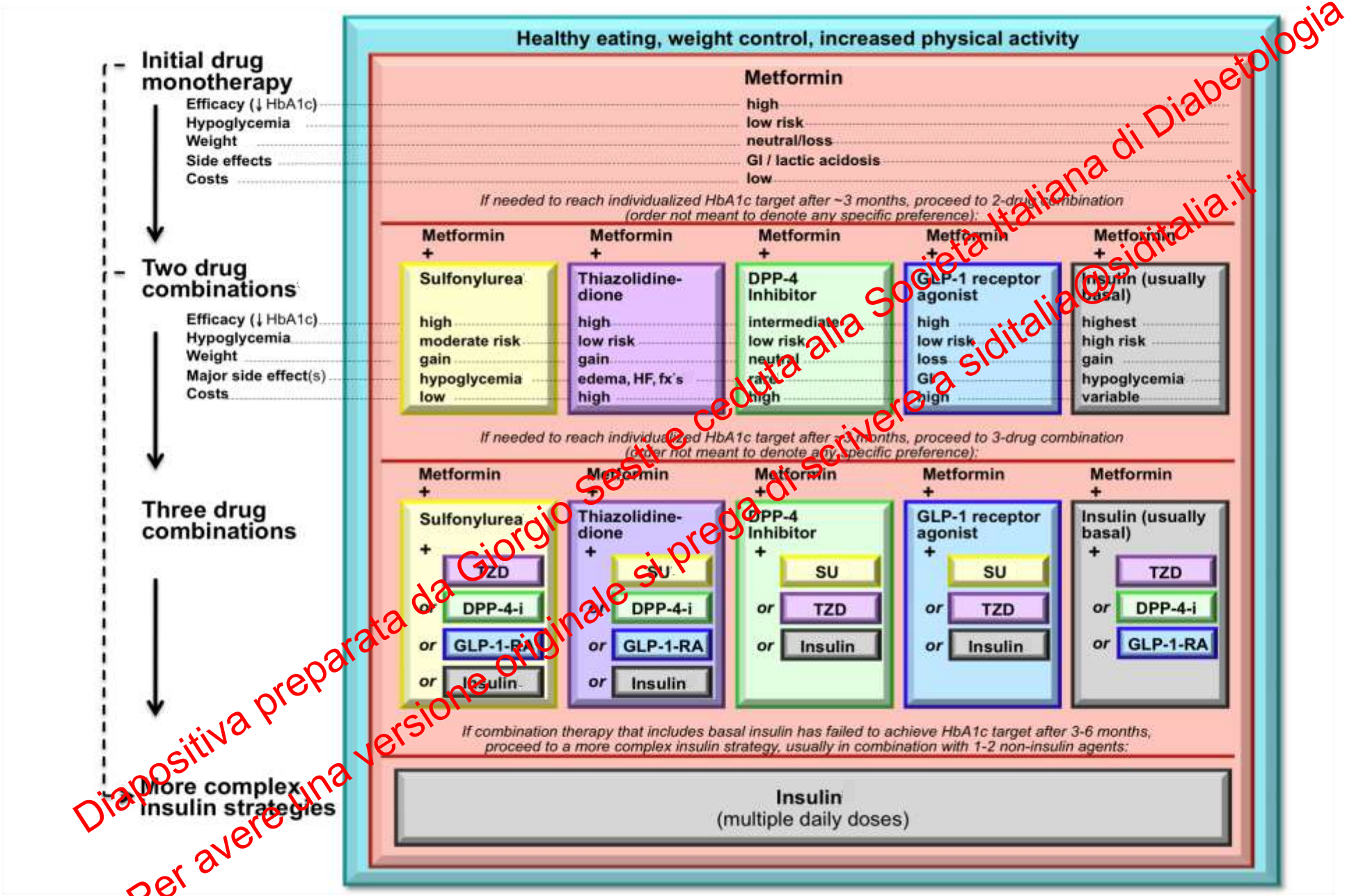
T2DM anti-hyperglycaemic therapy: general recommendations



Diabetes Care 35:1364-1379, 2012; Diabetologia 55:1577-1596, 2012

Sulfoniluree e glinidi:

1. **Controllo Metabolico**
2. **Effetti sulla beta cellula**
3. **Durability**
4. **Effetti sul peso**
5. **Ipoglicemie**
6. **Complicanze micro-vascolari**
7. **Complicanze macro-vascolari**

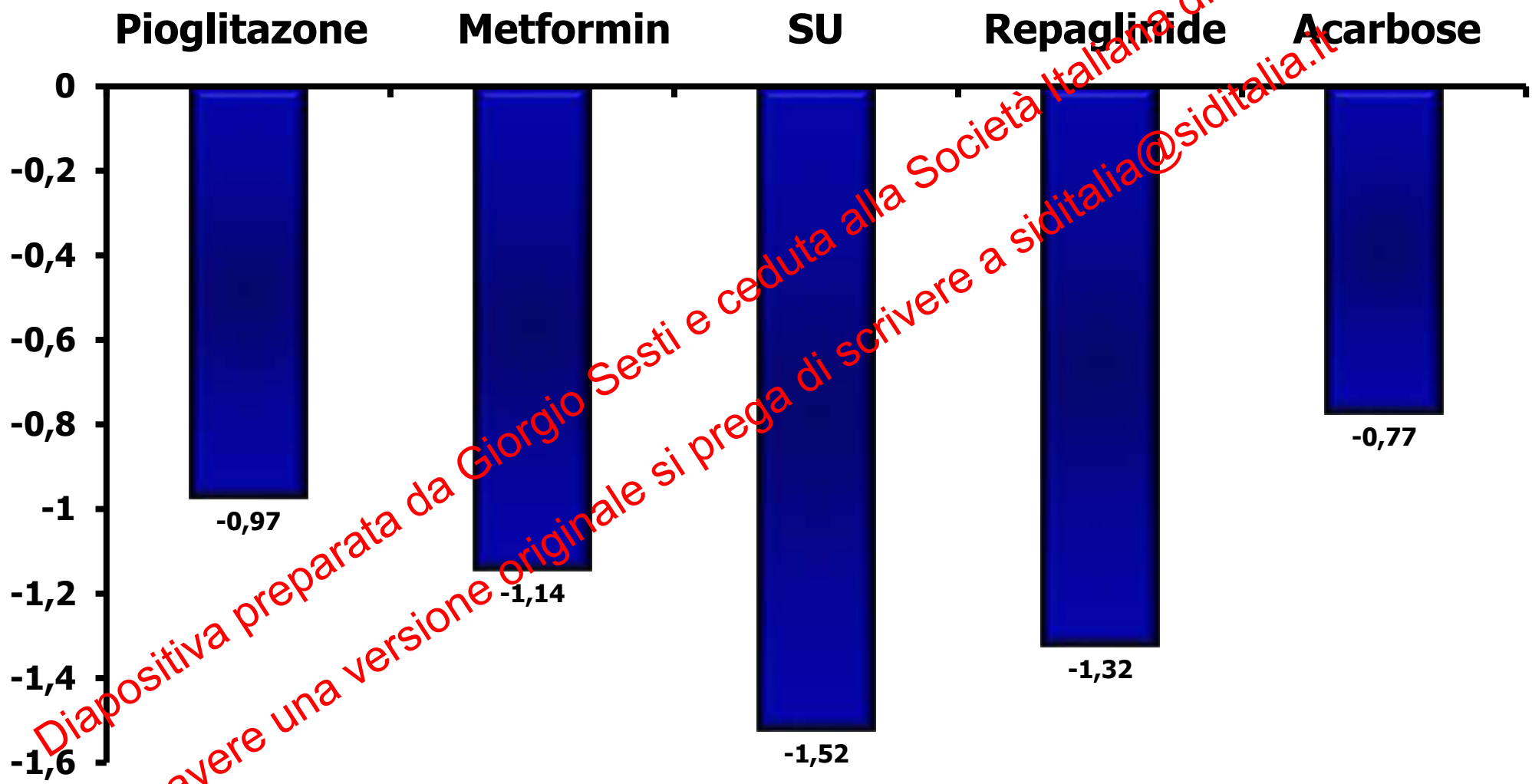
Weighted Mean Absolute Difference in Hemoglobin A1c Level between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet

Comparison*	Studies with Data on Mean Differences, *n*	Weighted Mean Absolute Difference in Hemoglobin A_{1c} Level between Groups (95% CI), %
Pioglitazone vs. control	9	−0.97 (−1.18 to −0.75)
Rosiglitazone vs. control	8	−1.16 (−1.39 to −0.92)
Metformin vs. control	15	−1.14 (−1.4 to −0.87)
Sulfonylureas vs. control	11	−1.52 (−1.75 to −1.28)
Repaglinide vs. control	4	−1.32 (−1.9 to −0.8)
Nateglinide vs. control	4	−0.54 (−0.8 to −0.27)
Acarbose vs. control	28	−0.77 (−0.9 to −0.64)

UKPDS 33 (10 years follow-up) Chlorpropamide vs. Conventional	**-1.2%**
UKPDS 33 (10 years follow-up) Glibenclamide vs. Conventional	**-0.7%**

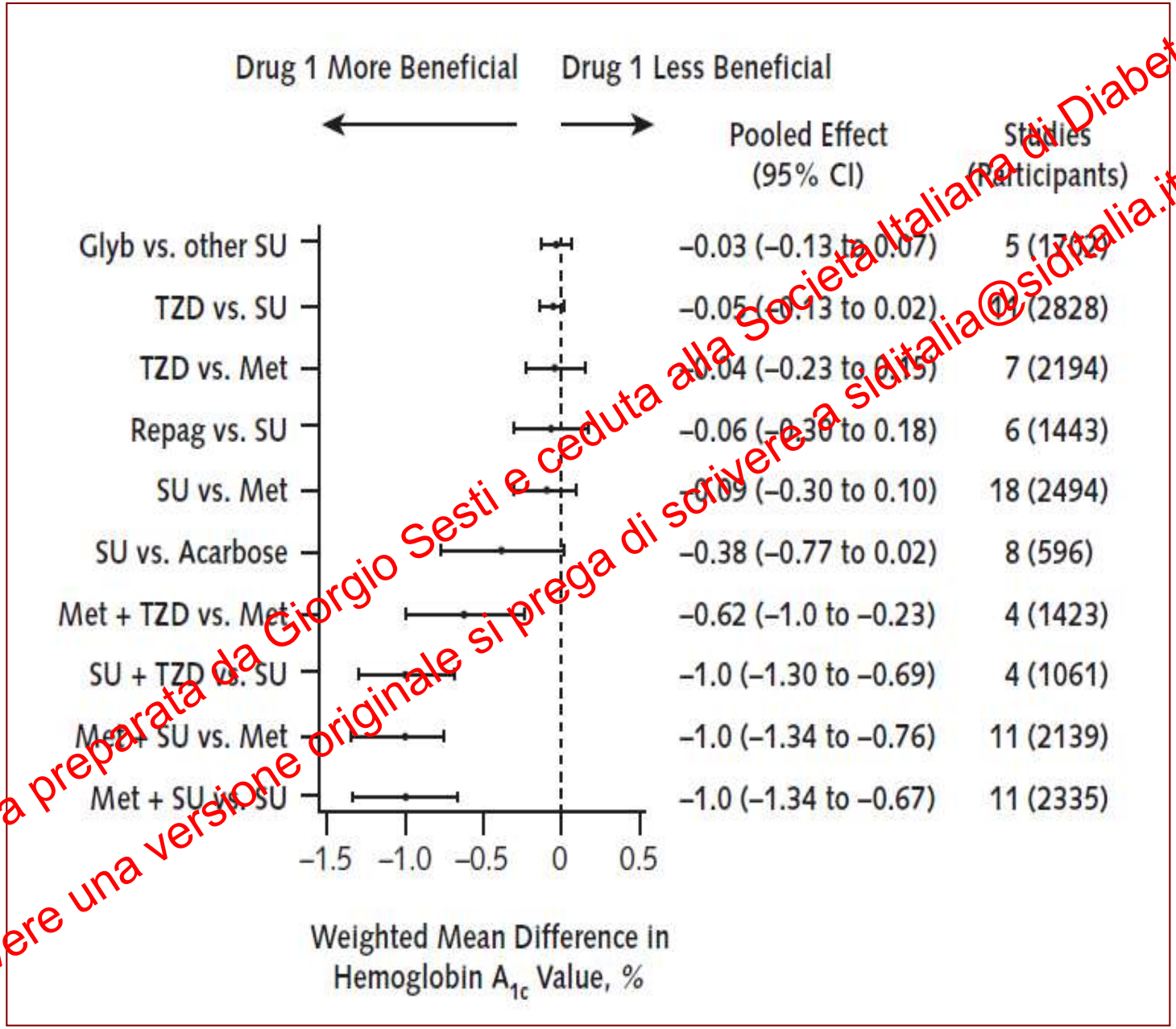
Bolen S. et al. Ann Intern Med 147:386-399, 2007

Weighted Mean Absolute Difference in Hemoglobin A1c Level between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet



Bolen S. et al. Ann Intern Med 147:386-399, 2007

Weighted mean difference in HbA1c with use of oral medications for T2DM



Bolen S. et al. Ann Intern Med 147:386-399, 2007

Effect of hypoglycemic agents as add-on therapy to metformin in randomized, placebo-controlled clinical trials

Study	*n* (T/P)	Duration (weeks)	Age (years)	BMI (kg/m^2)	HbA1$_c$ (%)	ΔHbA1$_c$[a] (%)
α-GI						
Phillips [7]	40/43	24	58.4/62.4	30.8/30.1	8.1/7.8	−0.3
Rosenstock [8]	74/74	24	57.0/55.9	32.4/32.5	8.5/8.2	−0.8
Halimi [9]	59/70	24	56.0/55.0	30.1/29.7	8.6/8.5	−0.9
Josse [10]	41/42	48	57.4/57.4	29.4/29.4	na/na	−0.9
Van [11]	77/75	32	57.9/57.9	30.0/29.4	8.5/8.4	−0.6
Sulphonylureas						
Feinglos [12]	61/61	16	57.7/58.8	31.7/32.1	7.5/7.6	−0.5
Charpentier [16]	147/75	20	56.8/56.7	29.5/29.2	6.4/6.8	−0.7
Marre [13]	204/104	16	58.3/57.5	29.9/29.9	7.8/8.1	−0.8
Goldstein [17]	87/76	18	54.6/56.6	31.7/31.6	8.7/8.7	−1
Blonde [18]	322/153	16	55.5/57.6	30.7/30.6	9.4/9.5	−1.4
Glinides						
Moses [19]	277/279	24	57.2/57.8	33.2/31.8	8.3/8.6	−1.1
Marre [20]	315/152	24	57.6/56.4	29.4/29.6	8.1/8.2	−0.3
Thiazolidinediones						
Gomez-Perez [14]	141/134	26	52.9/53.4	27.8/28.5	9.9/9.8	−1.3
Einhorn [21]	168/160	16	55.5/55.7	32.1/32.1	9.9/9.8	−0.4
Bailey [22]	288/280	24	58.1/57.6	32.2/32.1	7.4/7.5	−0.2

-0.61

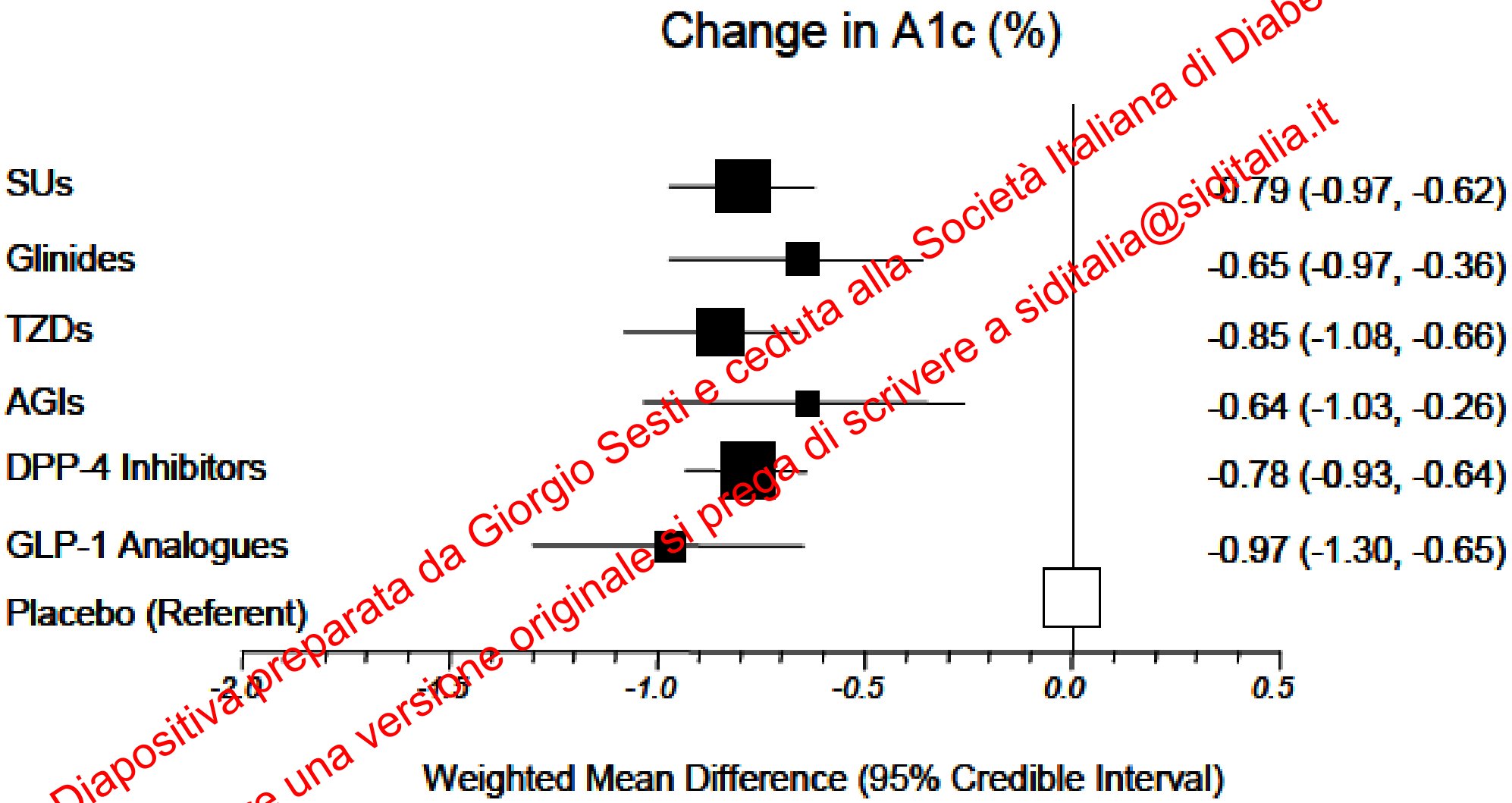
-0.85

-0.70

-0.42

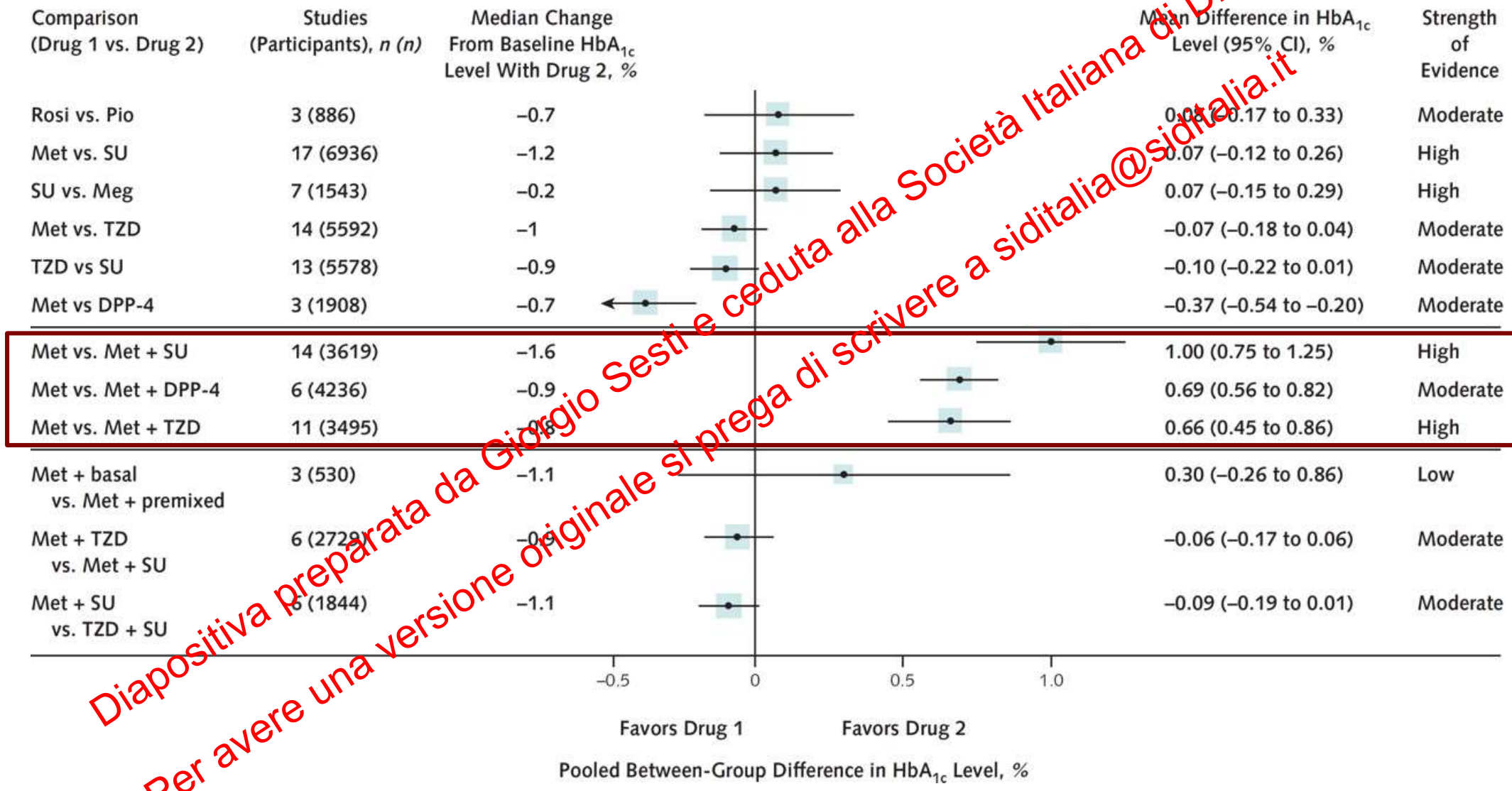
Monami M. et al Diabetes Res Clin Pract 79:196-203, 2008

Meta-analysis of RCTs with at least 3 months' duration, evaluating antidiabetic drugs added to metformin



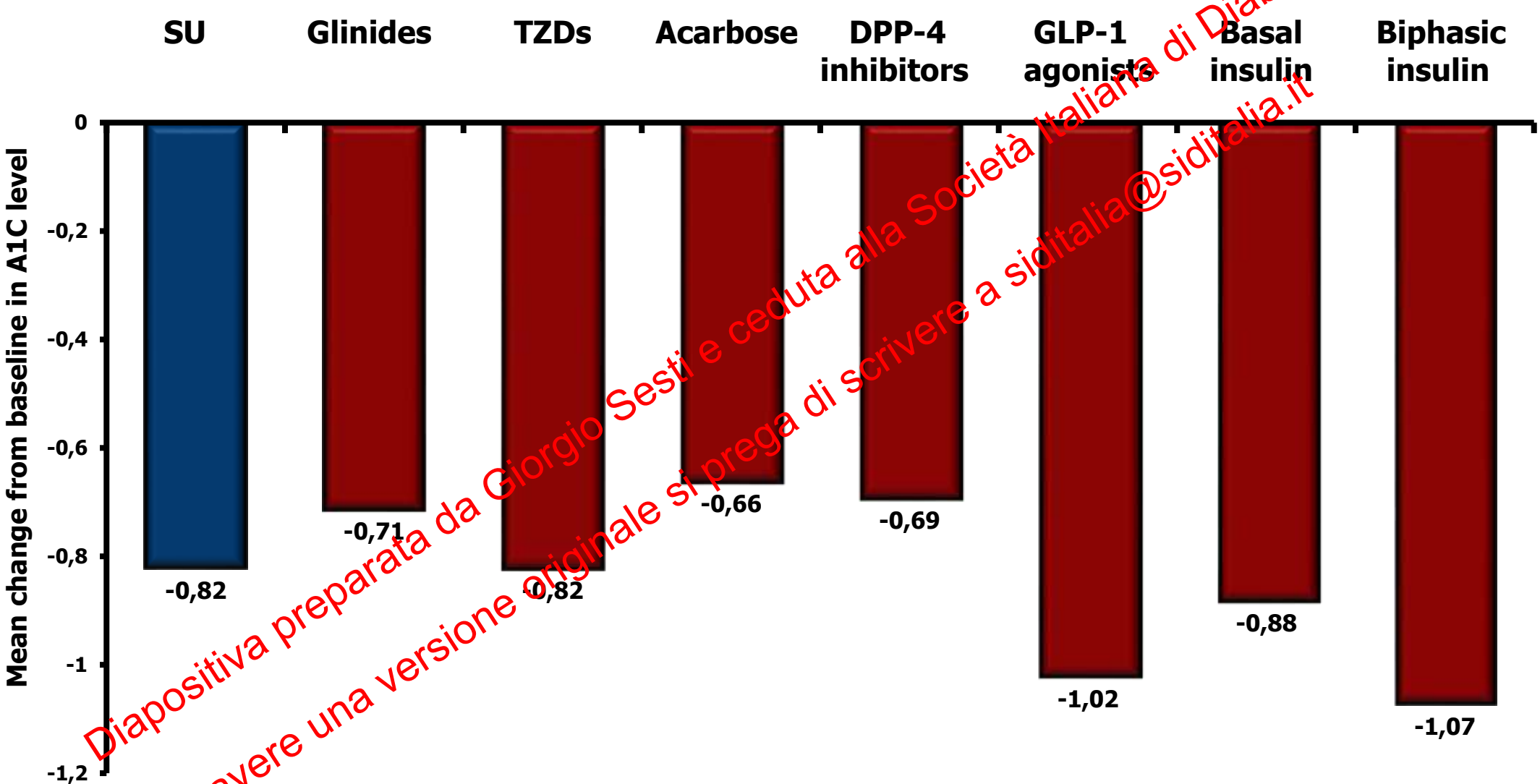
Phung OJ et al. JAMA 303:1410-1418, 2010

Pooled between-group differences in HbA1c level with monotherapy and combination therapies. A network meta-analysis of randomized trials at least 24 weeks in duration



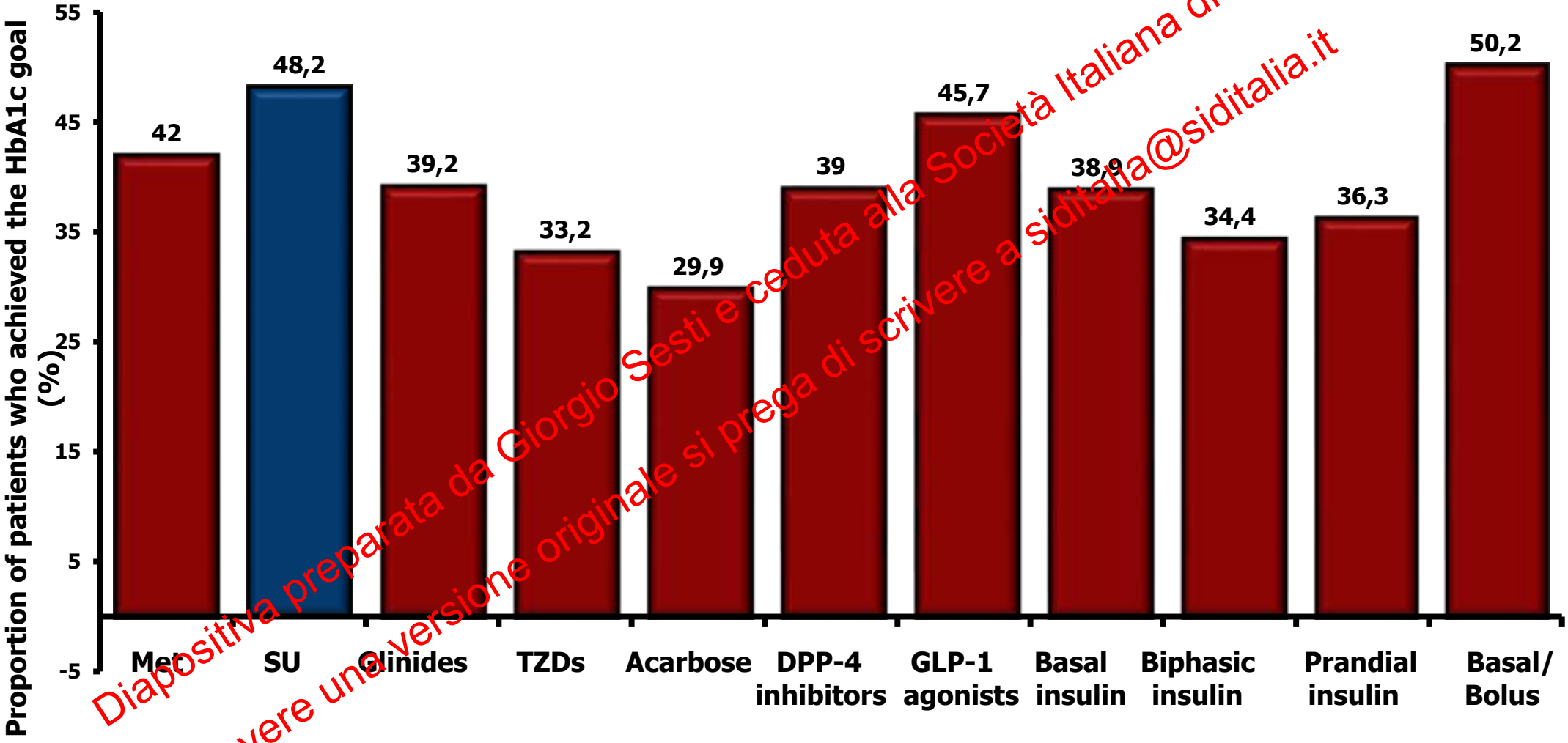
Bennett W L et al. Ann Intern Med 154 602-613, 2011

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: mean change from baseline in A1C



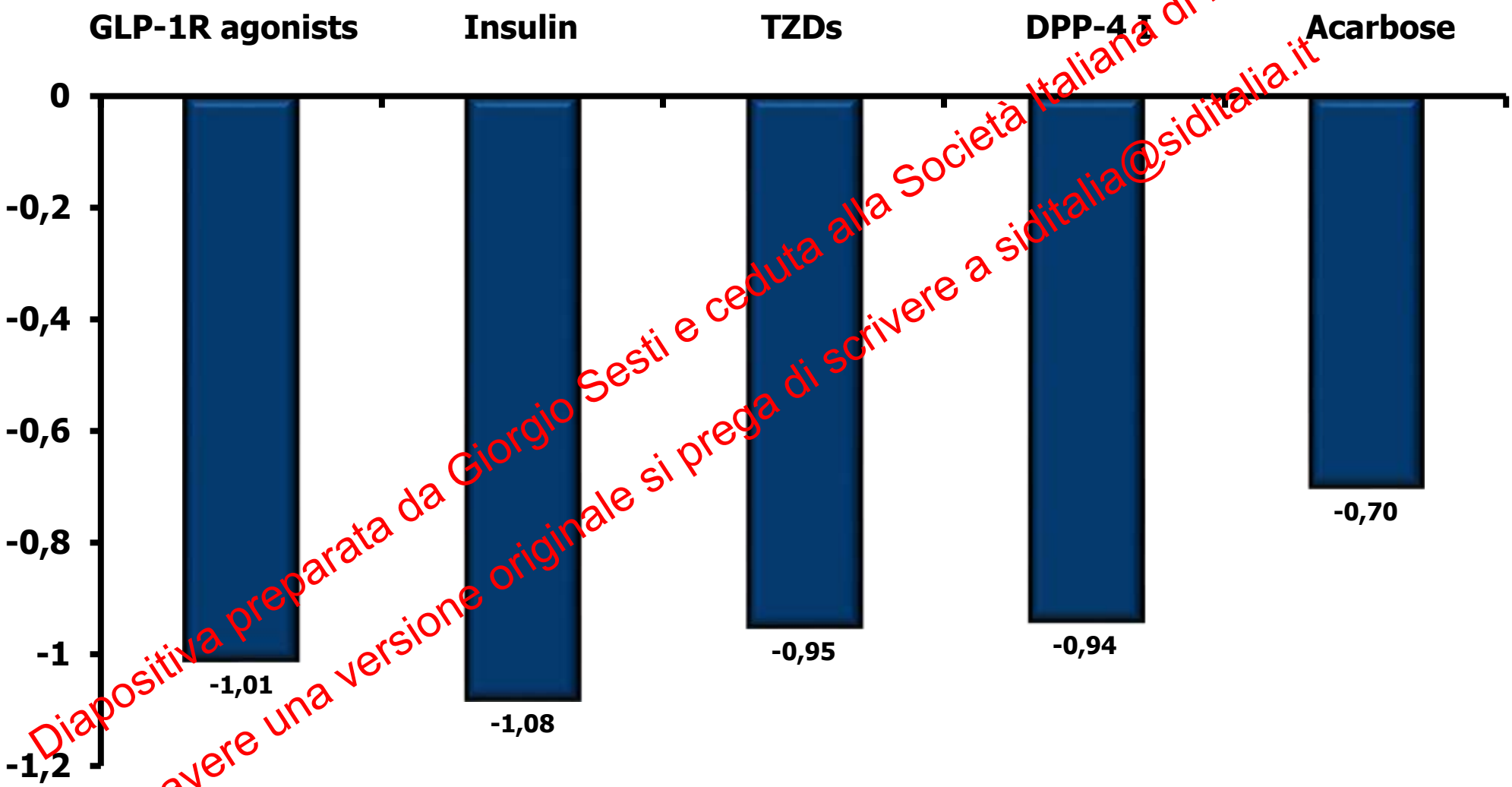
Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients



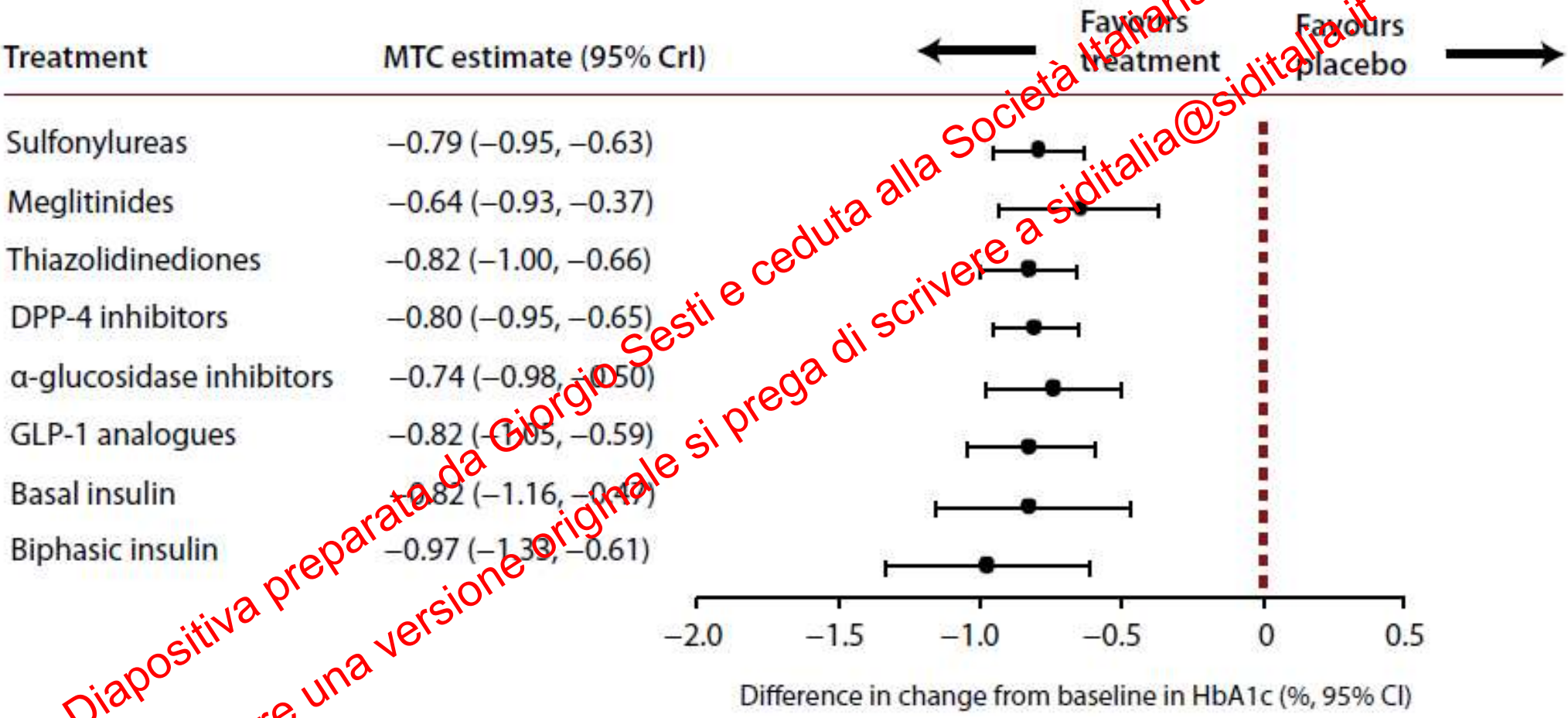
Esposito K. et al. Diabetes Obes and Metab 14: 228–233, 2012

Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control in T2DM: a network meta-analysis



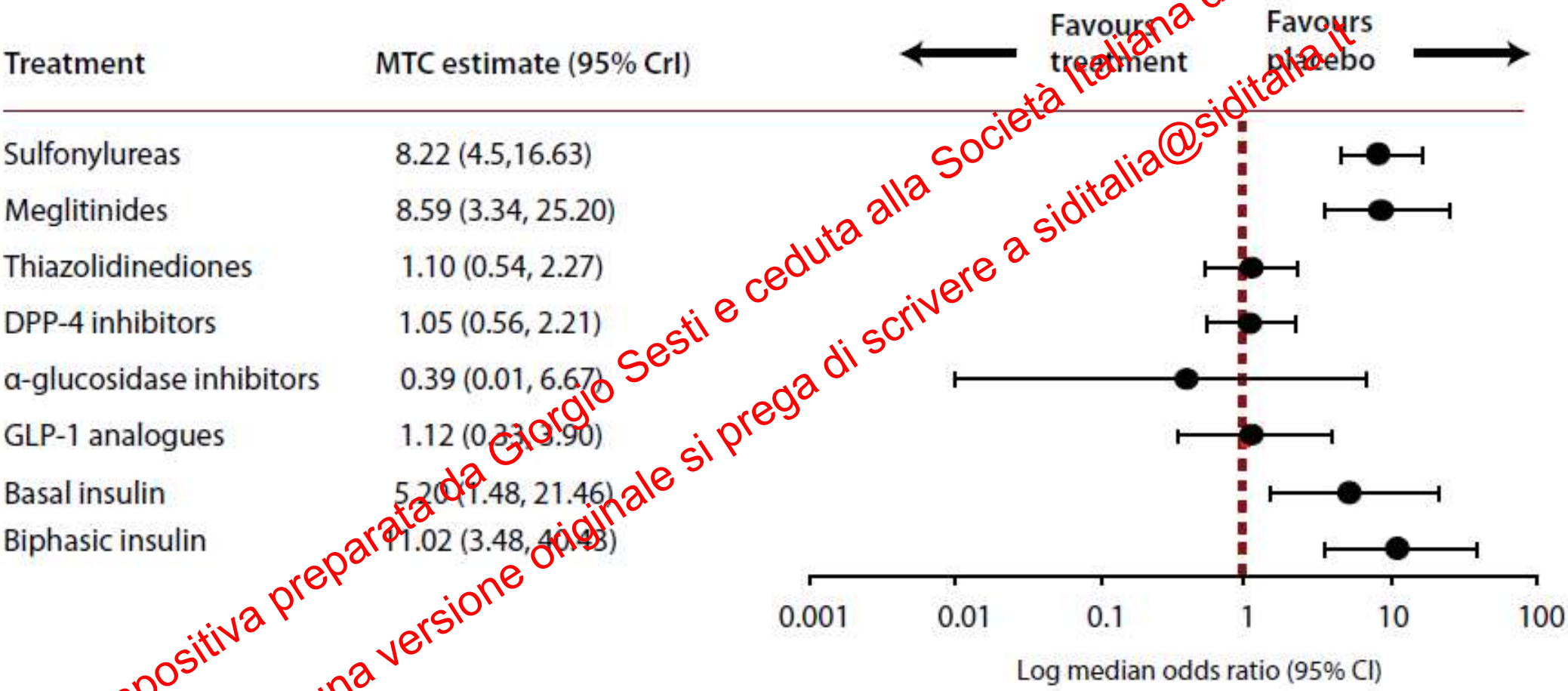
Gross JL et al. Ann Intern Med 154:672-679, 2011

Mixed-treatment comparison showing the effect of adding second-line antihyperglycemic agents vs. placebo to metformin on change from baseline in HbA1c



McIntosh B et al. Open Medicine 5:e35, 2011

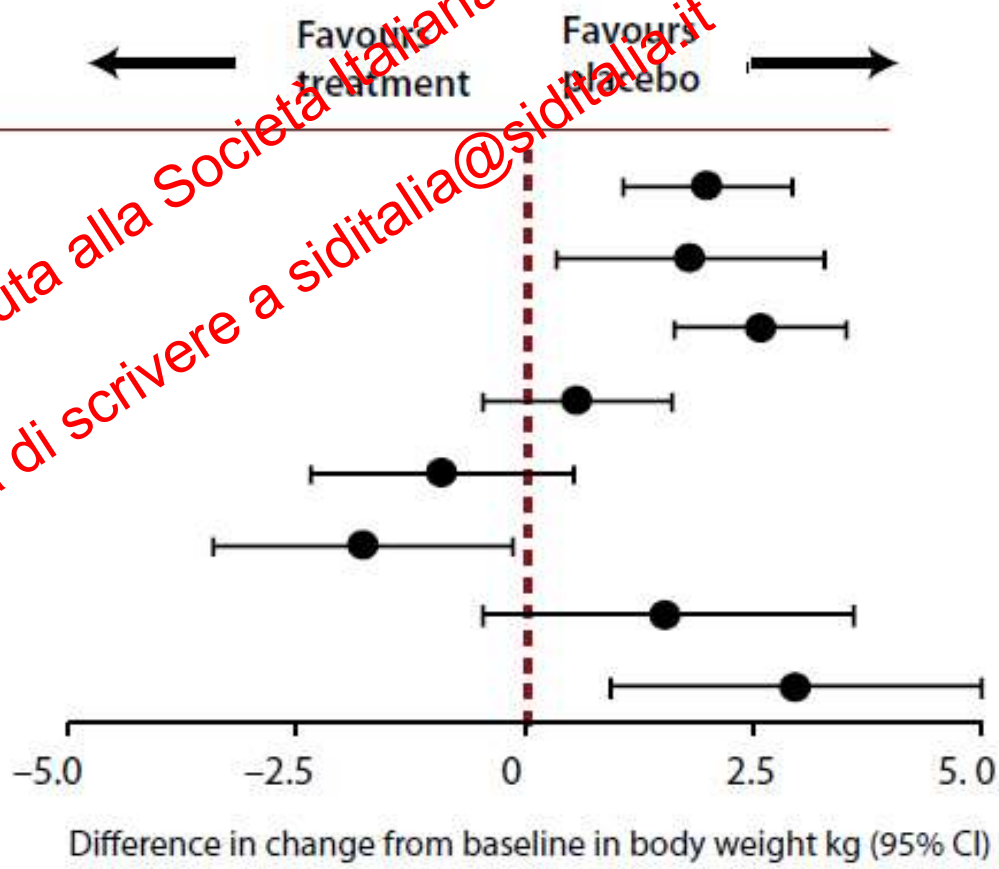
Mixed-treatment comparison showing the effect of adding second-line antihyperglycemic agents vs. placebo to metformin on odds of at least 1 event of overall hypoglycemia



McIntosh B et al. Open Medicine 5:e35, 2011

Mixed-treatment comparison showing the effect of adding second-line antihyperglycemic agents vs. placebo to metformin on change from baseline in body weight

Treatment	MTC estimate (95% CI)
Sulfonylureas	2.01 (1.09, 2.94)
Meglitinides	1.80 (0.35, 3.29)
Thiazolidinediones	2.59 (1.66, 3.51)
DPP-4 inhibitors	0.57 (–0.45 to 1.60)
α-glucosidase inhibitors	–0.92 (–2.35, 0.51)
GLP-1 analogues	–1.79 (–3.43, –0.14)
Basal insulin	1.56 (–0.46, 3.63)
Biphasic insulin	2.96 (0.96, 5.00)



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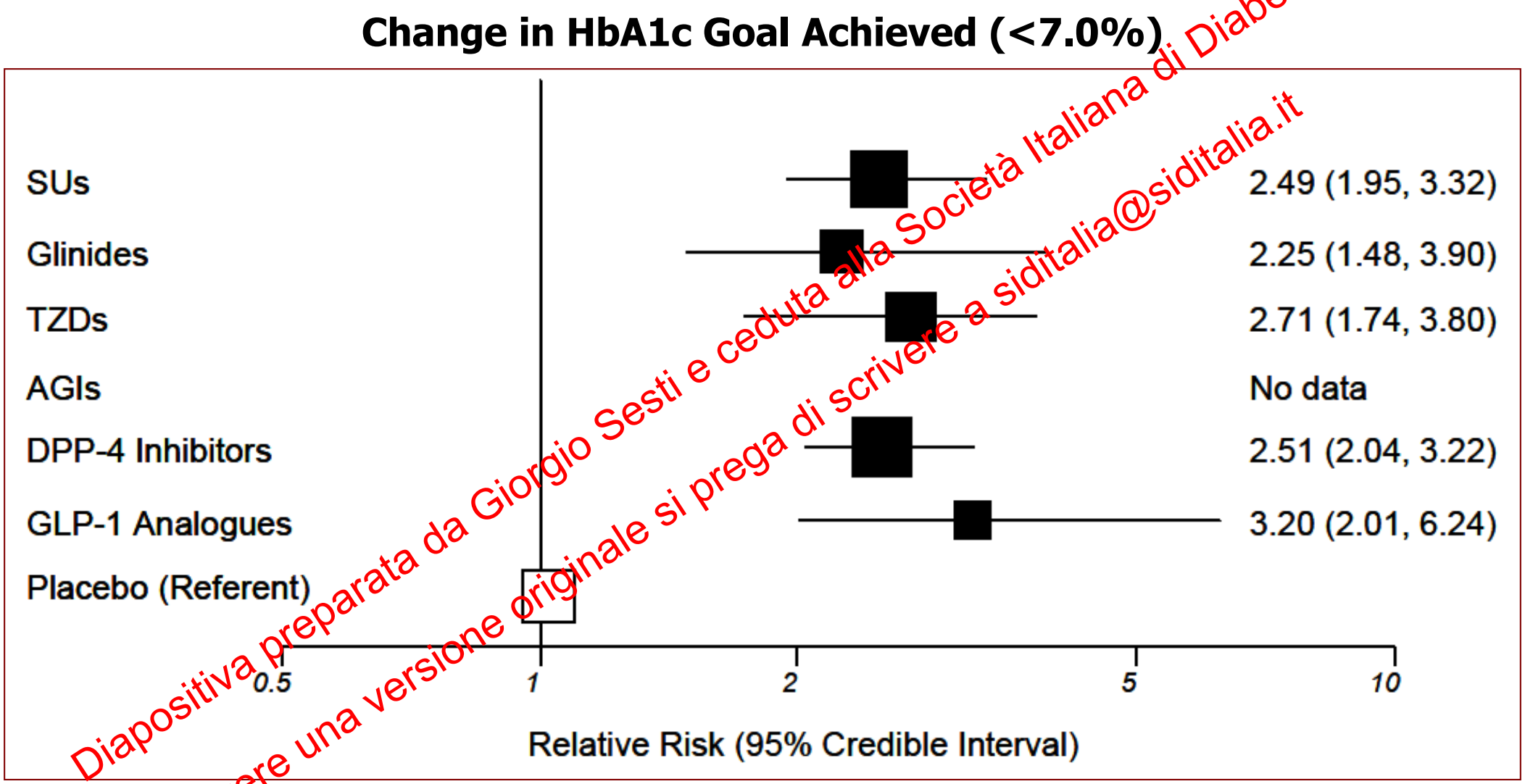

Phung OJ et al. JAMA 303:1410-1418, 2010

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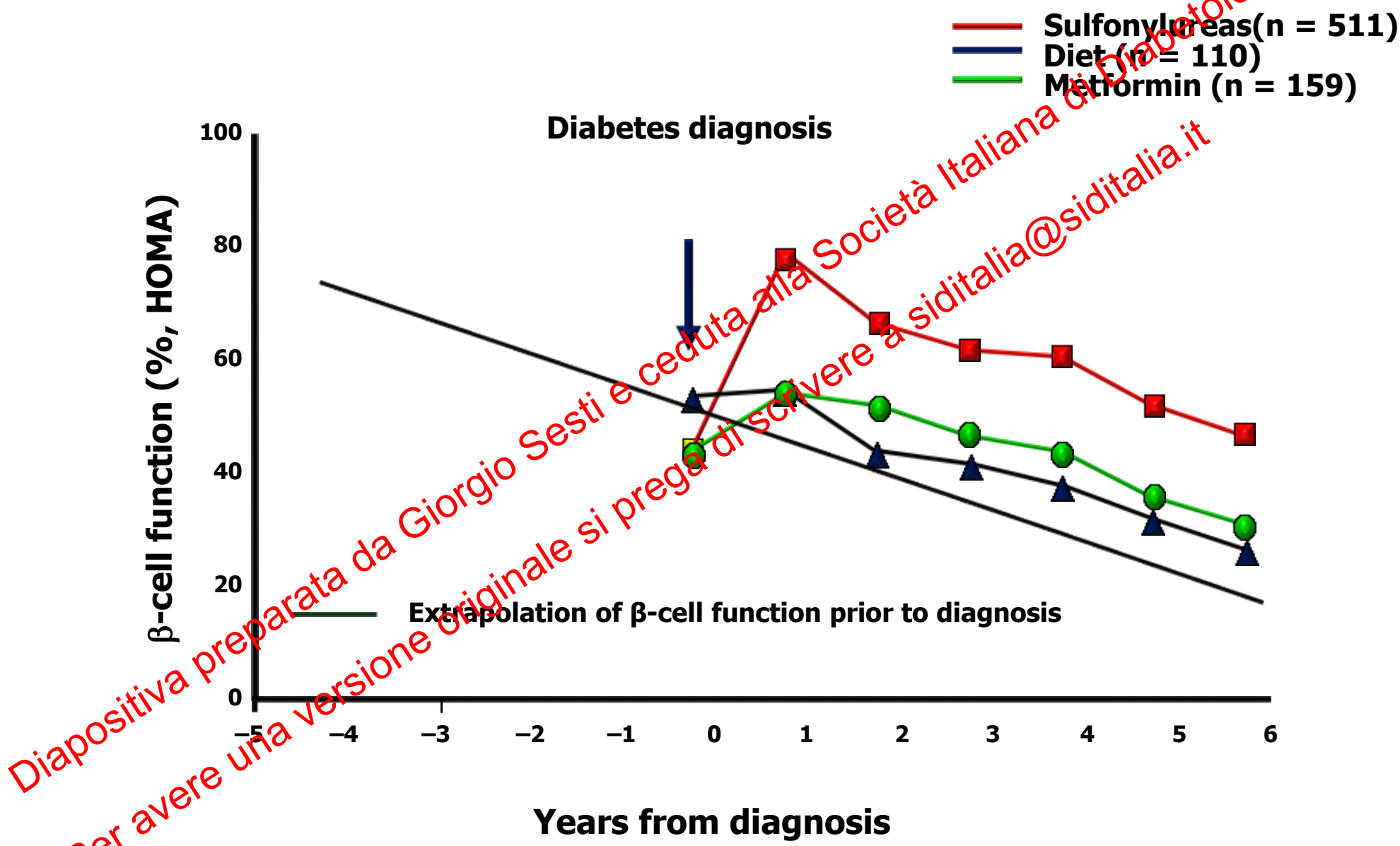
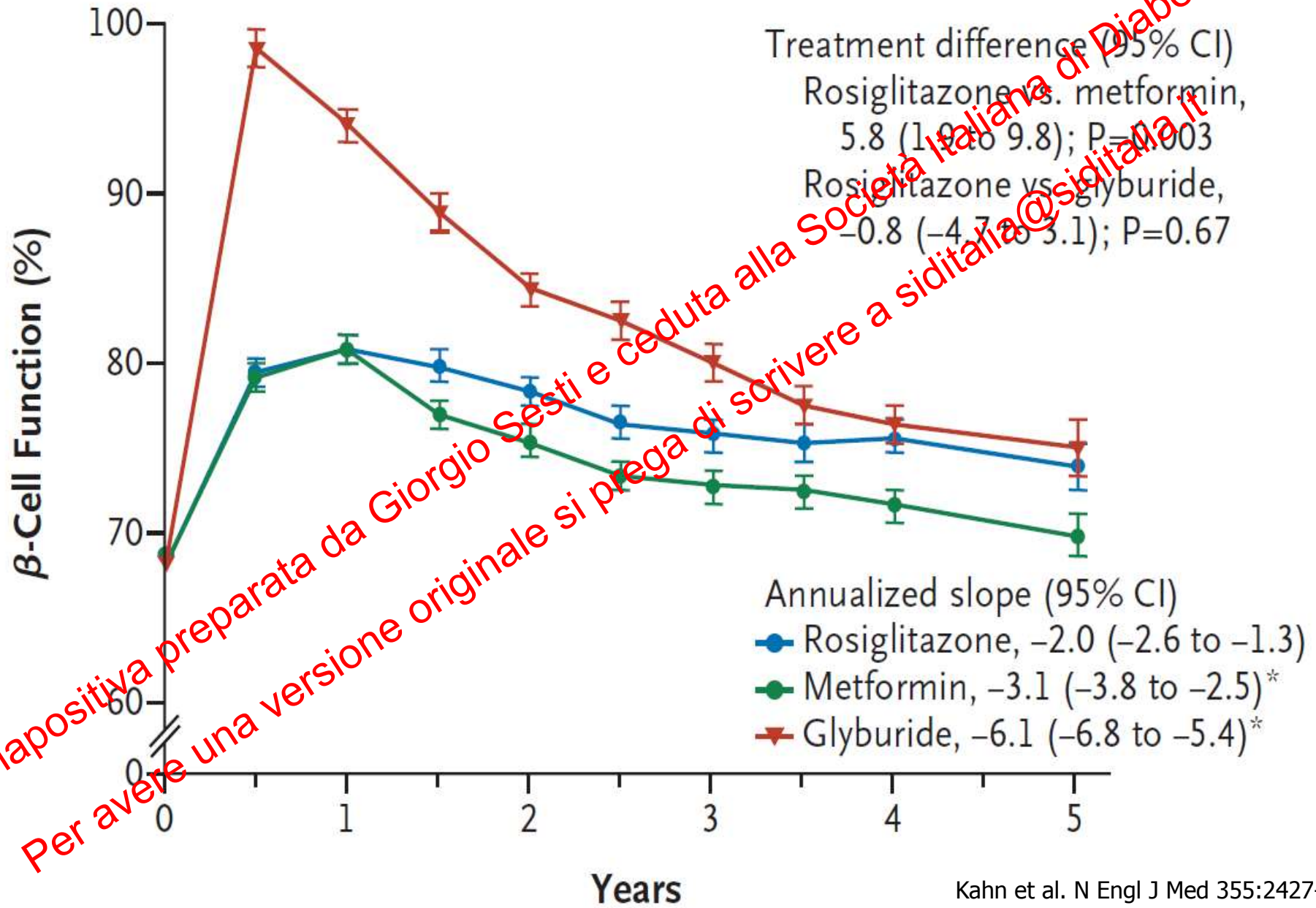
UKPDS: β-cell function progressively declines



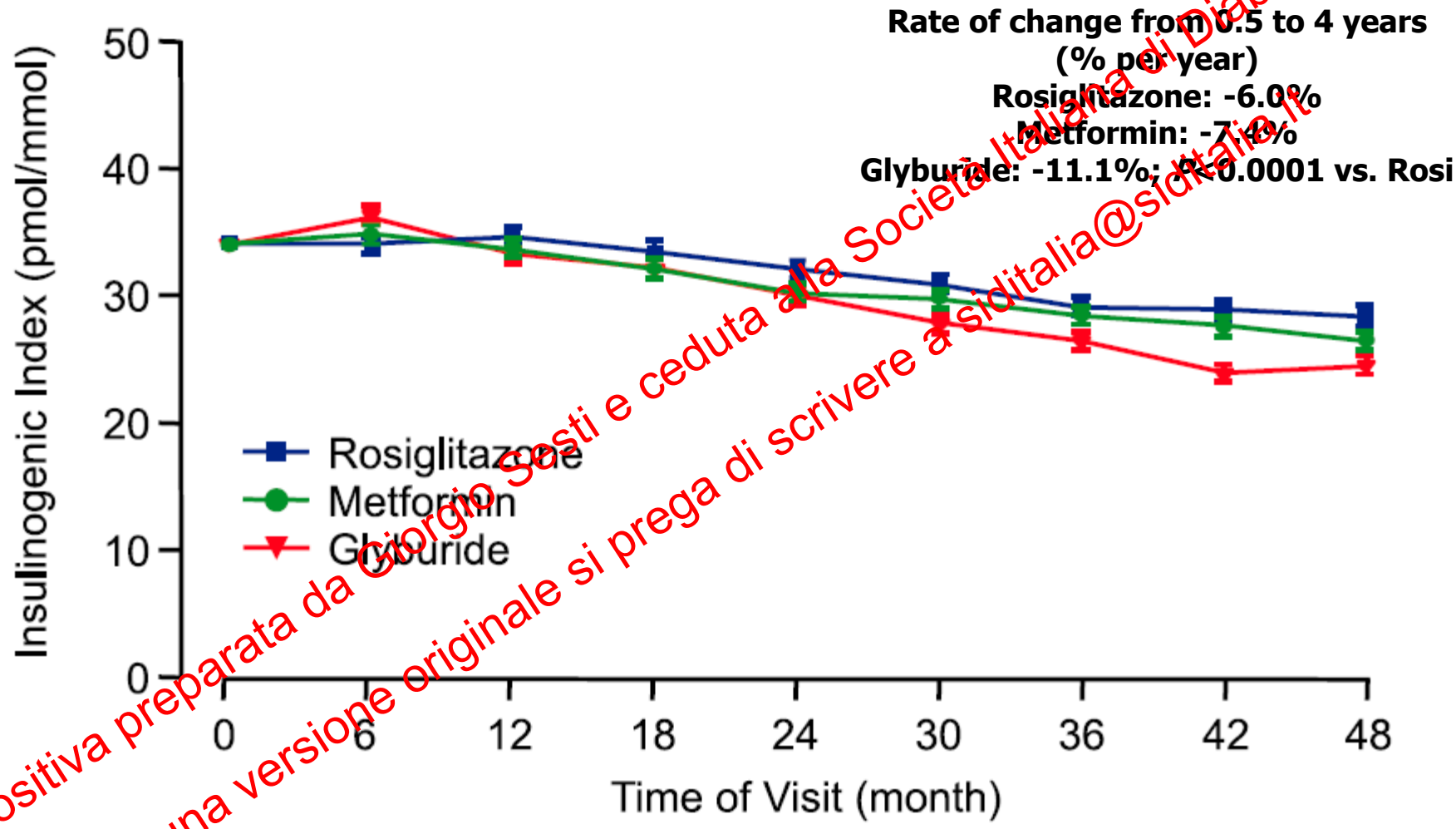
UKPDS 16. Diabetes 44:1249–1258 1995. Lebovitz 7:139–153, 1999

ADOPT: β-Cell Function According to Treatment Group



Kahn et al. N Engl J Med 355:2427-2443, 2006

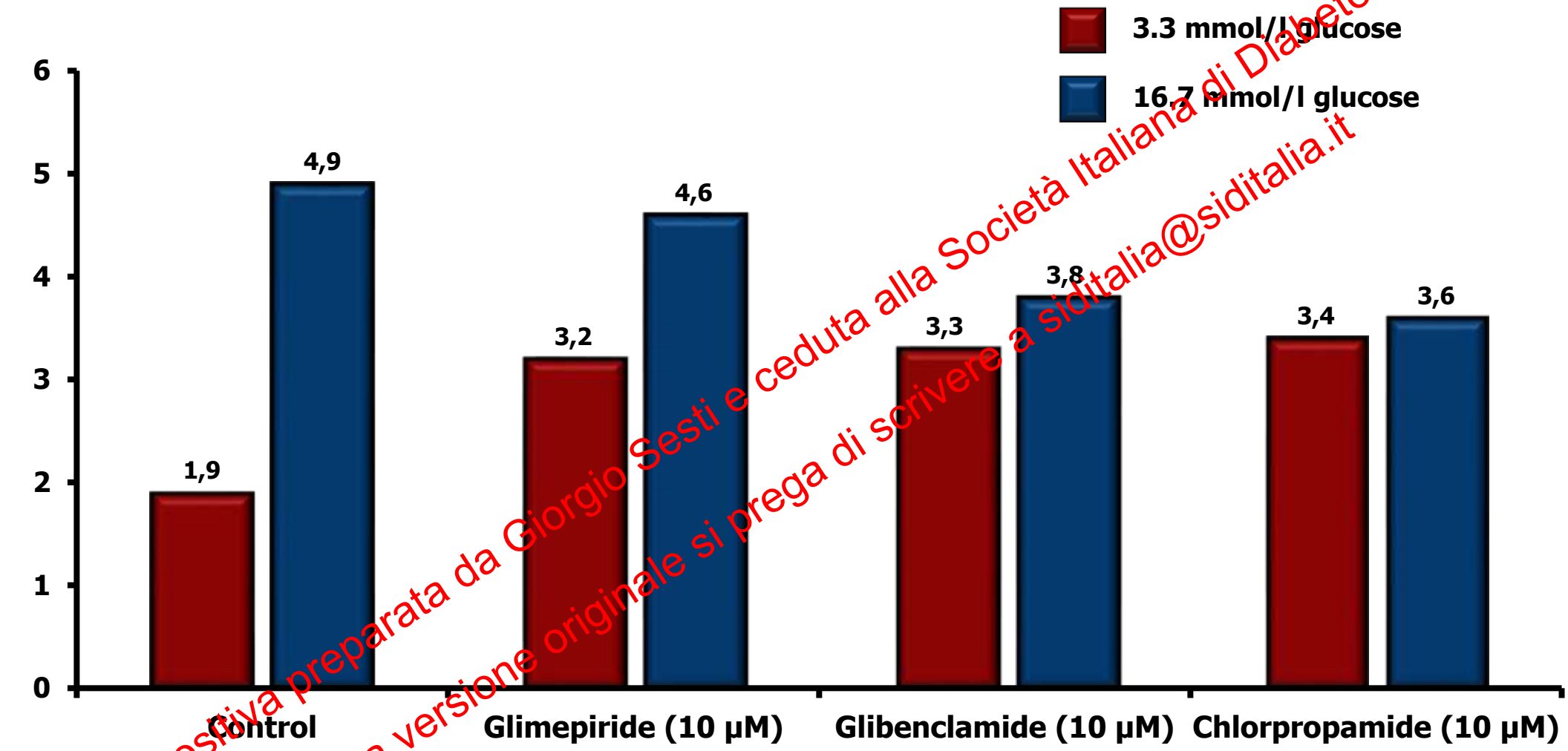
ADOPT: Baseline adjusted geometric mean levels in the full cohort within each treatment group over 4 years of follow-up for OGTT-derived dynamic measure of the early insulin response



Kahn SE et al. Diabetes 60:1552–1560, 2011

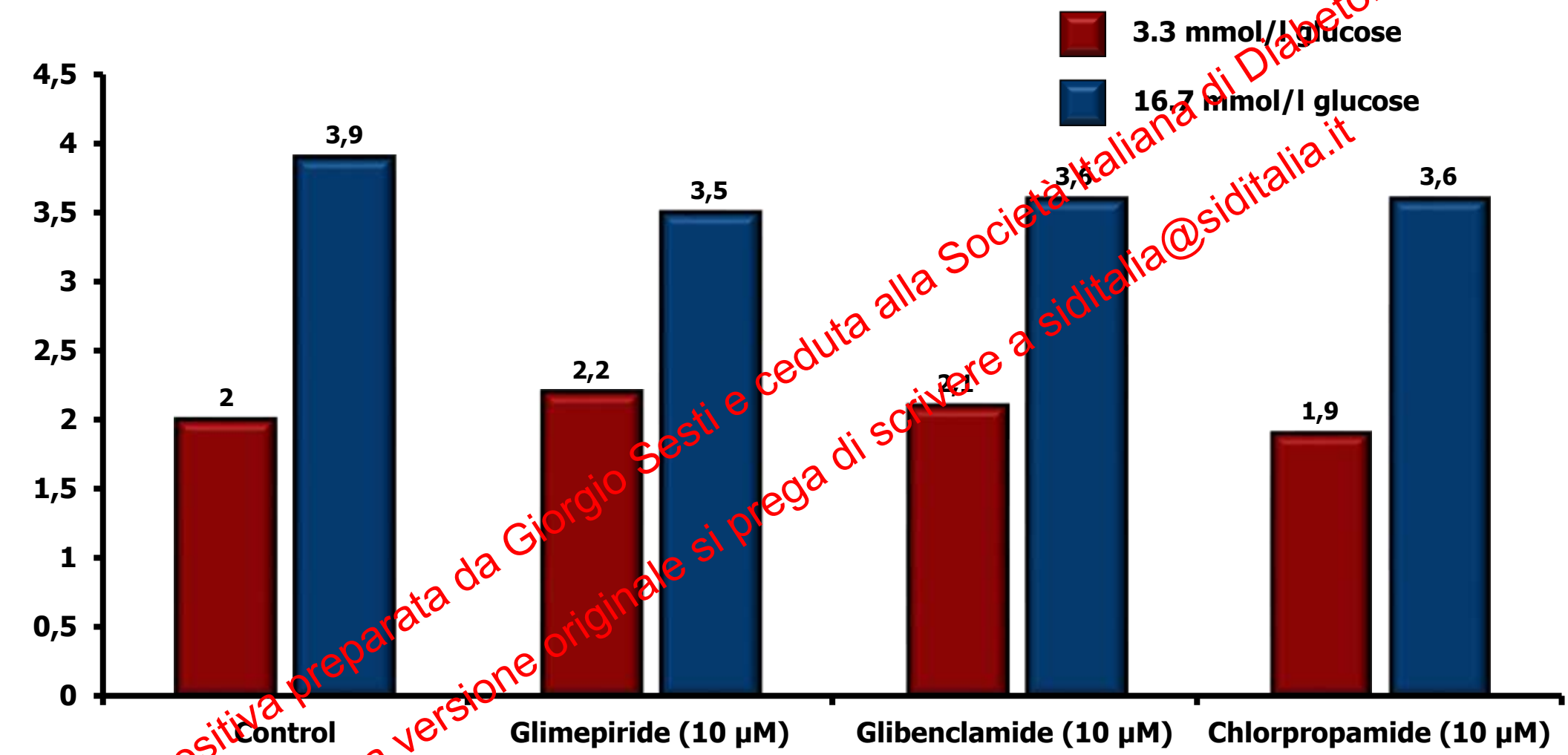
In vitro and ex vivo data

Insulin release (% of insulin content) in response to acute glucose stimulation from human islets exposed for 24-h to sulphonylureas (n = 10)



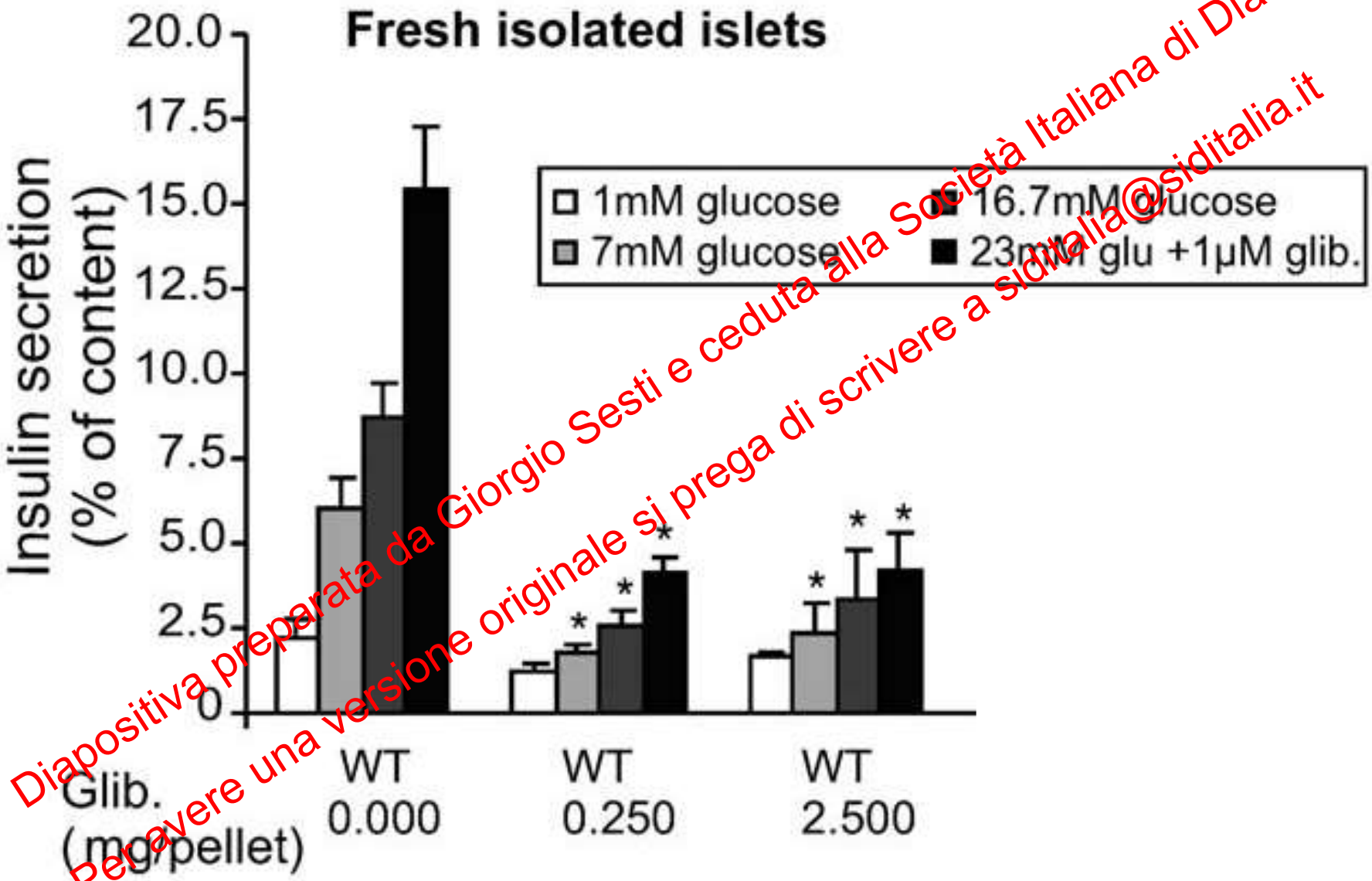
Del Guerra S et al. J Diabetes Complications 19:60-4, 2005

Impaired insulin release (% of insulin content) in human islets pre-exposed for 24-h to sulphonylureas was reverted by an additional 48-h incubation in drug-free conditions



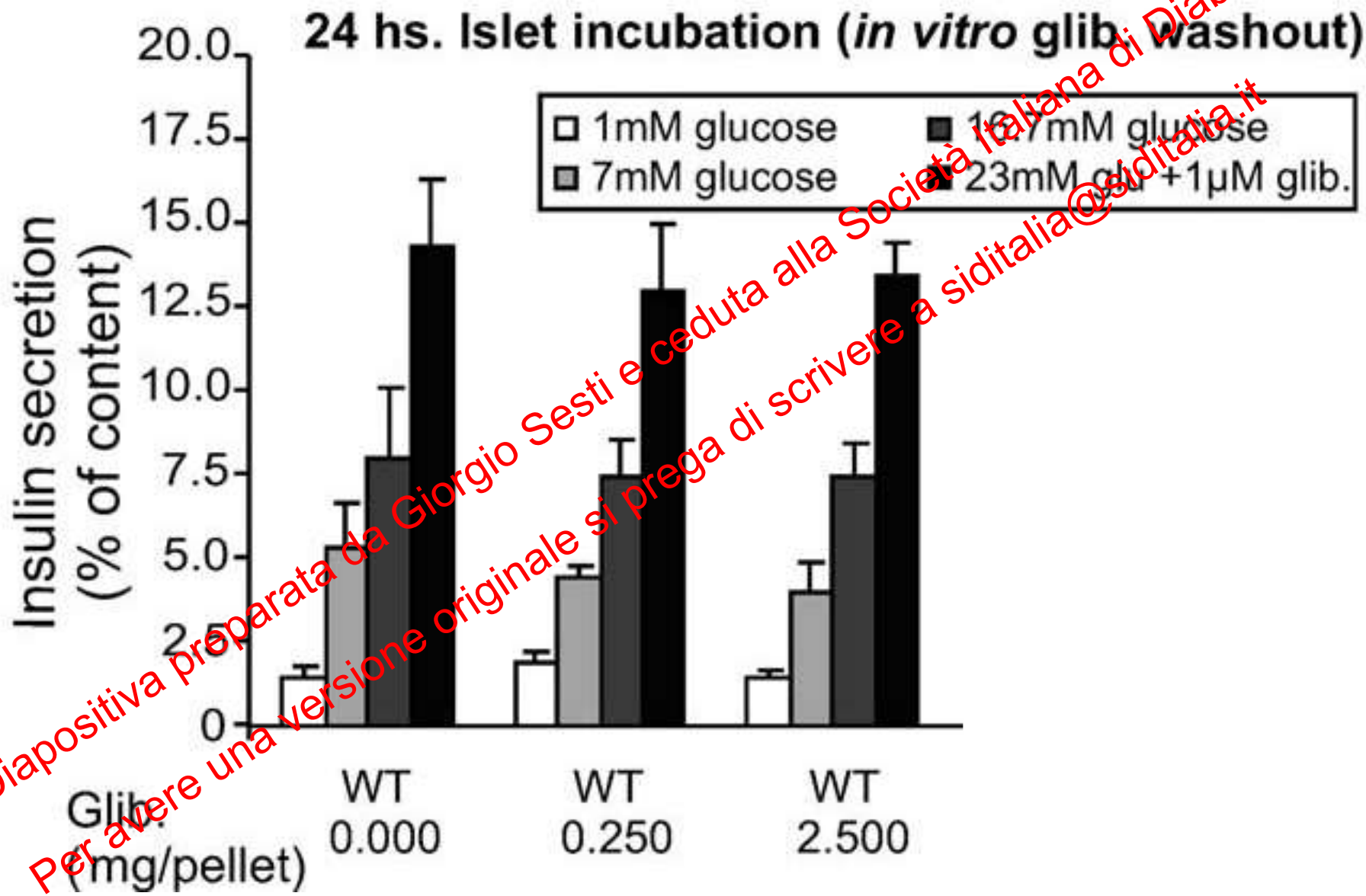
Del Guerra S et al. J Diabetes Complications 19:60-4, 2005

Chronic Antidiabetic Sulfonylureas In Vivo: Reversible Effects on Mouse Pancreatic beta-Cells



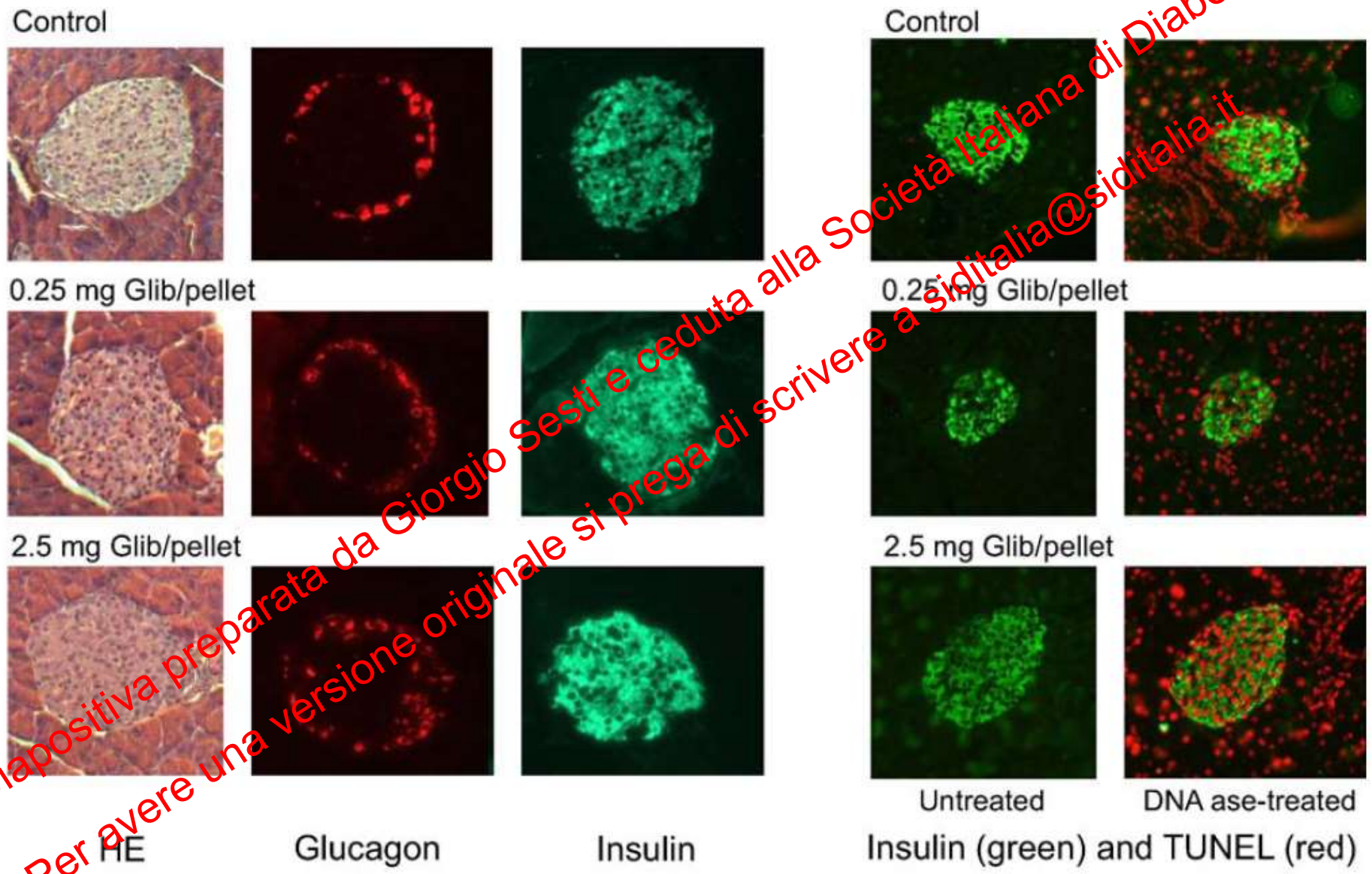
Remedi MS et al. PLoS Med 5: e206, 2008

Chronic Antidiabetic Sulfonylureas In Vivo: Reversible Effects on Mouse Pancreatic beta-Cells



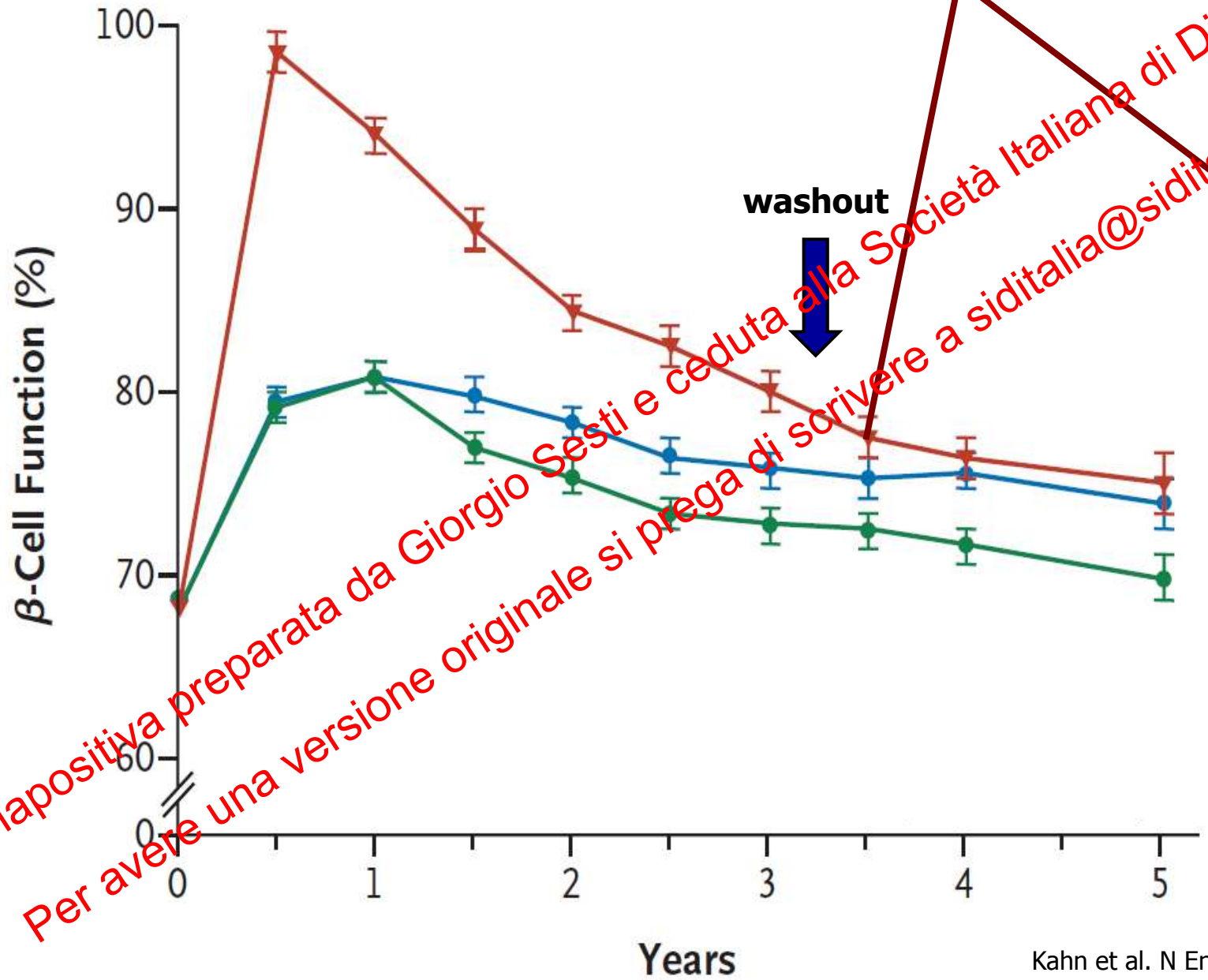
Remedi MS et al. PLoS Med 5: e206, 2008

Absence of beta-cell apoptosis in islets from control or high dose (0.25 and 2.5 mg/pellet) glibenclamide-pelleted mice after 56 days



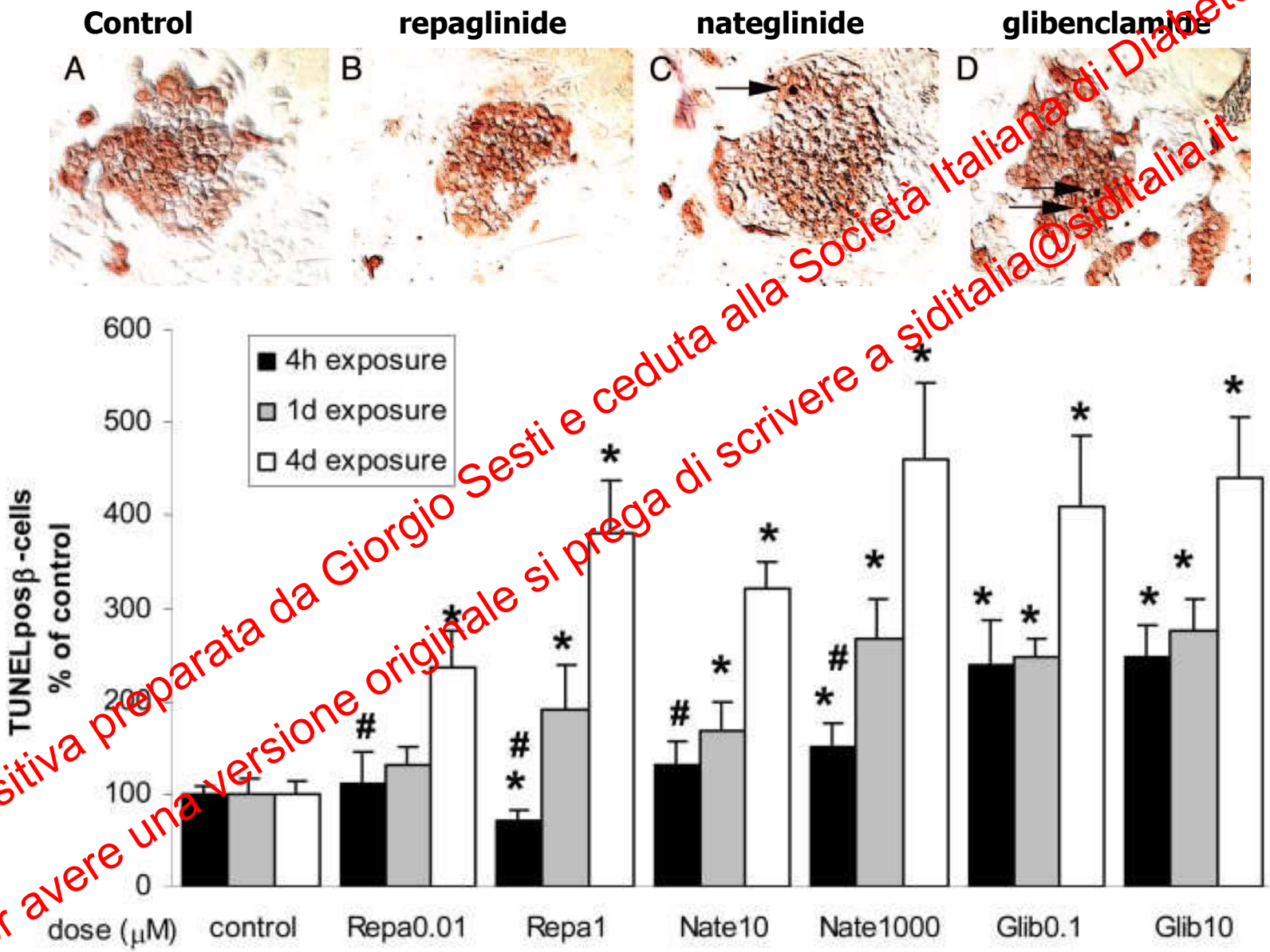
Remedi, MS et al. PLoS Med 5: e206, 2008

ADOPT: β-Cell Function According to Treatment Group



Kahn et al. N Engl J Med 355:2427-2443, 2006

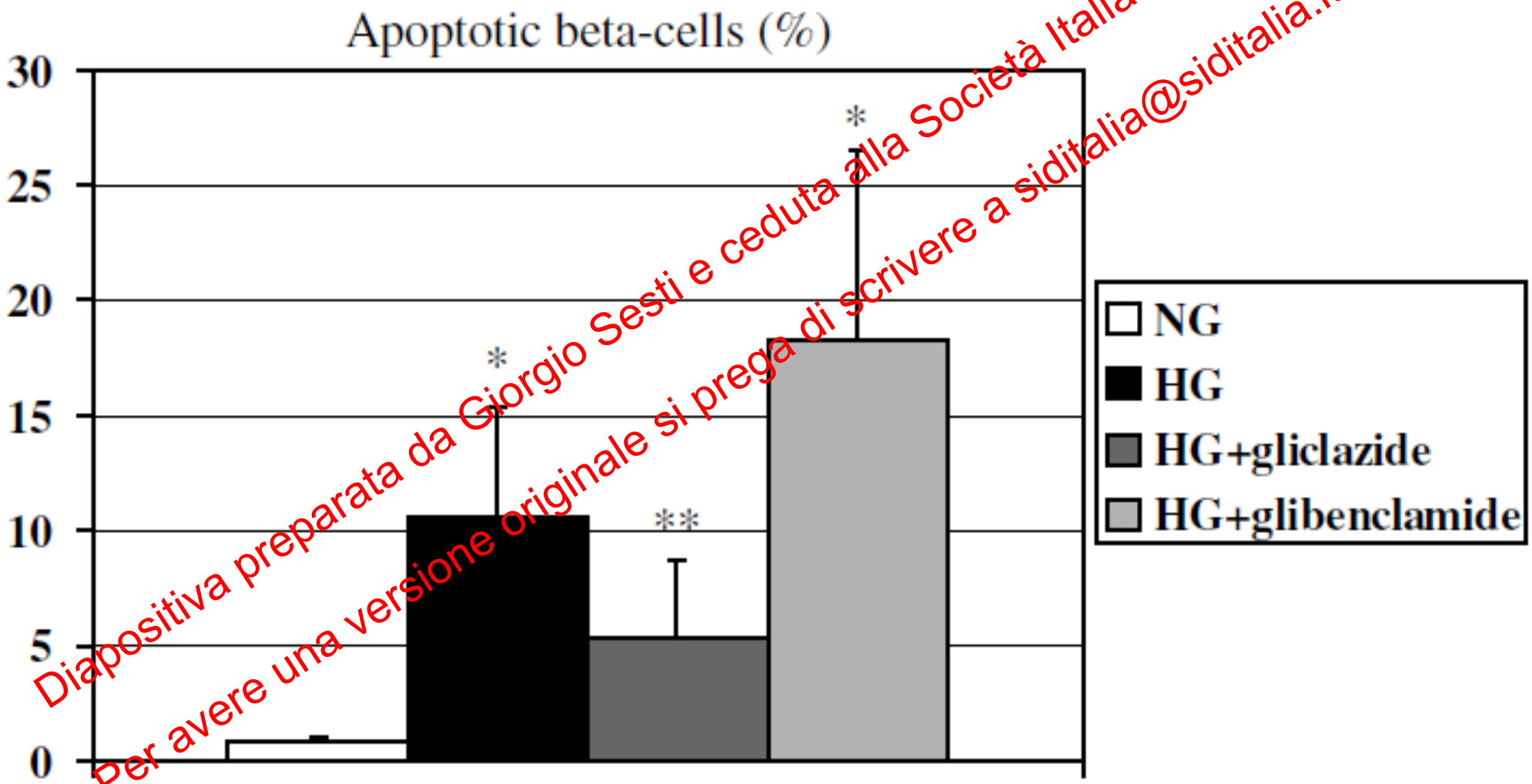
Effects of repaglinide, nateglinide, and glibenclamide on beta-cell apoptosis in human islets



Maedler K et al.J Clin Endocrinol Metab 90: 501–506, 2005

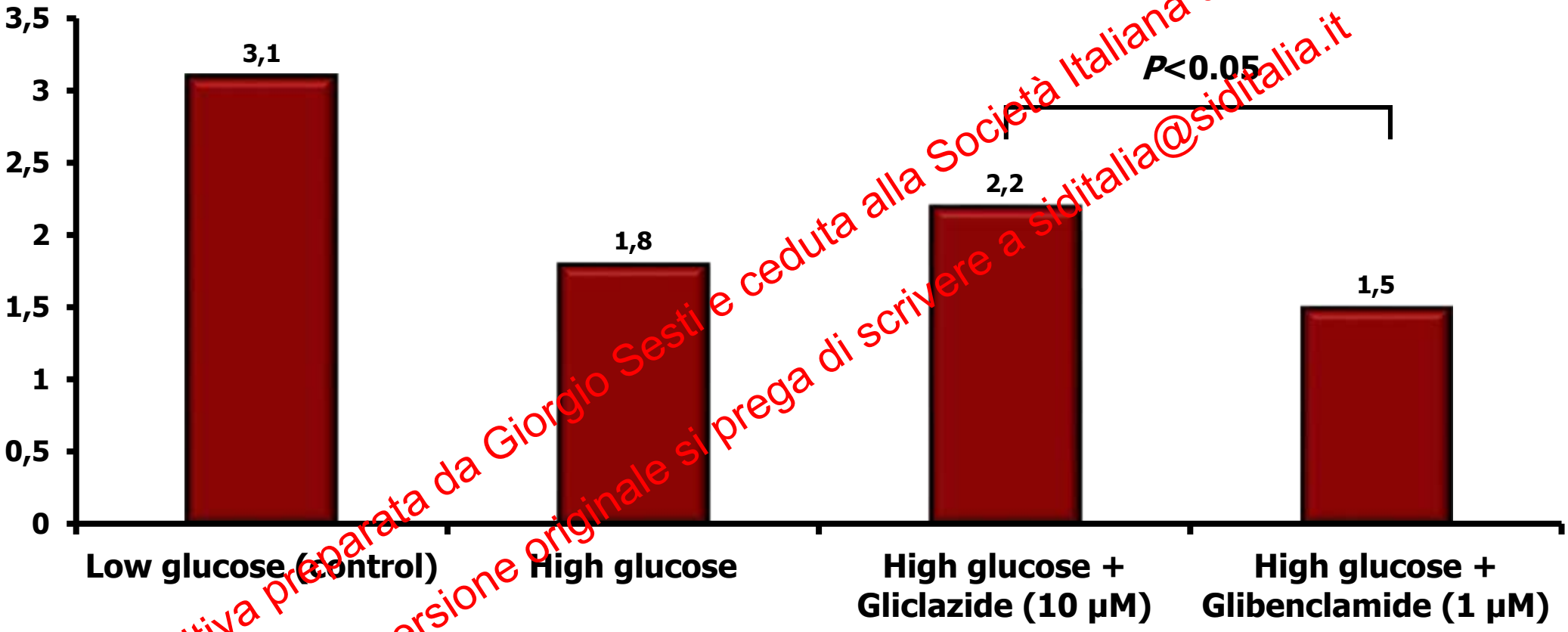
Gliclazide protects human islet beta-cells from apoptosis induced by intermittent high glucose

Beta-cell apoptosis in human islets exposed for 5 days to 5.5 mmol/L glucose (NG), alternating 5.5 and 16.7 mmol/L glucose (HG), HG with gliclazide or HG with glibenclamide



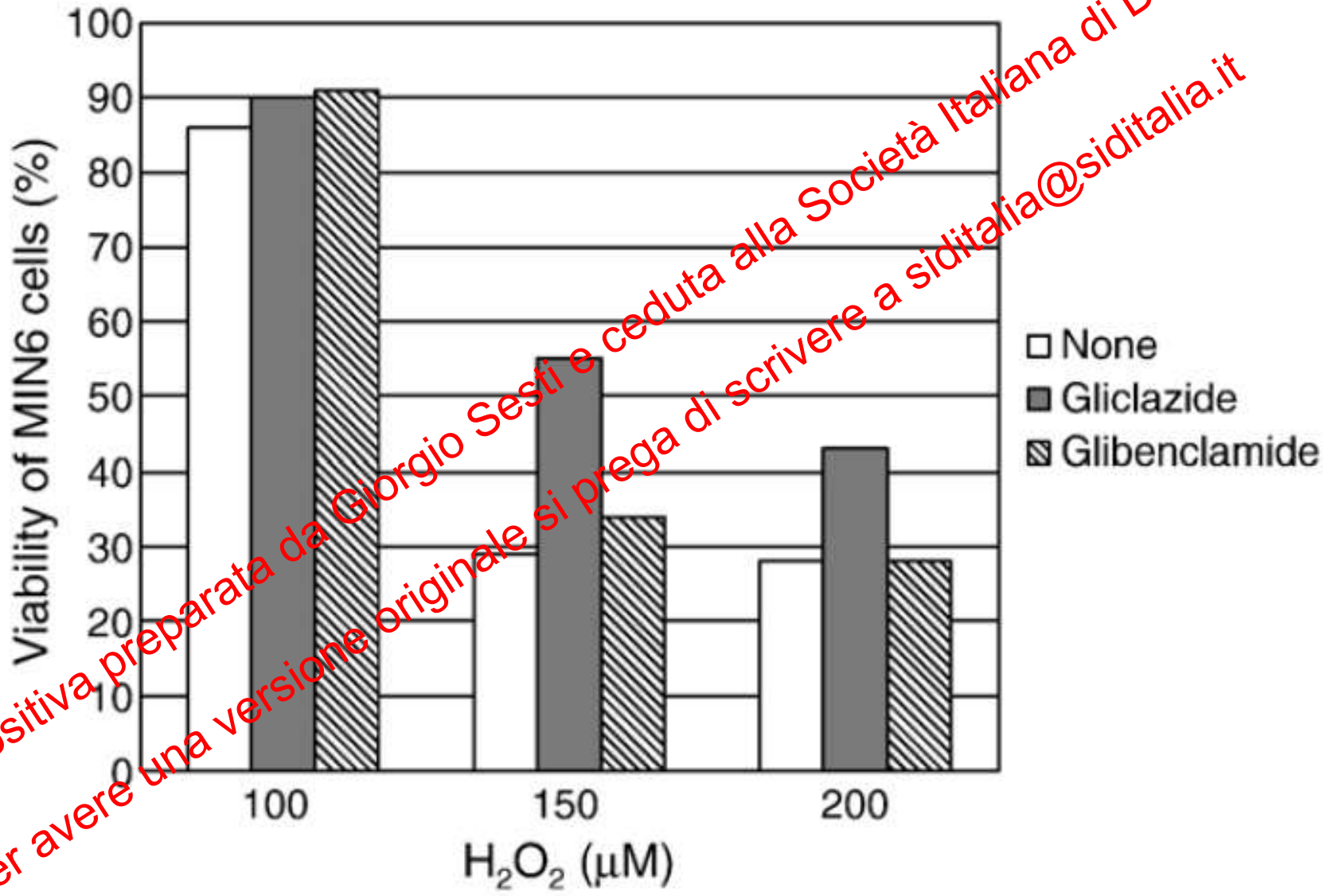
Del Guerra S et al. Diabetes Metab Res Rev 23: 234–238, 2007

Insulin release (% of insulin content) in response to acute glucose stimulation from human islets exposed for 5 days to 5.5 mmol/L glucose (NG), alternating 5.5 and 16.7 mmol/L glucose (HG), HG with gliclazide or HG with glibenclamide



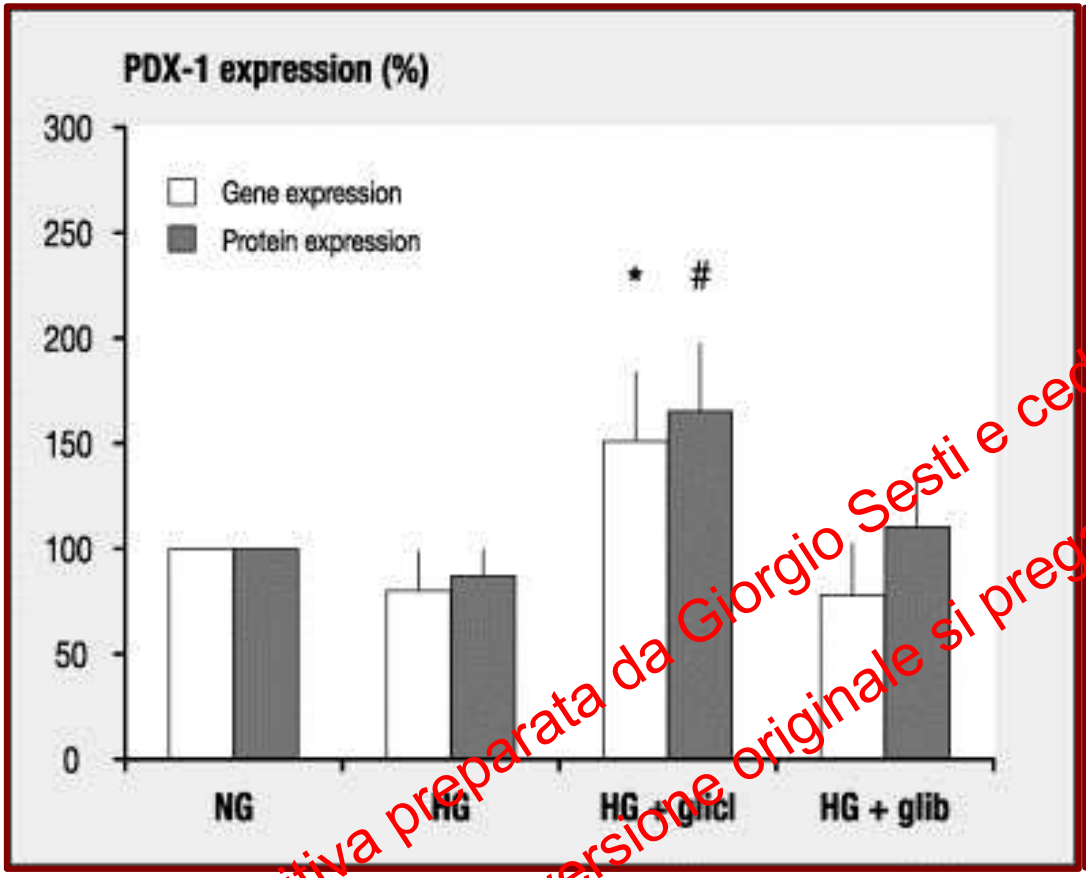
Del Guerra S et al. Diabetes Metab 35:293-298, 2009

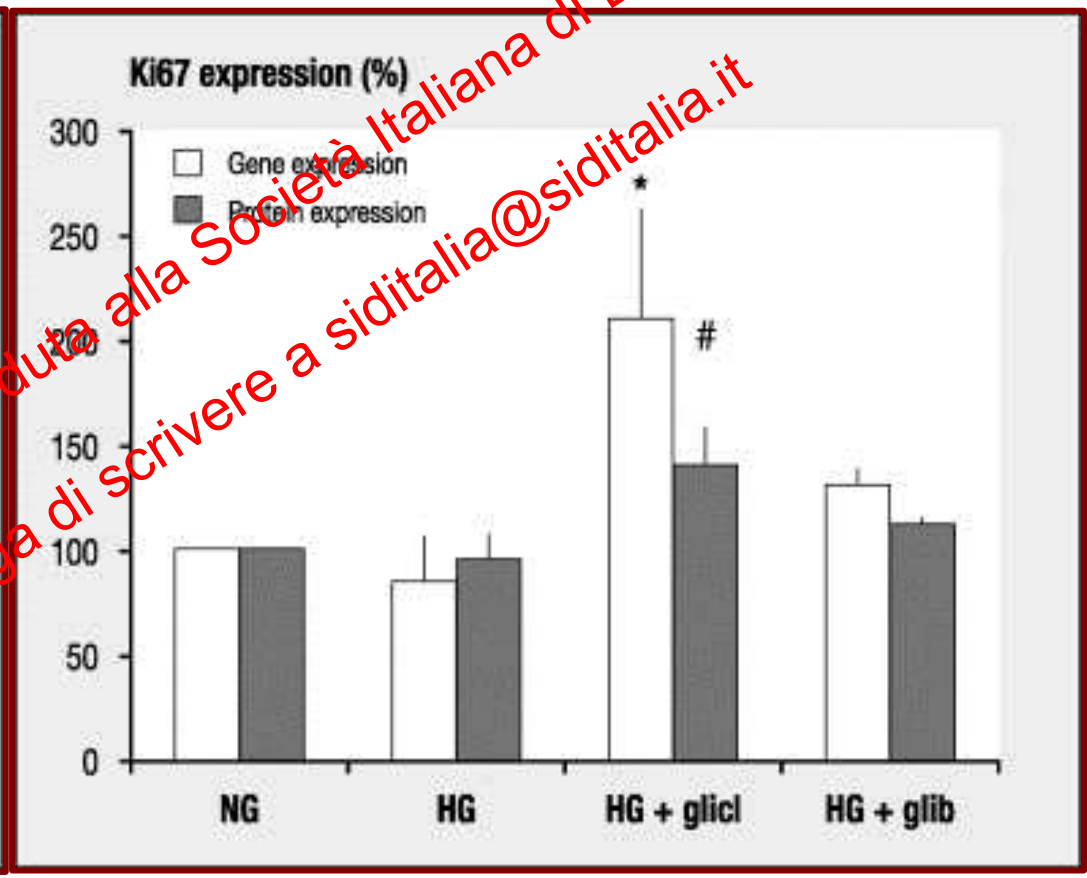
Viability of MIN6 beta cell exposed to H_2O_2 in the presence of gliclazide (5 µmol/L) or glibenclamide (5 µmol/L)



Kimoto K et al. Biochem Biophys Res Commun 303:112-9, 2003

Exposure to gliclazide, but not glibenclamide, significantly induced expression of PDX-1, a fundamental beta-cell differentiation transcription factor, and Ki67, a marker of proliferation in human islets





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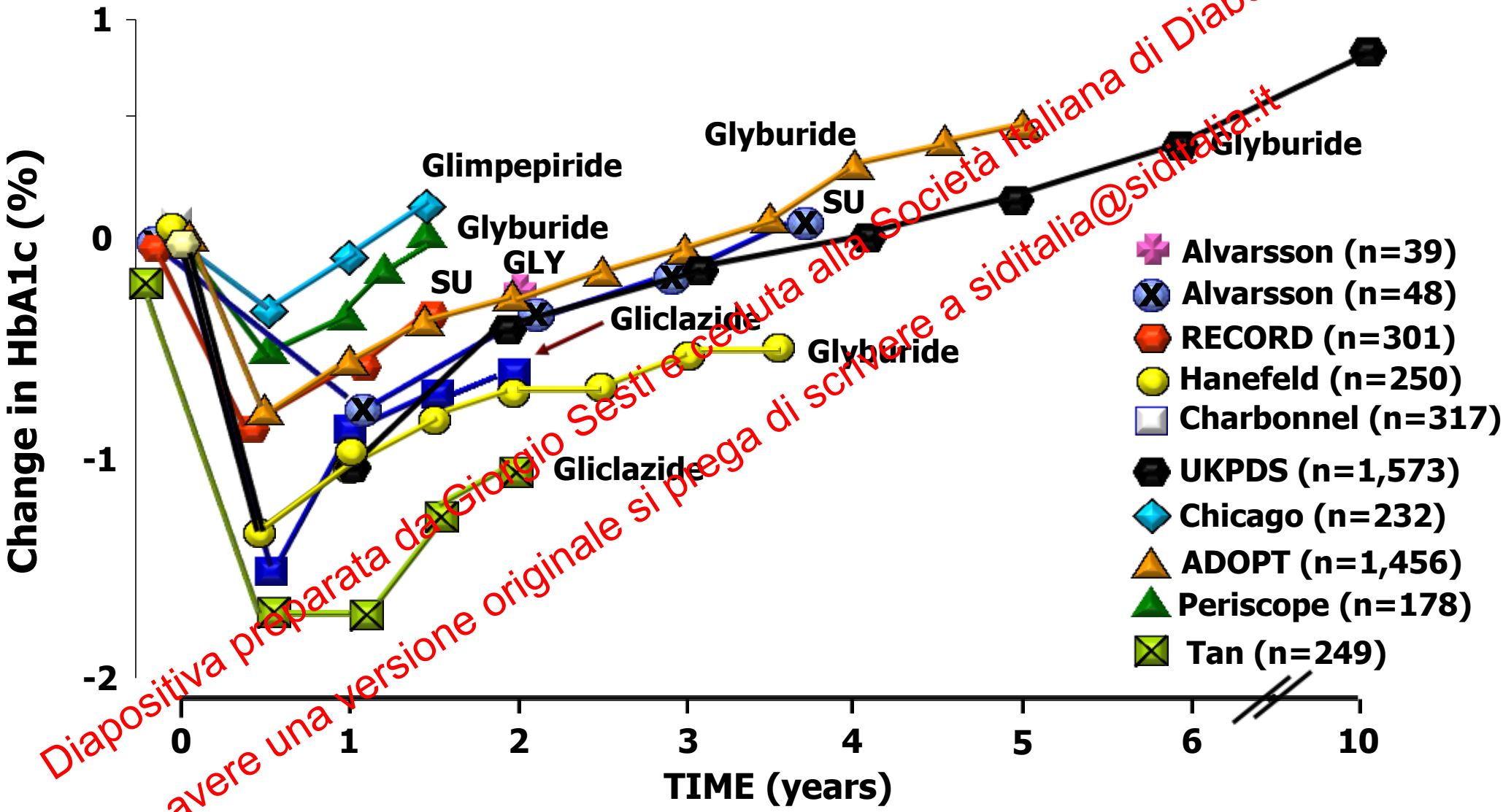
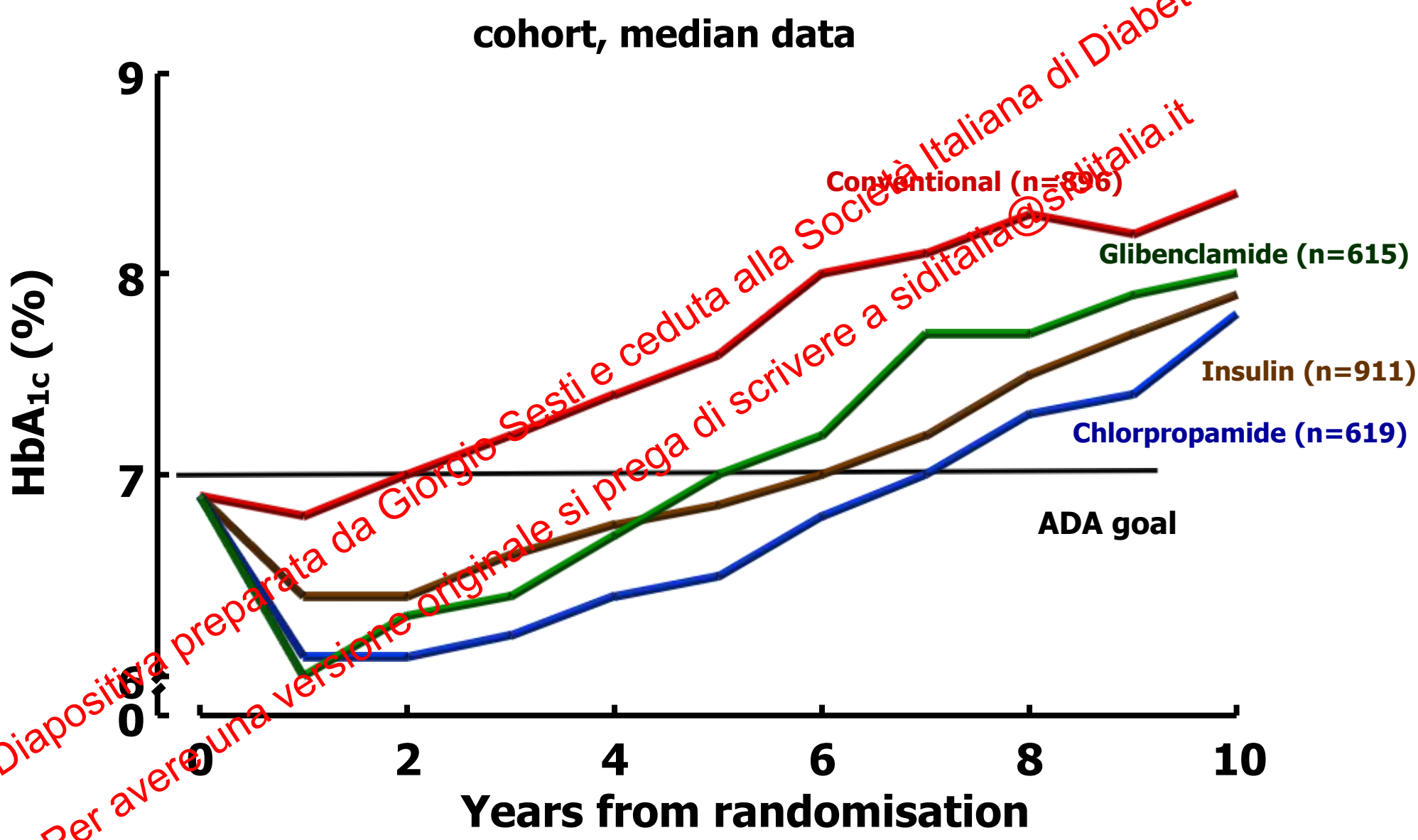
Summary of studies examining the effect of sulfonylurea (SU) treatment vs. placebo or vs. active-comparator on A1C in type 2 diabetic subjects



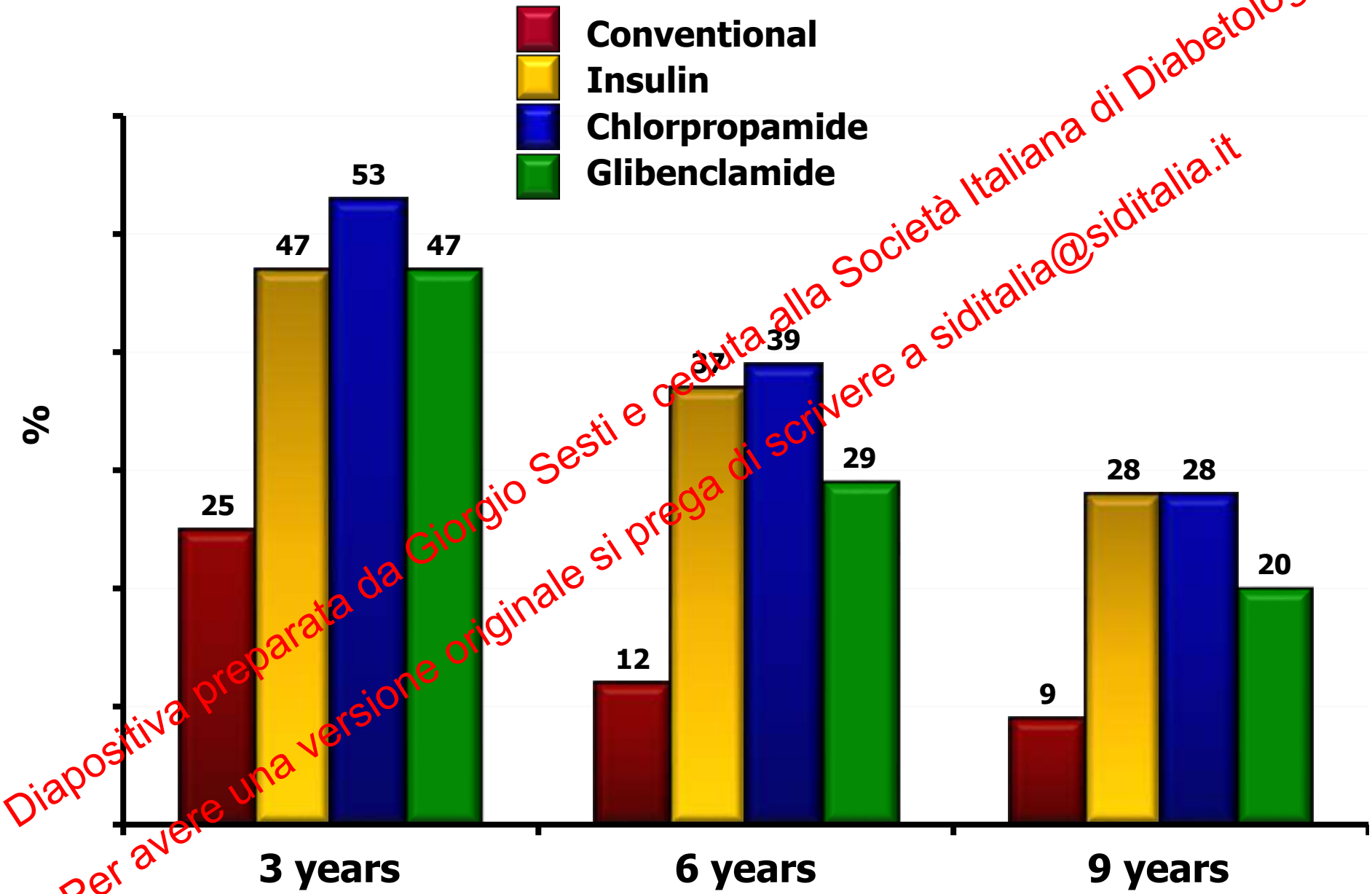
DeFronzo R A Diabetes 58:773-795, 2009

UKPDS 33: Over time, glycaemic control deteriorates



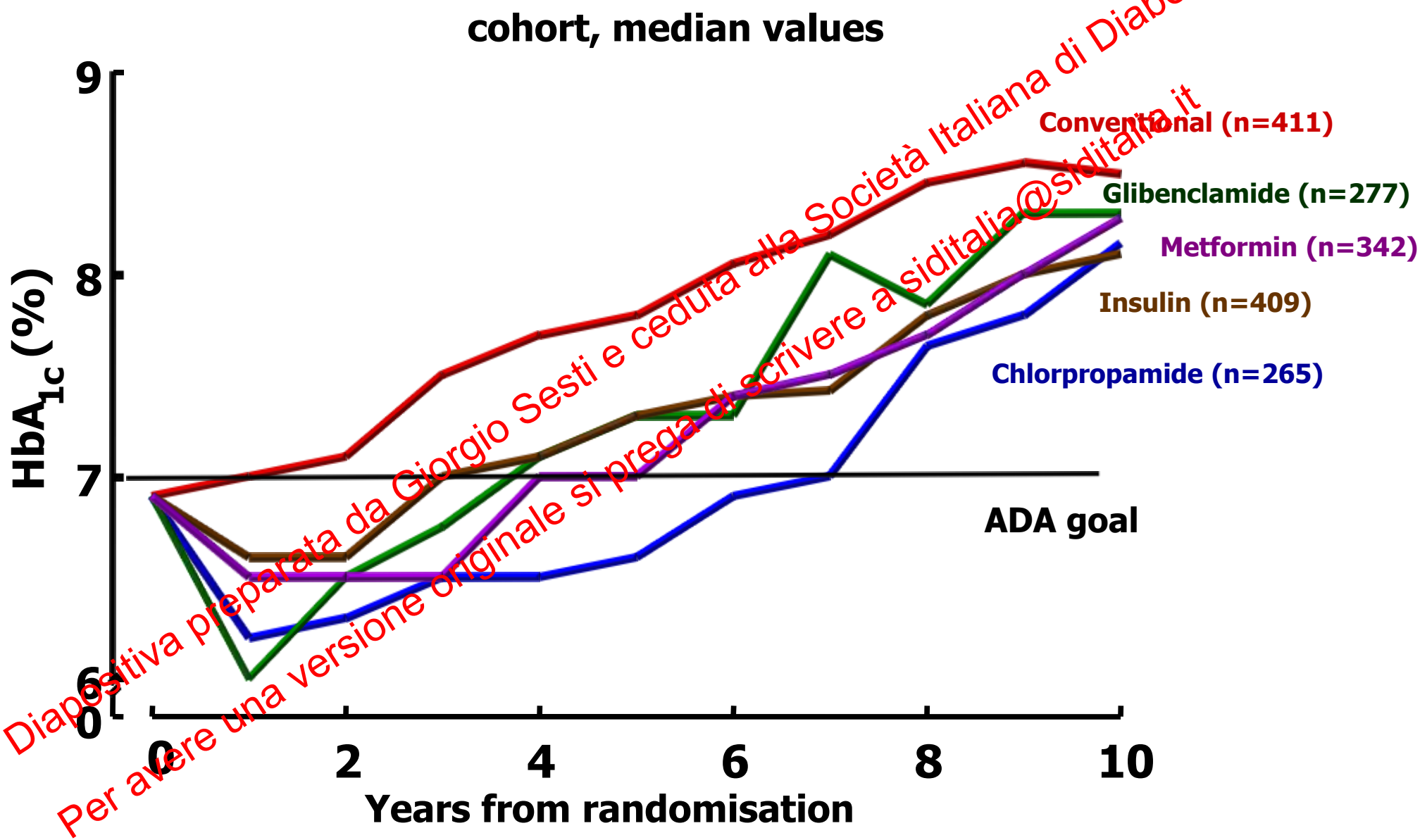
Lancet 352:837-853, 1998

UKPDS 49: Proportion of patients who attain HbA1c < 7.0%



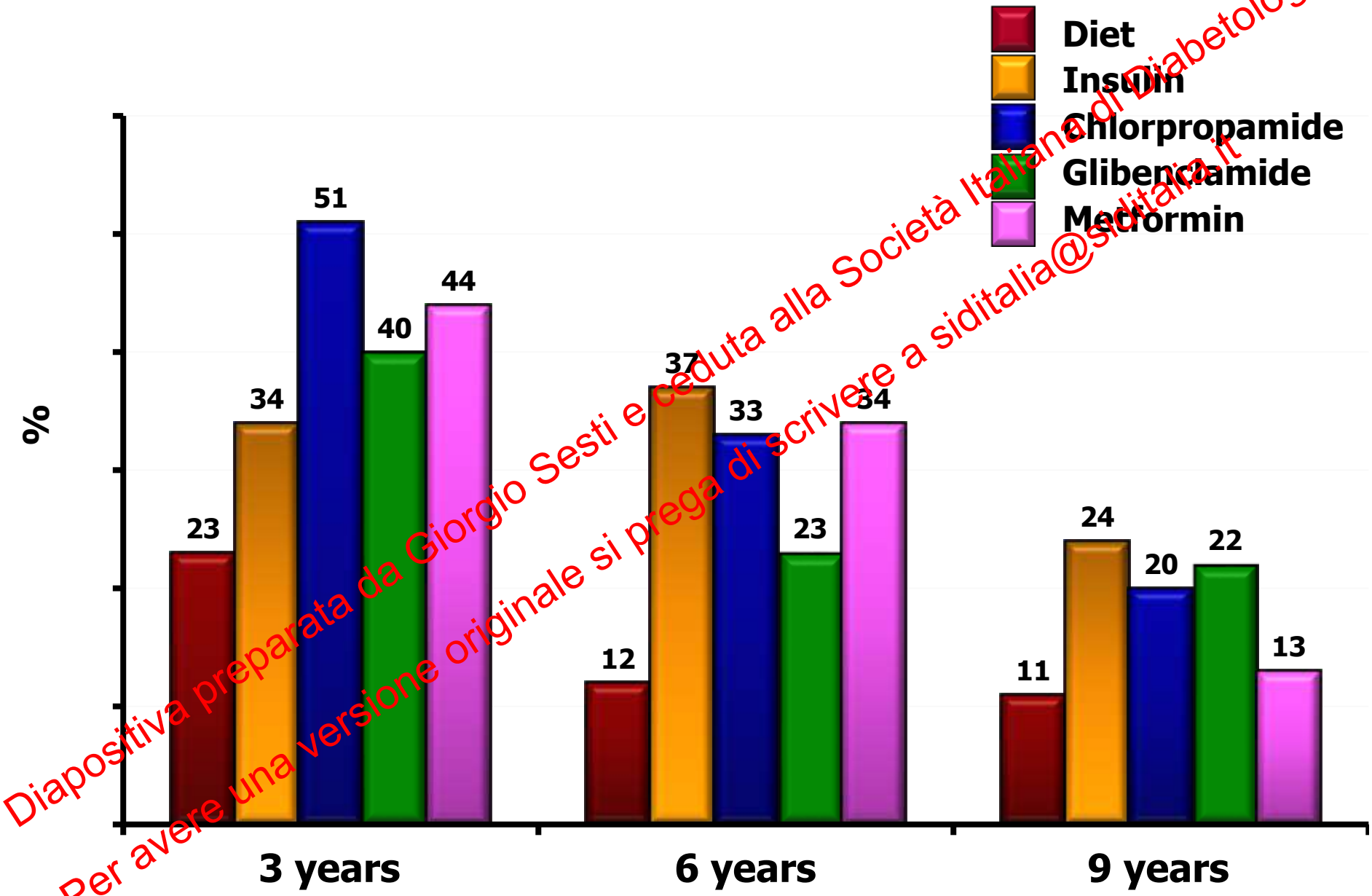
Turner RC et al. JAMA 281: 2005-2012, 1999

UKPDS 34: Over time, glycaemic control deteriorates in overweight T2DM



UKPDS 34. Lancet 352:854–865, 1998

UKPDS 49: Proportion of patients who attain HbA1c < 7.0%



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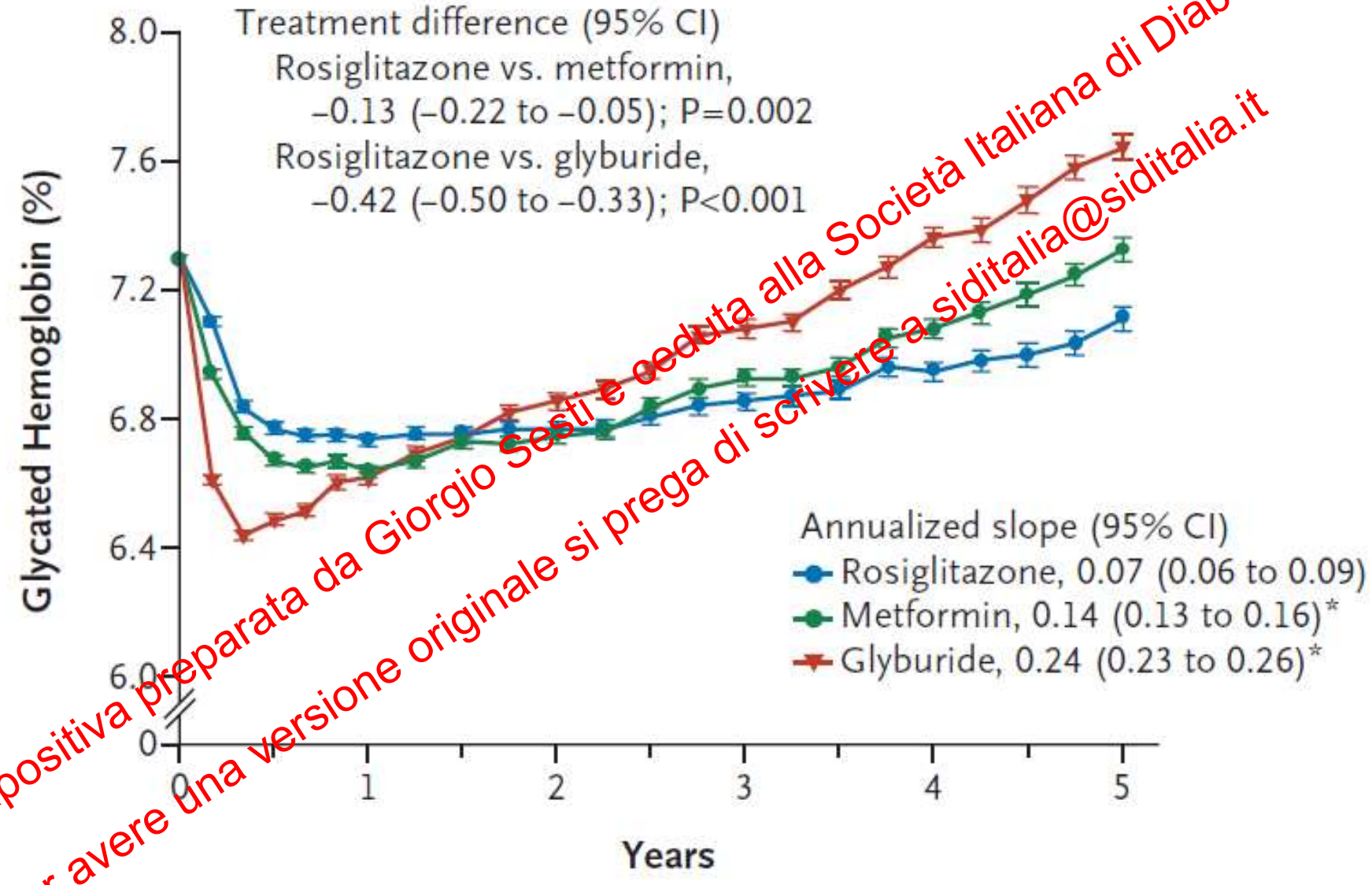
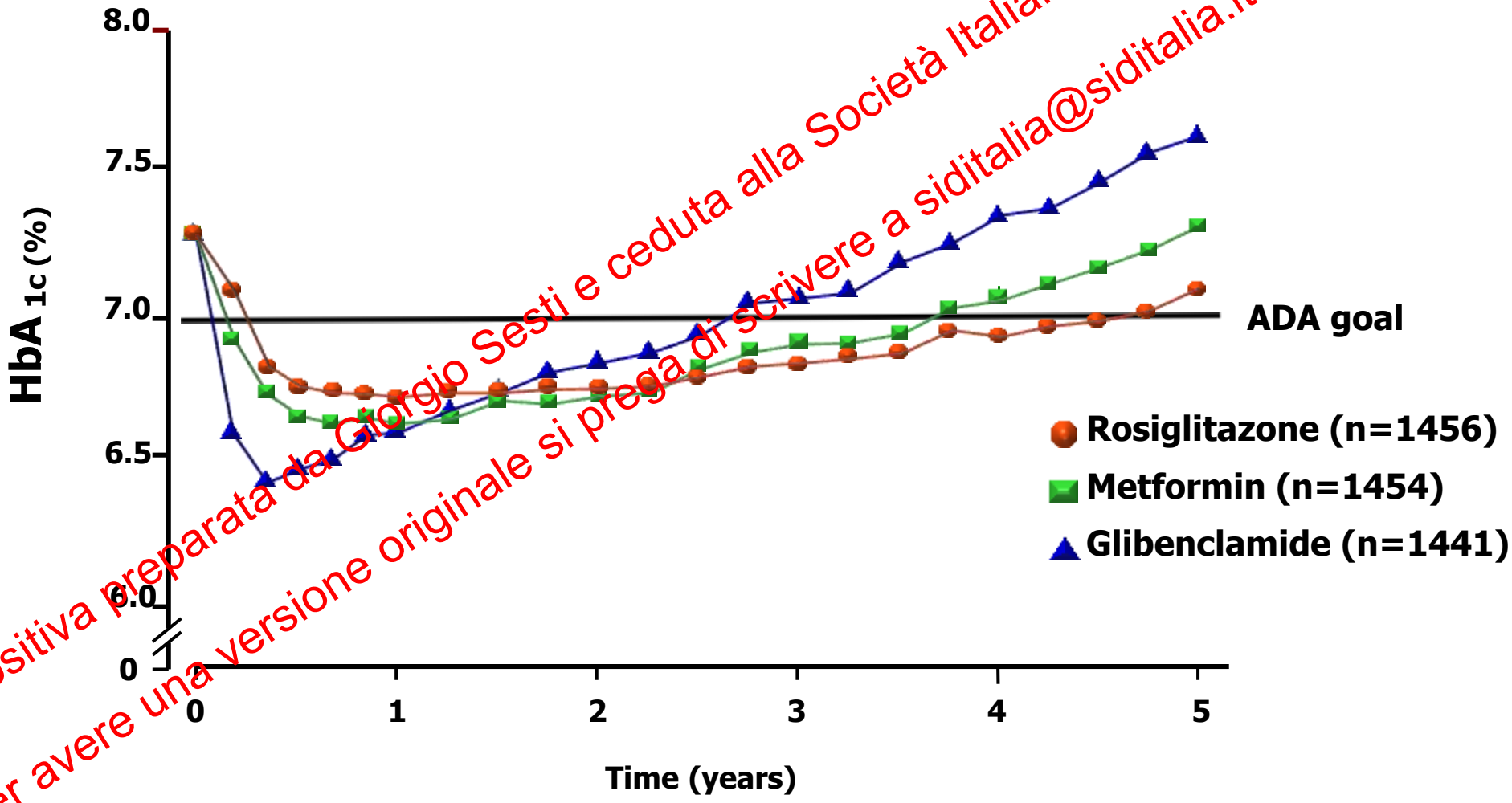
ADOPT: Treatments and HbA1c



Kahn et al. N Engl J Med 355:2427-2443, 2006

ADOPT: Treatments and HbA1c

Rosiglitazone vs. Metformin –0.13, *P*=0.002
Rosiglitazone vs. Glibenclamide –0.42, *P*<0.001



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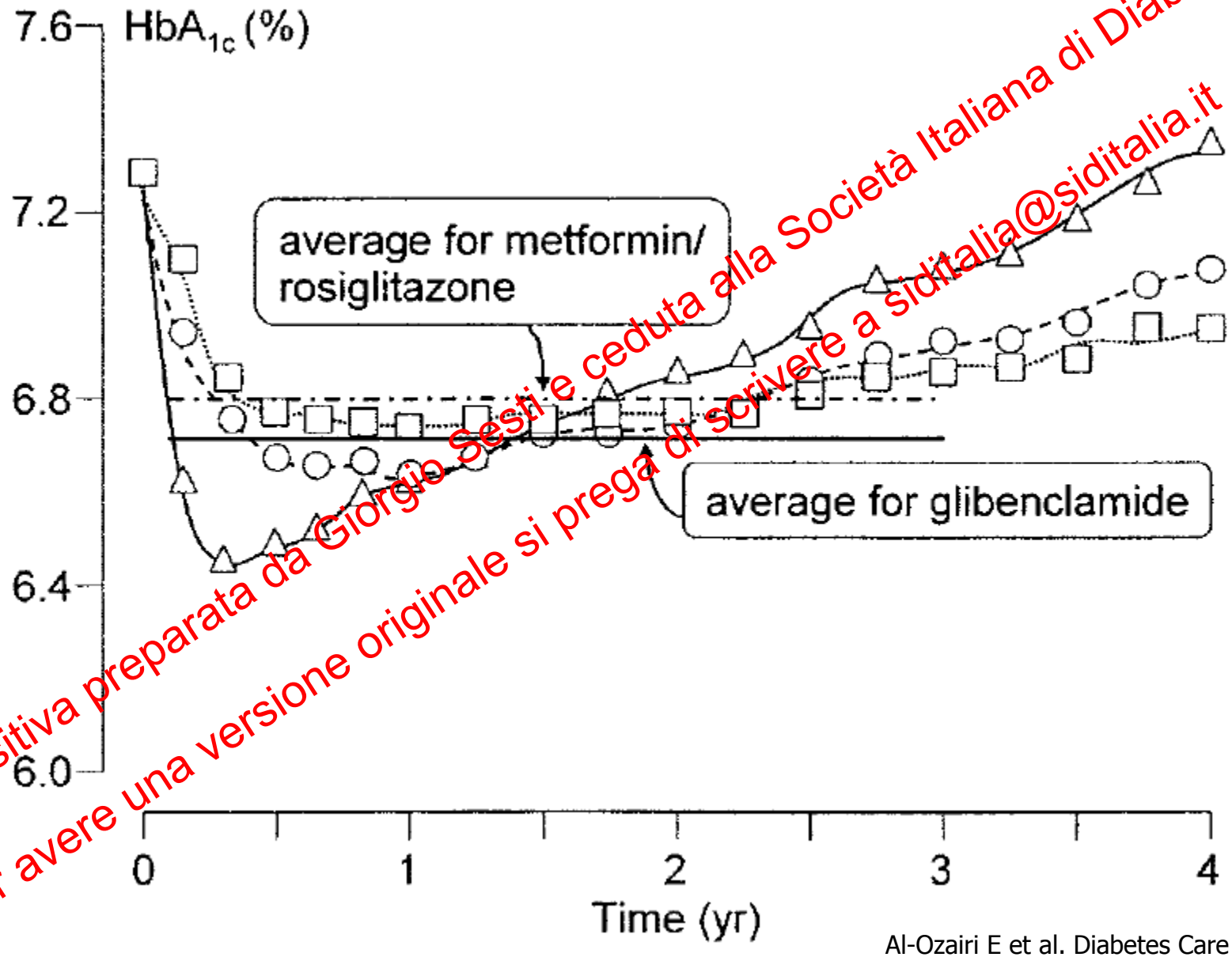
Time course of HbA1C in ADOPT redrawn to show average blood glucose control over the first 3 years



Al-Ozairi E et al. Diabetes Care 30: 1677-1680, 2007

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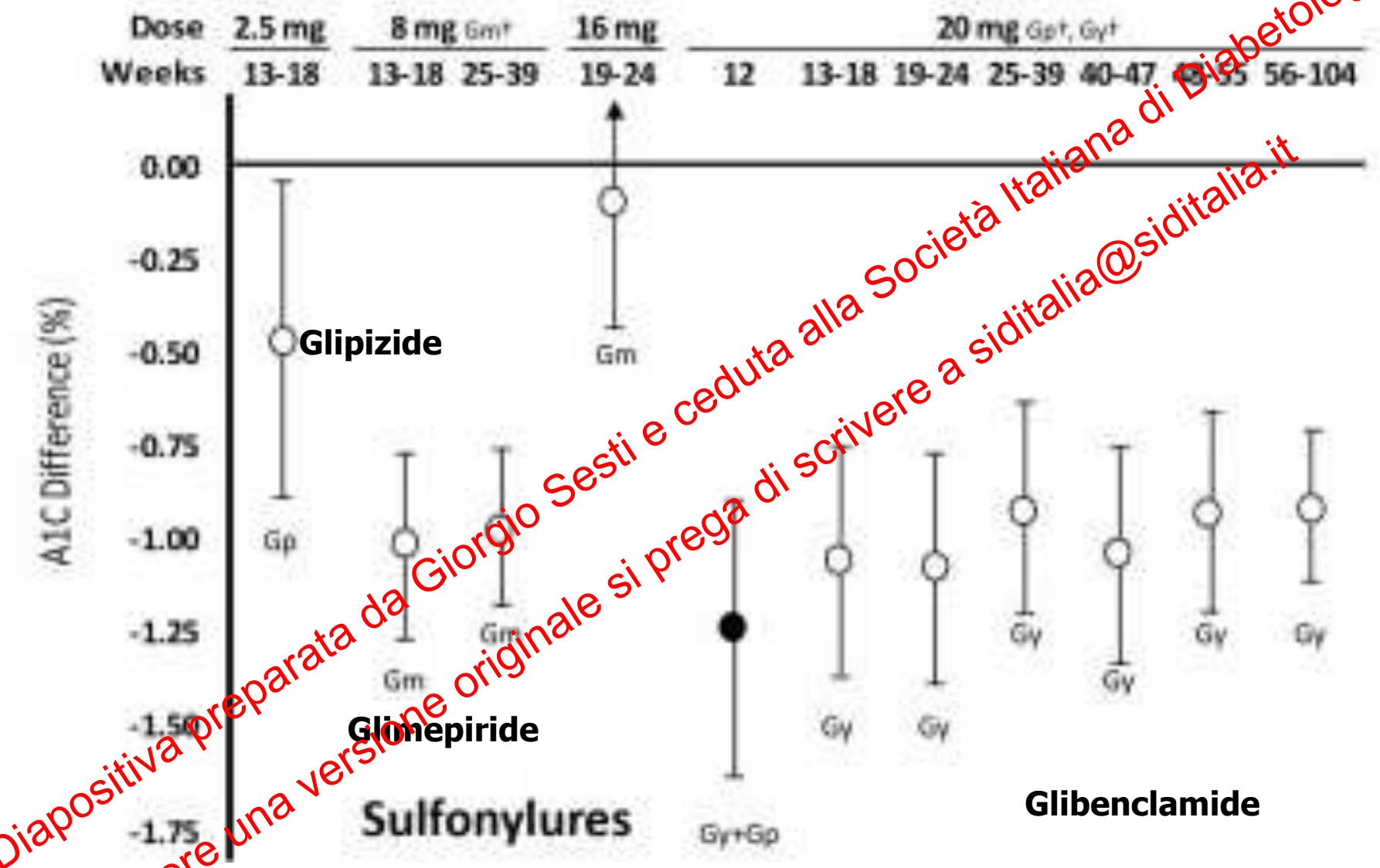
Blood glucose control with glibenclamide (glyburide) compared with metformin and rosiglitazone in the ADOPT study

	Glibenclamide	Metformin	Rosiglitazone
Mean A1C (%)*			
Year 1†	6.5	6.7	6.8
Year 2	6.8	6.7	6.8
Year 3	7.0	6.9	6.8
Years 1–3†	6.7	6.8	6.8

Al-Ozairi E et al. Diabetes Care 30: 1677-1680, 2007

Treatment effects on A1C by SU class, dose, and time: a meta-analysis



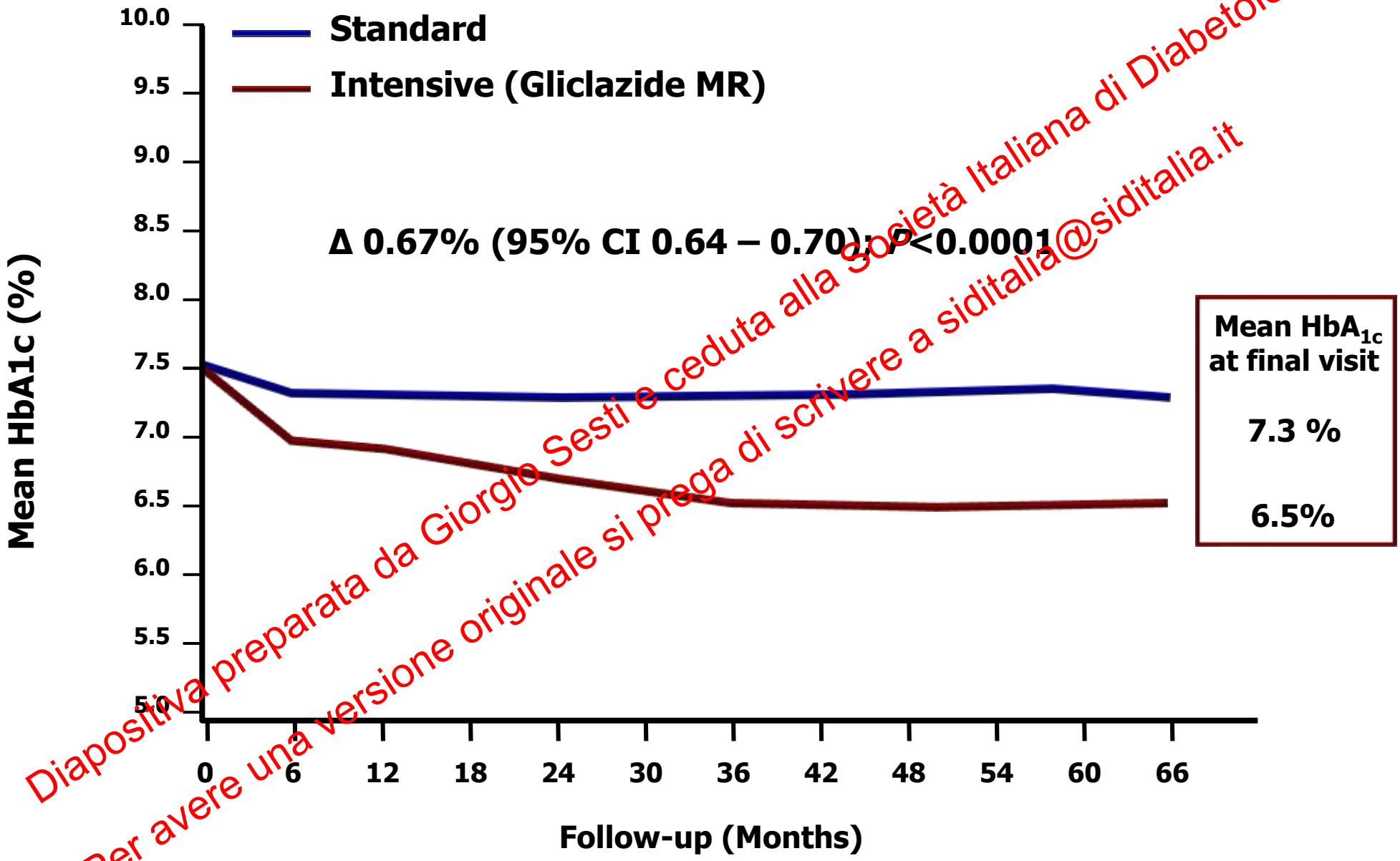
Sherifali D et al. Diabetes Care 33:1859–1864, 2010

ADVANCE: Glucose control drugs at end of follow-up

	Randomized treatment	
	Intensive (n=4828)	Standard (n=4741)
Gliclazide MR	90.5%	1.6%
Other Sulfonylureas	1.9%	57.1%
Metformin	73.8%	67.0%
Thiazolidinediones	16.9%	10.9%
Acarbose	19.1%	12.9%
Glinides	1.2%	2.8%
Insulin	40.5%	24.1%

N Engl J Med 358:2560-2572, 2008

Hemoglobin A_{1c}: ADVANCE



ADVANCE collaborative group. N Engl J Med 358:2560-72, 2008

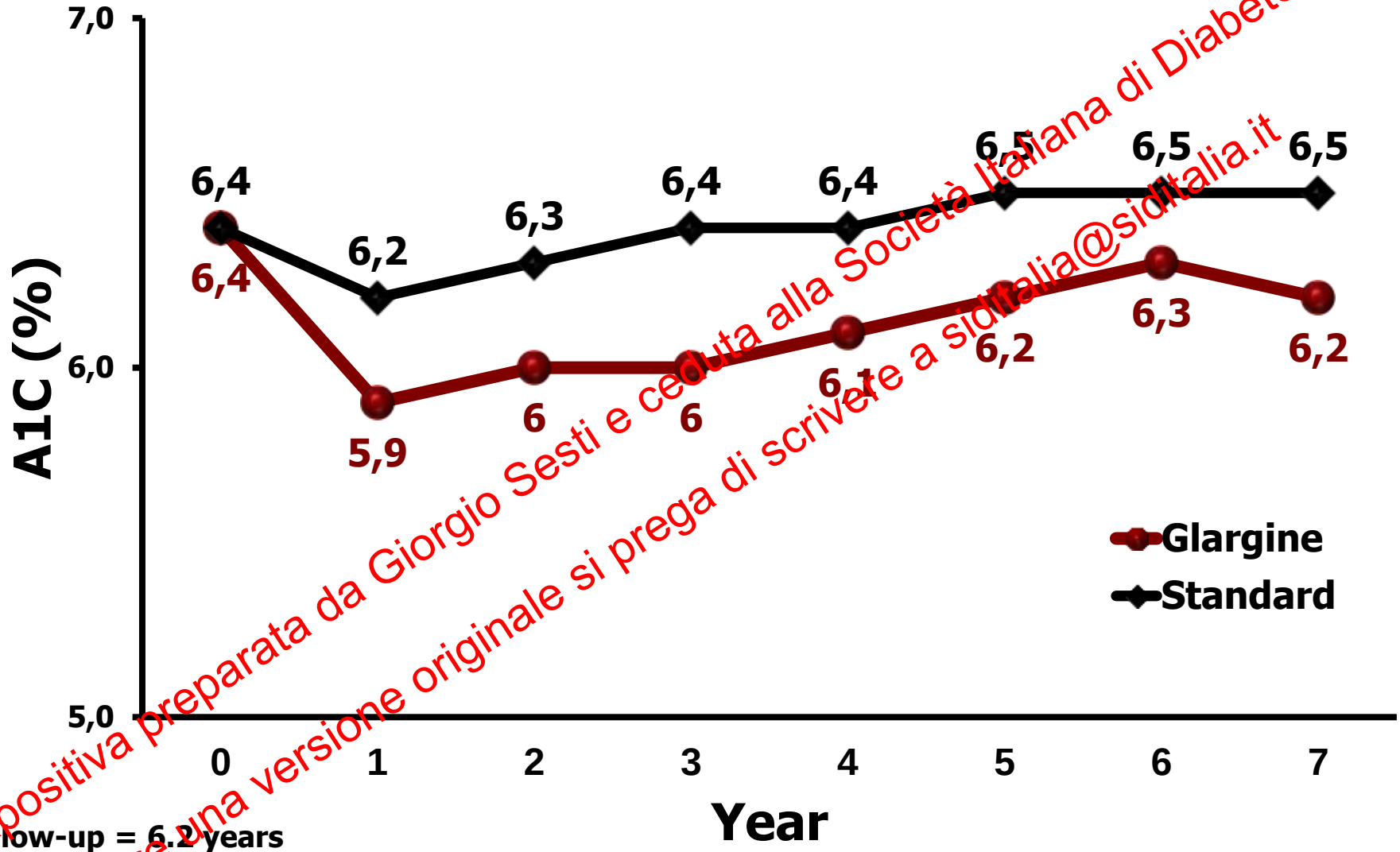
Drug Use at Study End

	Insulin Glargine	Standard Care	*P*
No Oral Agents (%)	35	19	<0.001
1 Oral Agents (%)	51	39	<0.001
2 Oral Agents (%)	12	28	<0.001
≥ 3 Oral Agents (%)	3	14	<0.001
Rapid insulin (%)	2	5	<0.001
Any Insulin (%)	80	11	<0.001
Metformin (%)	47	60	<0.001
Sulfonylurea (%)	25	47	<0.001

ORIGIN

ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

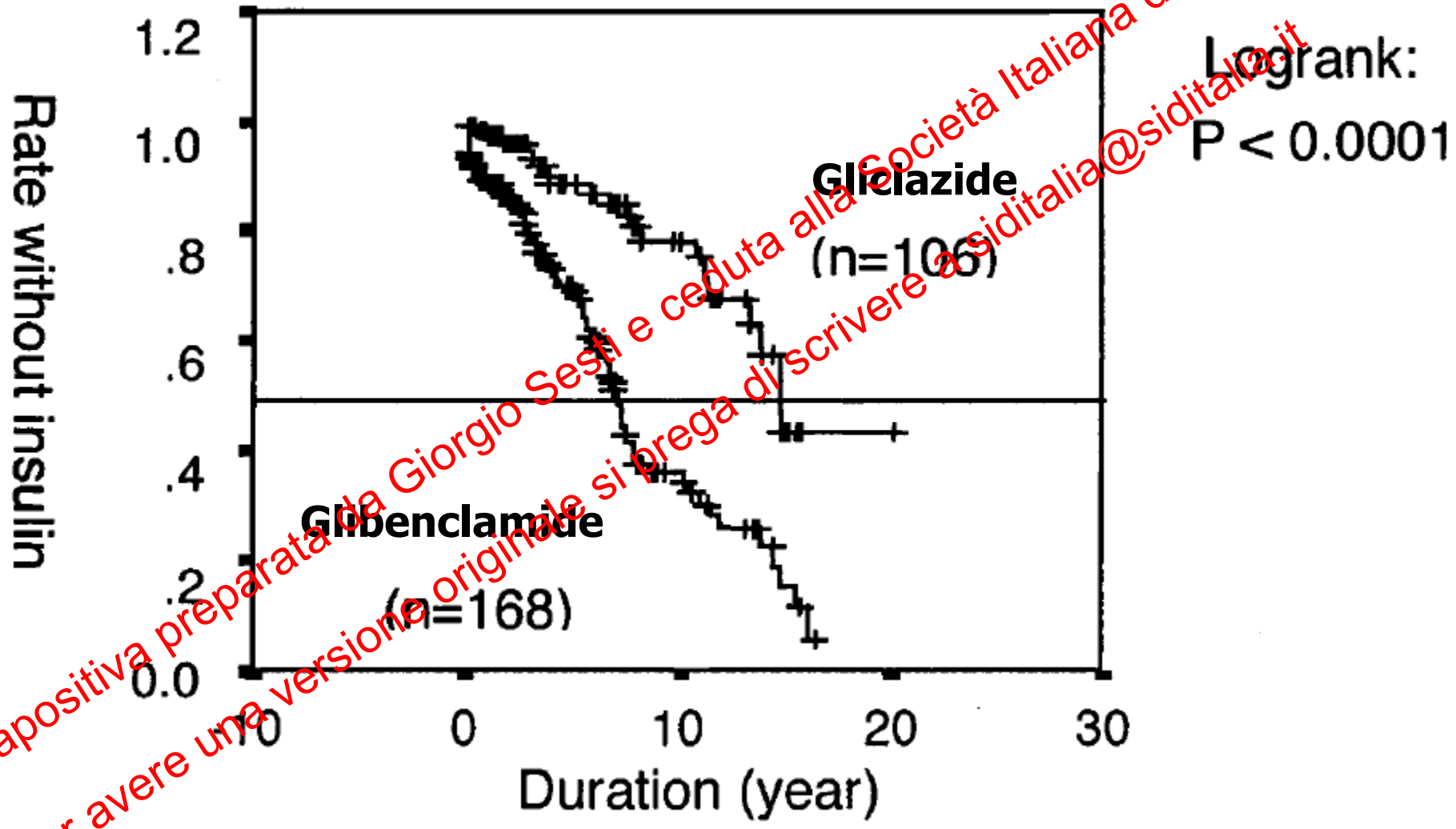
Median A1C Levels ORIGIN trial



Median follow-up = 6.2 years

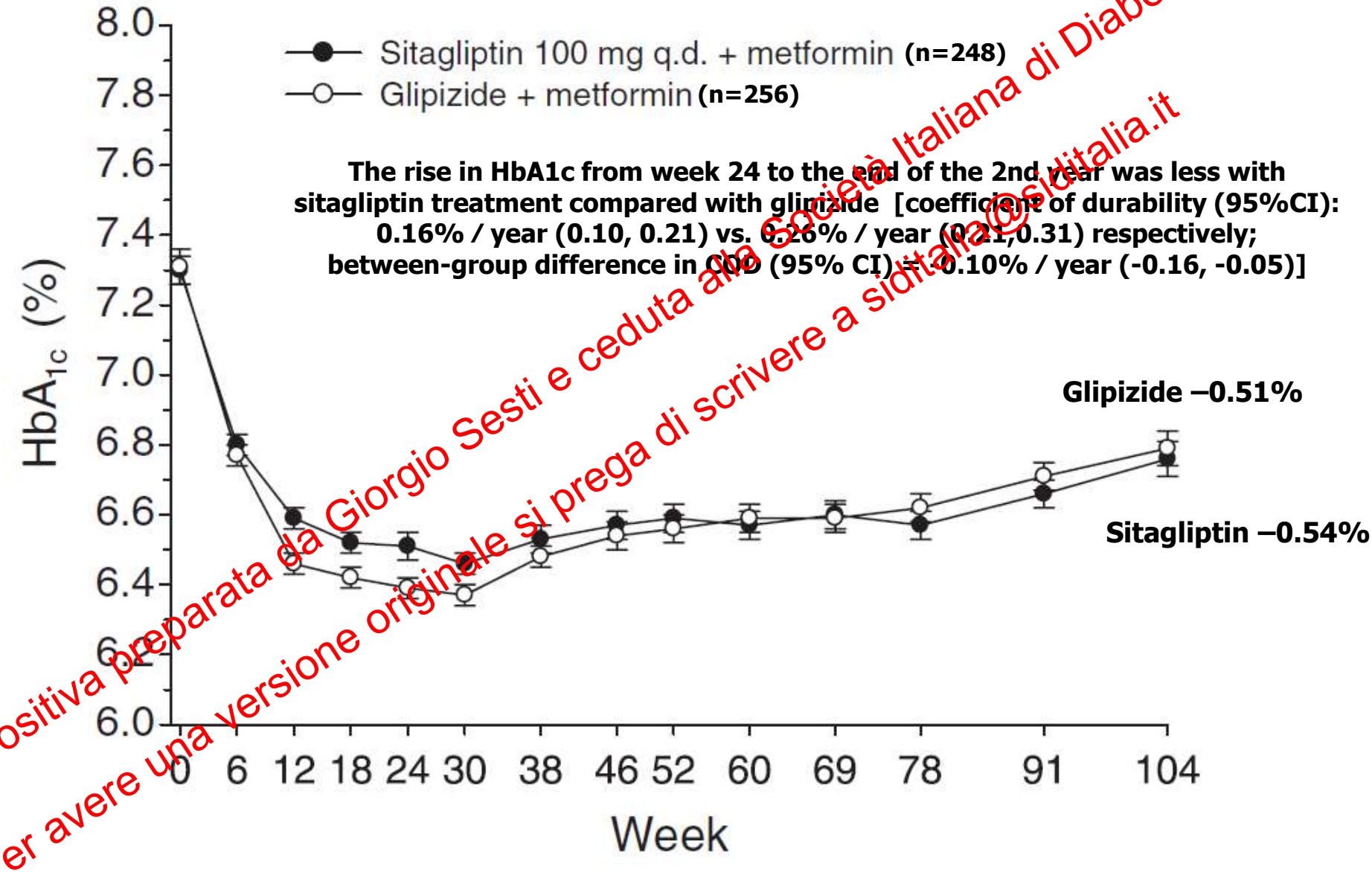
ORIGIN Trial Investigators, N Engl J Med 367: 319-28, 2012

Kaplan- Meier curve of the period until the start of insulin treatment from gliclazide or glibenclamide treatment: retrospective analysis in Japanese patients



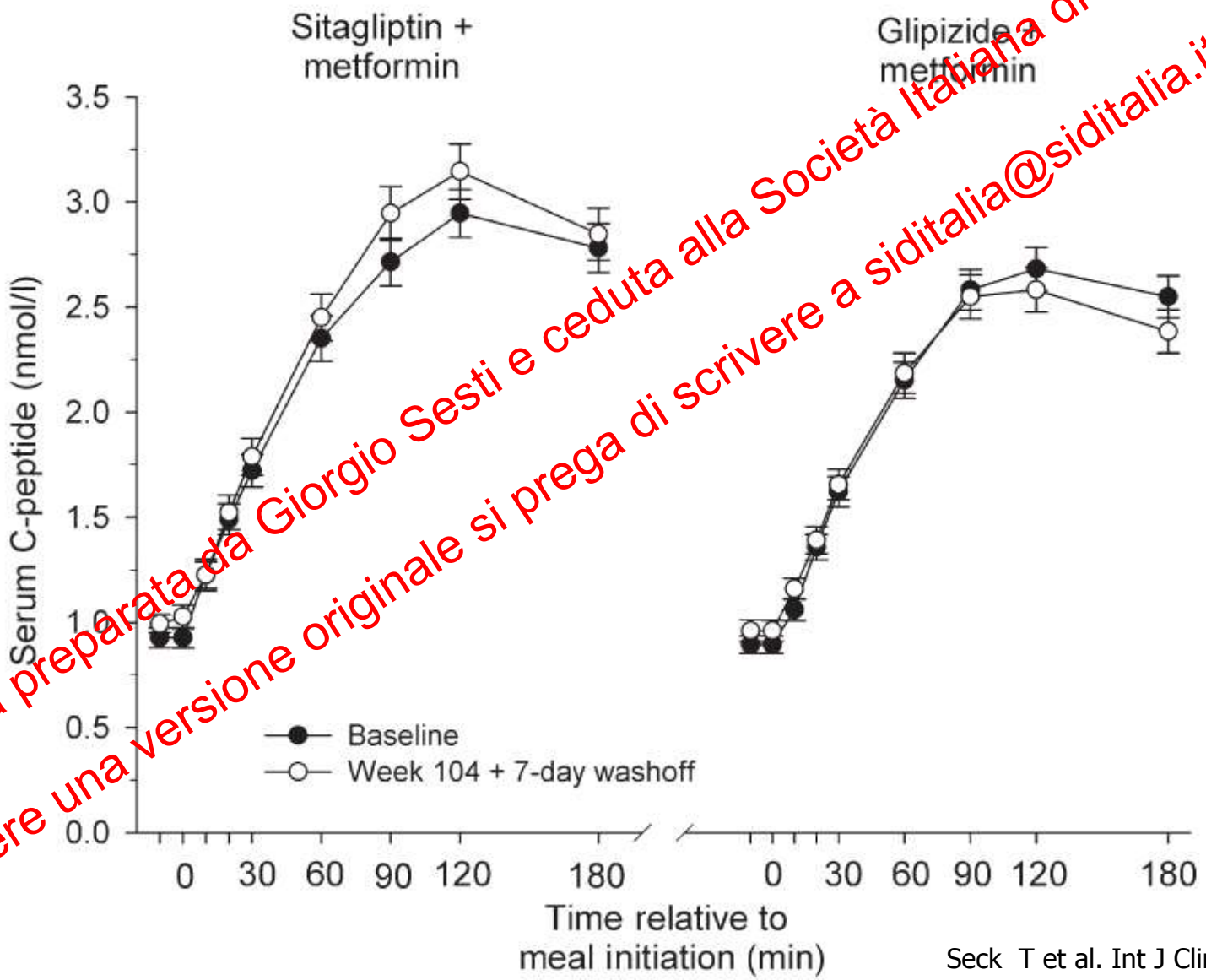
Satoh J et al. Diabetes Res. Clin. Pract 70: 291–297, 2005

Sitagliptin vs. Glipizide as add-on to Metformin: Sustained reduction in HbA1c over 2 year



Seck T et al. Int J Clin Pract 64:562-76, 2010

Serum C-peptide profiles during the nine-point meal tolerance test at baseline and following a 4- to 7-day wash off of study drug following 2 years of treatment with sitagliptin or glipizide added to metformin therapy



Seck T et al. Int J Clin Pract 64:562-76, 2010

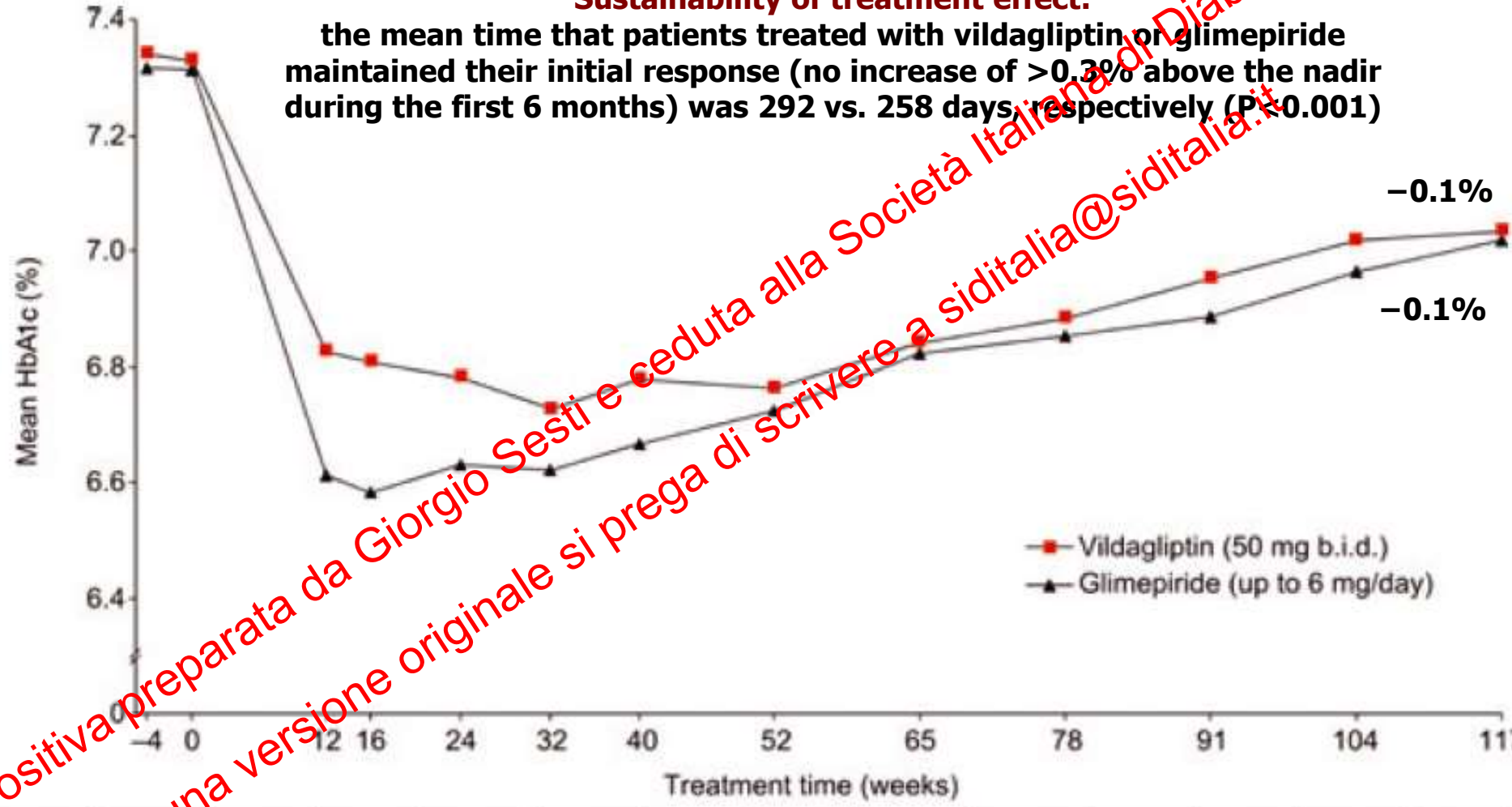
Baseline and study endpoint results for indices of beta-cell function from the 9-point meal tolerance tests administered following a 4- to 7-day wash off of study drug after 2 years of treatment with sitagliptin or glipizide added to metformin therapy

Treatment	*n*	Baseline mean ± SD	Study endpoint mean ± SD	Mean change from baseline (95% CI)
HOMA-β (%)				
Glipizide + Metformin	99	53.3 ± 37.4	58.2 ± 36.6	5.0 (−0.4, 10.3)
Sitagliptin + Metformin	90	60.4 ± 48.8	67.7 ± 56.1	7.3 (0.7, 14.0)
Dynamic beta cell sensitivity to glucose index (Φ_d) (10^{-9})				
Glipizide + Metformin	82	501.3 ± 365.5	425.5 ± 264.2	−75.8 (−148.7, −3.0)
Sitagliptin + Metformin	69	521.5 ± 468.3	470.5 ± 282.4	−51.0 (−162.8, 60.9)
Total beta cell sensitivity to glucose index (Φ_{total}) (10^{-9}/min)				
Glipizide + Metformin	81	11.3 ± 9.0	10.6 ± 4.4	−0.7 (−1.5, 0.1)
Sitagliptin + Metformin	68	12.0 ± 4.2	13.2 ± 5.1	1.1 (0.3, 1.9)
Basal beta cell sensitivity to glucose index (Φ_b) (10^{-9}/min)				
Glipizide + Metformin	91	6.2 ± 3.0	6.7 ± 3.3	0.5 (0.0, 1.0)
Sitagliptin + Metformin	76	6.8 ± 3.3	7.6 ± 3.4	0.8 (0.3, 1.3)

Seck T et al. Int J Clin Pract 64:562-76, 2010

Time course of mean HbA1c during 117 weeks of treatment, with vildagliptin plus metformin or glimepiride (up to 6 mg/day) plus metformin in patients aged <65 years

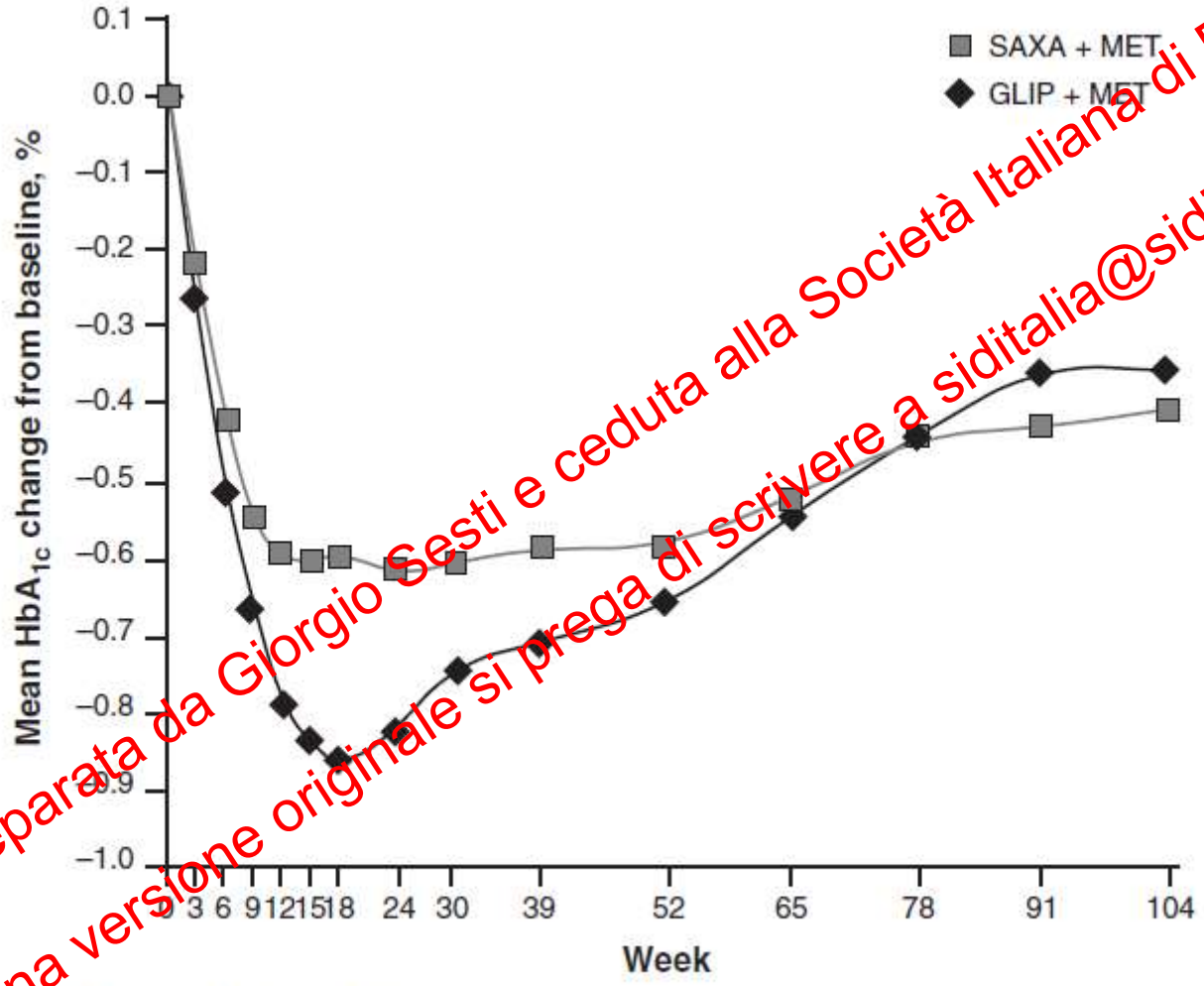
Sustainability of treatment effect:
the mean time that patients treated with vildagliptin or glimepiride maintained their initial response (no increase of >0.3% above the nadir during the first 6 months) was 292 vs. 258 days, respectively (P<0.001)



Week	−4	0	12	16	24	32	40	52	65	78	91	104	117
Vildagliptin (*n*)	1134	1154	1078	1040	1035	968	942	890	845	796	758	691	444
Glimepiride (*n*)	1103	1129	1021	969	978	928	884	861	813	763	722	666	436

Matthews DR et al. Diabetes Obes Metab12: 780–789, 2010.

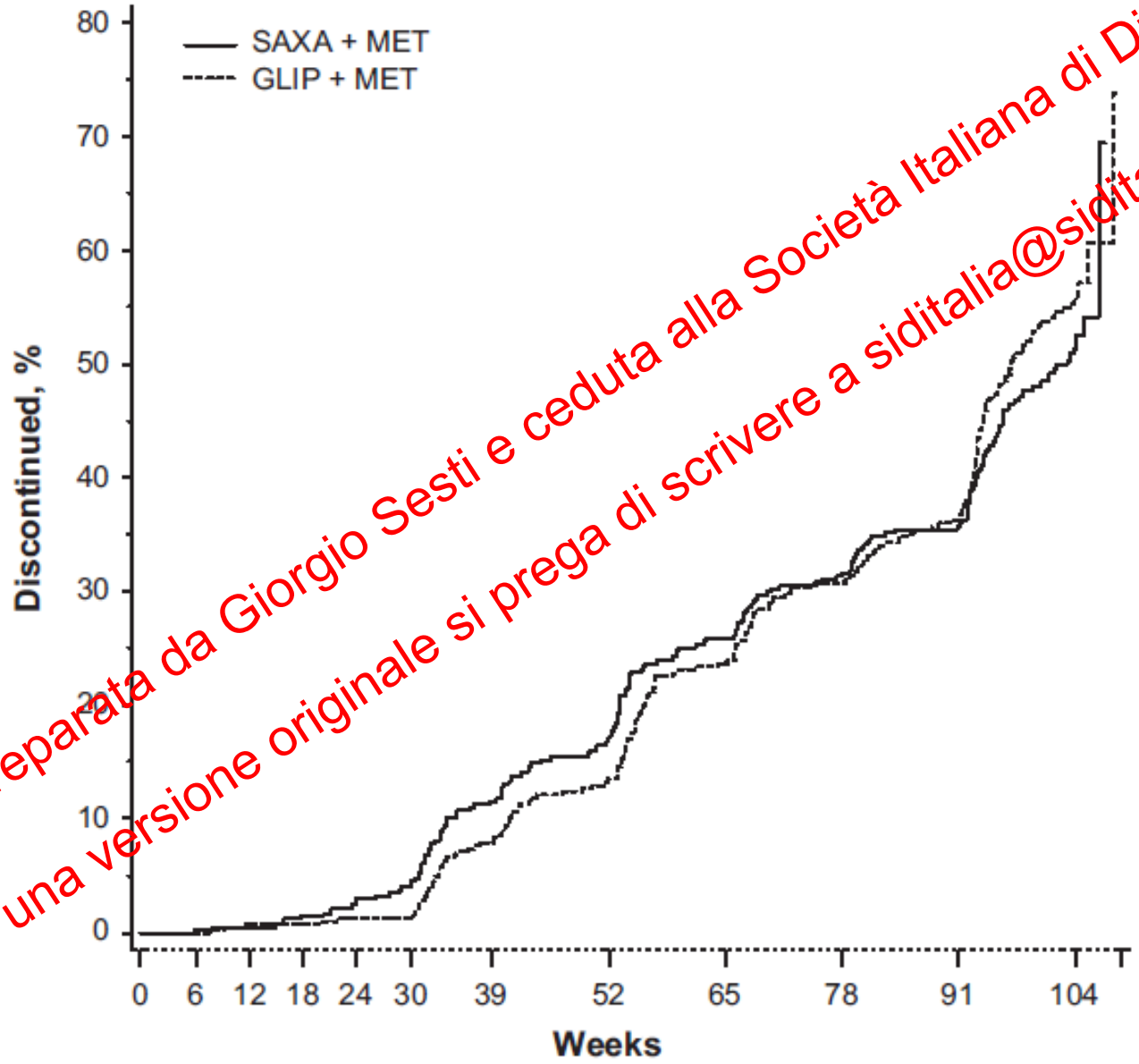
Change in HbA1c over time



Number of patients with observed data				
SAXA + MET	(*n* = 423)	316	253	184
GLIP + MET	(*n* = 423)	323	251	160

Göke B, et al. Int J Clin Pract 67:307-16, 2013

Kaplan–Meier analysis of time to discontinuation owing to insufficient glycemic control

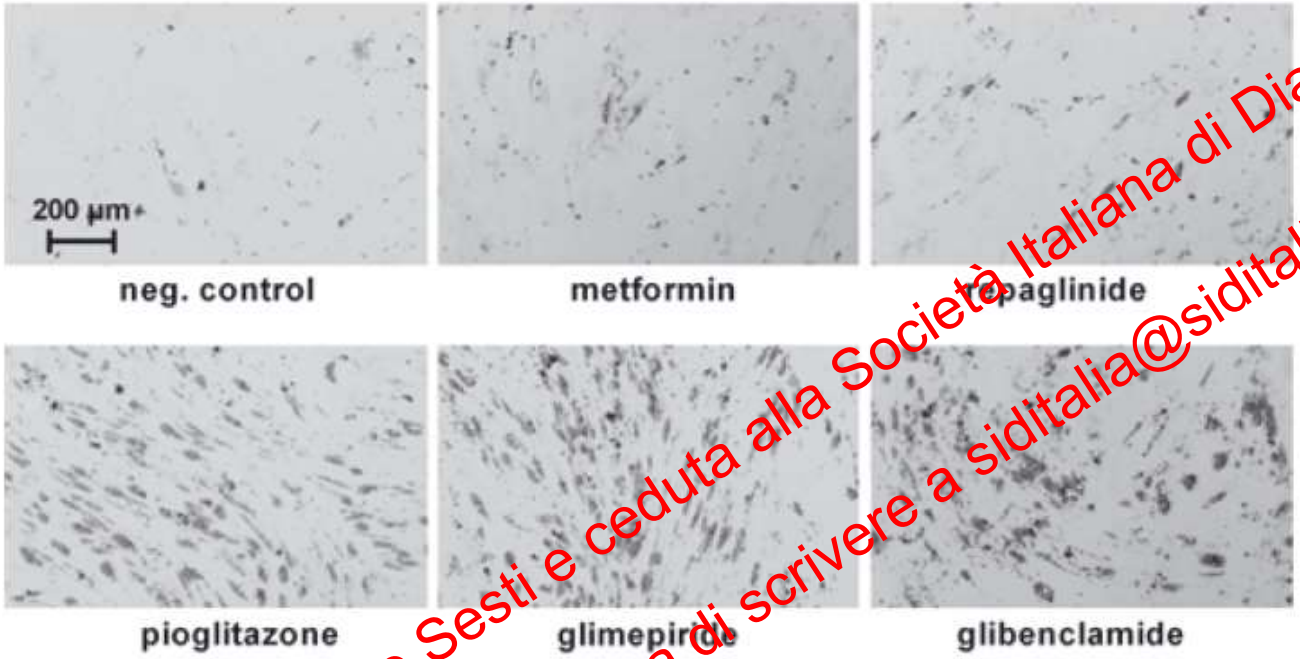


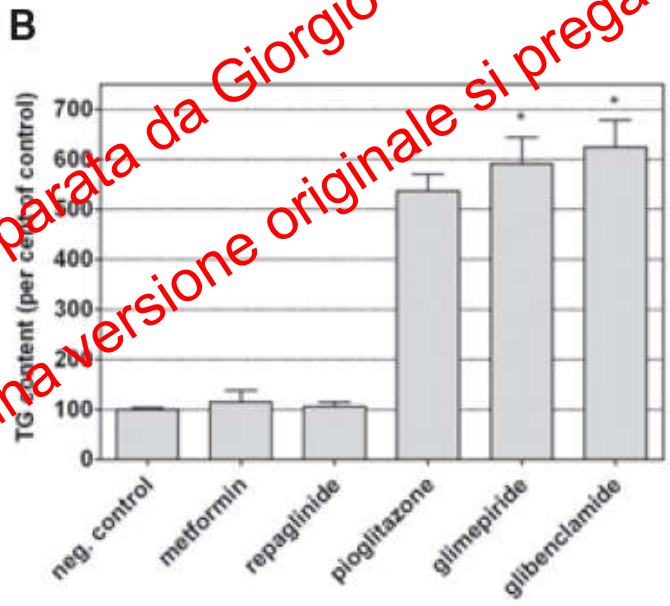
Göke B, et al. Int J Clin Pract 67:307-16, 2013

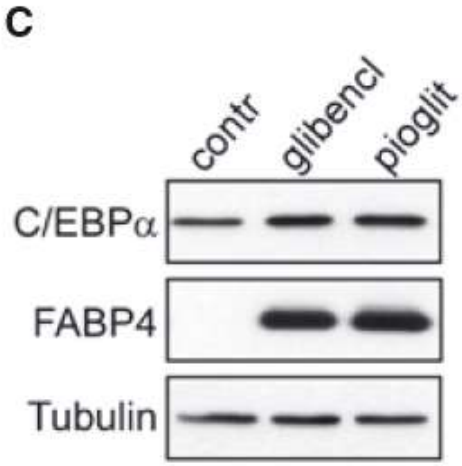
Sulfoniluree e glinidi:

1. Controllo Metabolico
2. Effetti sulla beta cellula
3. Durability
4. **Effetti sul peso**
5. Ipoglicemie
6. Complicanze micro-vascolari
7. Complicanze macro-vascolari

Glitazone-like action of glimepiride and glibenclamide in primary human adipocytes

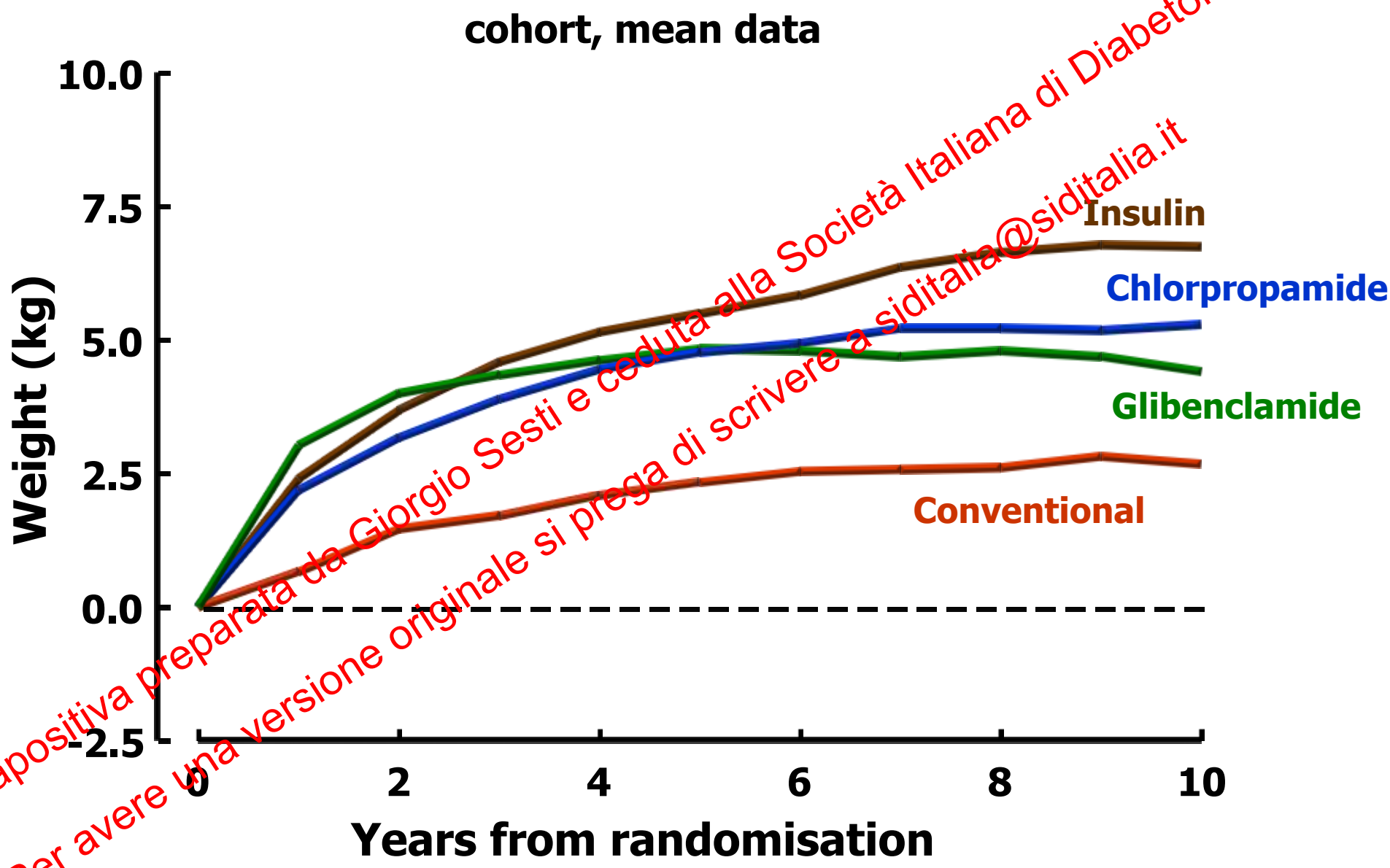






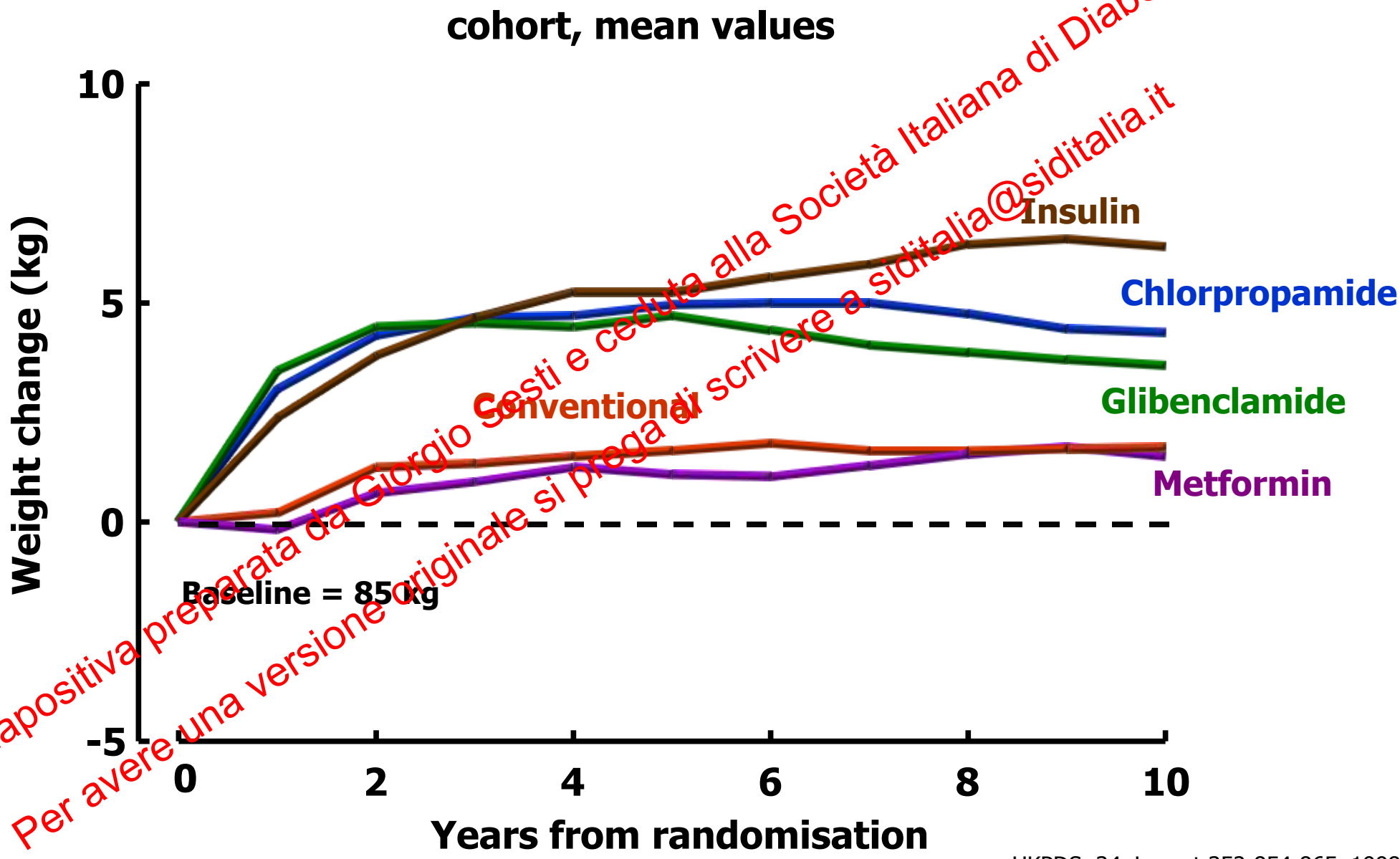
Mayer P. et al. Diabetes Obes and Metab 13: 791–799, 2011

UKPDS 33: Treatments and weight change



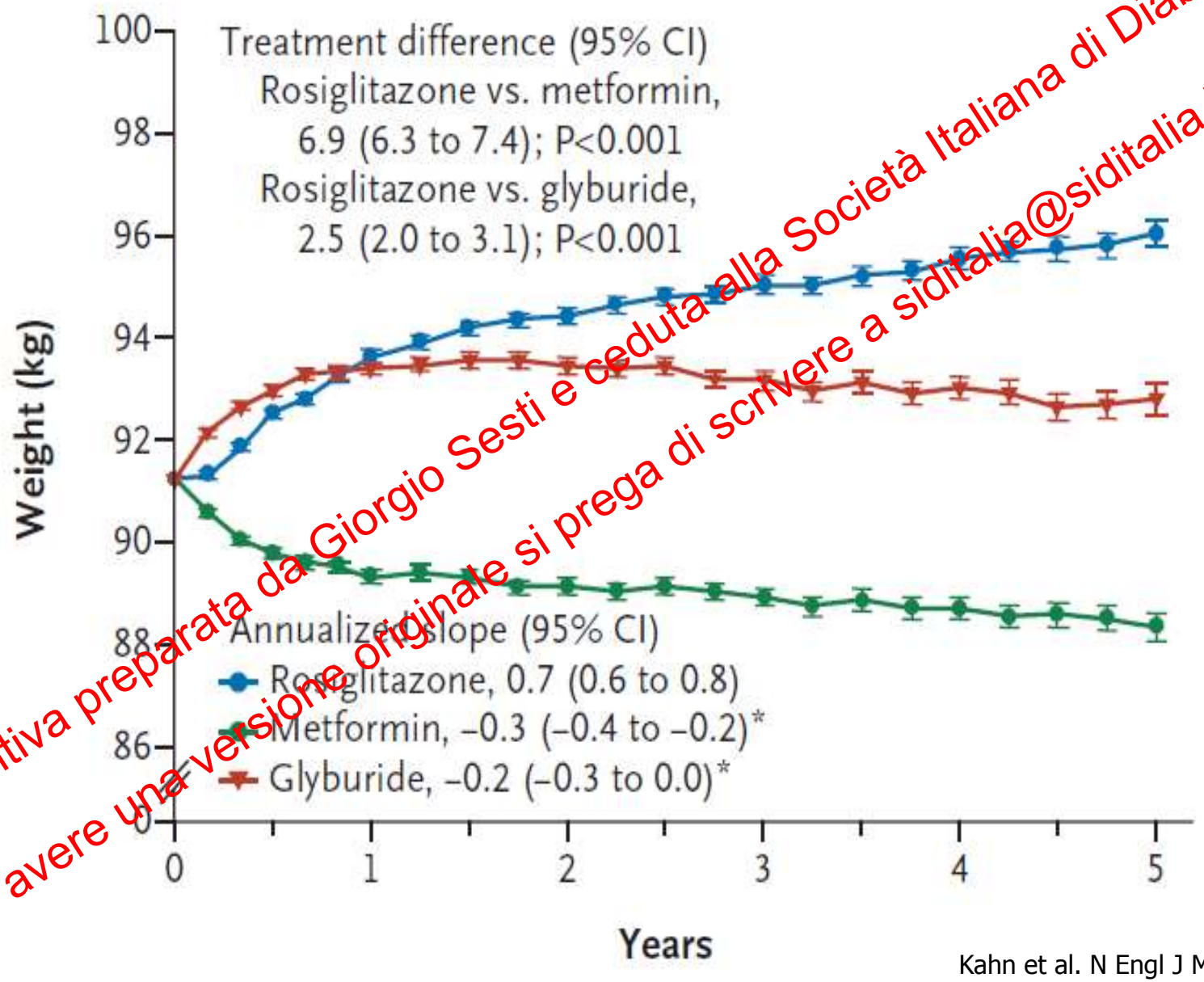
UKPDS 33 Lancet 352:837-853, 1998

UKPDS 34: Treatments and weight change in overweight T2DM



UKPDS 34. Lancet 352:854-865, 1998

ADOPT: Treatments and weight change



Kahn et al. N Engl J Med 355:2427-2443, 2006

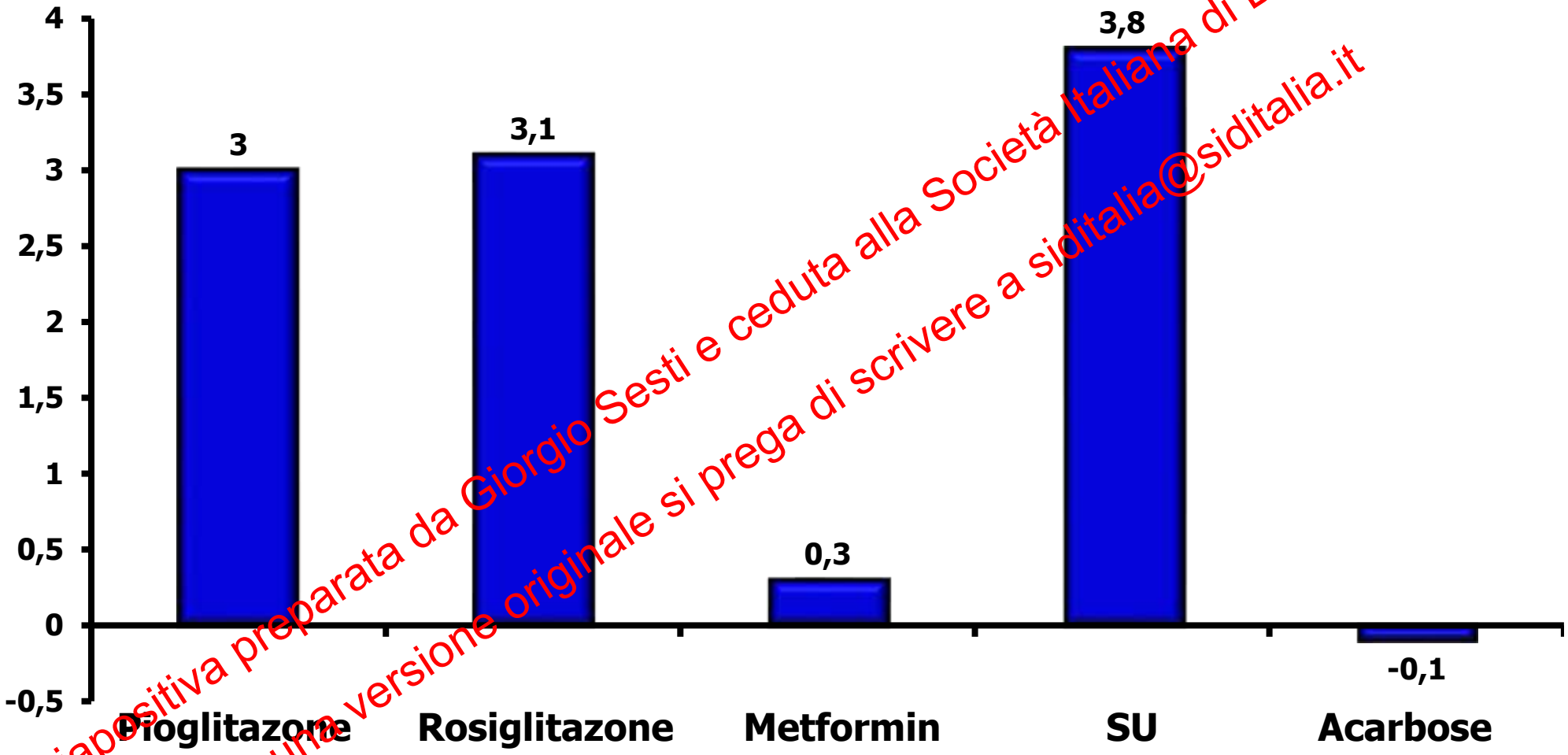
Weighted Mean Absolute Difference in Body Weight between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet

Comparison*	Studies with Data on Mean Differences, *n*	Weighted Mean Absolute Difference in Body Weight between Groups (95% CI), *kg*
Pioglitazone vs. control	6	3.0 (2.0 to 3.9)
Rosiglitazone vs. control	4	3.1 (1.1 to 5.1)
Metformin vs. control	8	0.3 (−0.3 to 0.9)
Sulfonylureas vs. control	4	3.8 (3.6 to 4.0)
Meglitinides vs. control	2	Not applicable
Acarbose vs. control	16	−0.1 (−0.5 to 0.2)

* The control group consisted of placebo or diet.

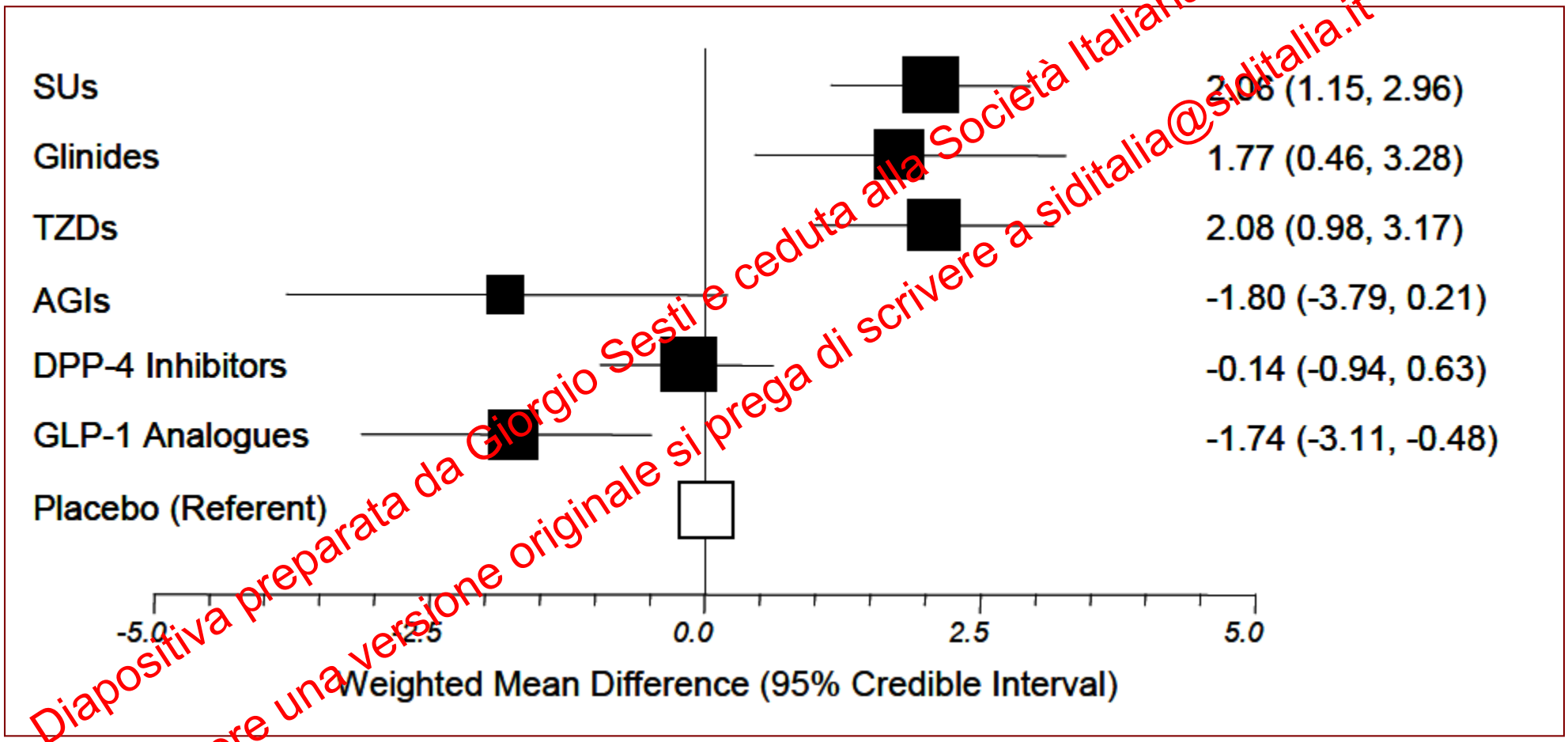
Bolen S. et al. Ann Intern Med 147:386-399, 2007

Weighted Mean Absolute Difference in Body Weight between Groups for Randomized, Controlled Trials Comparing Oral Diabetes Medications with Placebo or Diet



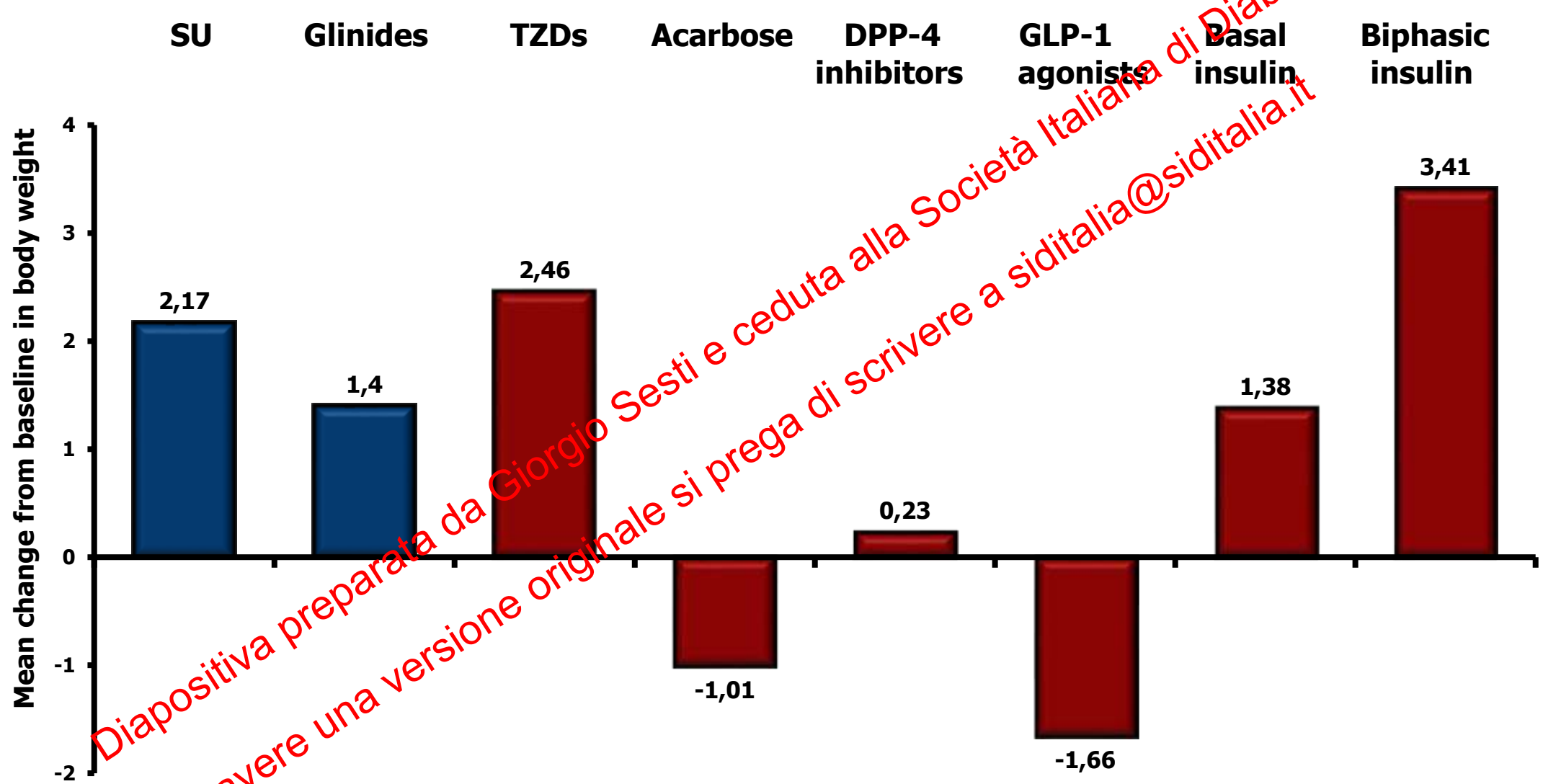
Bolen S. et al. Ann Intern Med 147:386-399, 2007

Meta-analysis of RCTs with at least 3 months' duration, evaluating antidiabetic drugs added to metformin



Phung OJ et al. JAMA 303:1410-1418, 2010

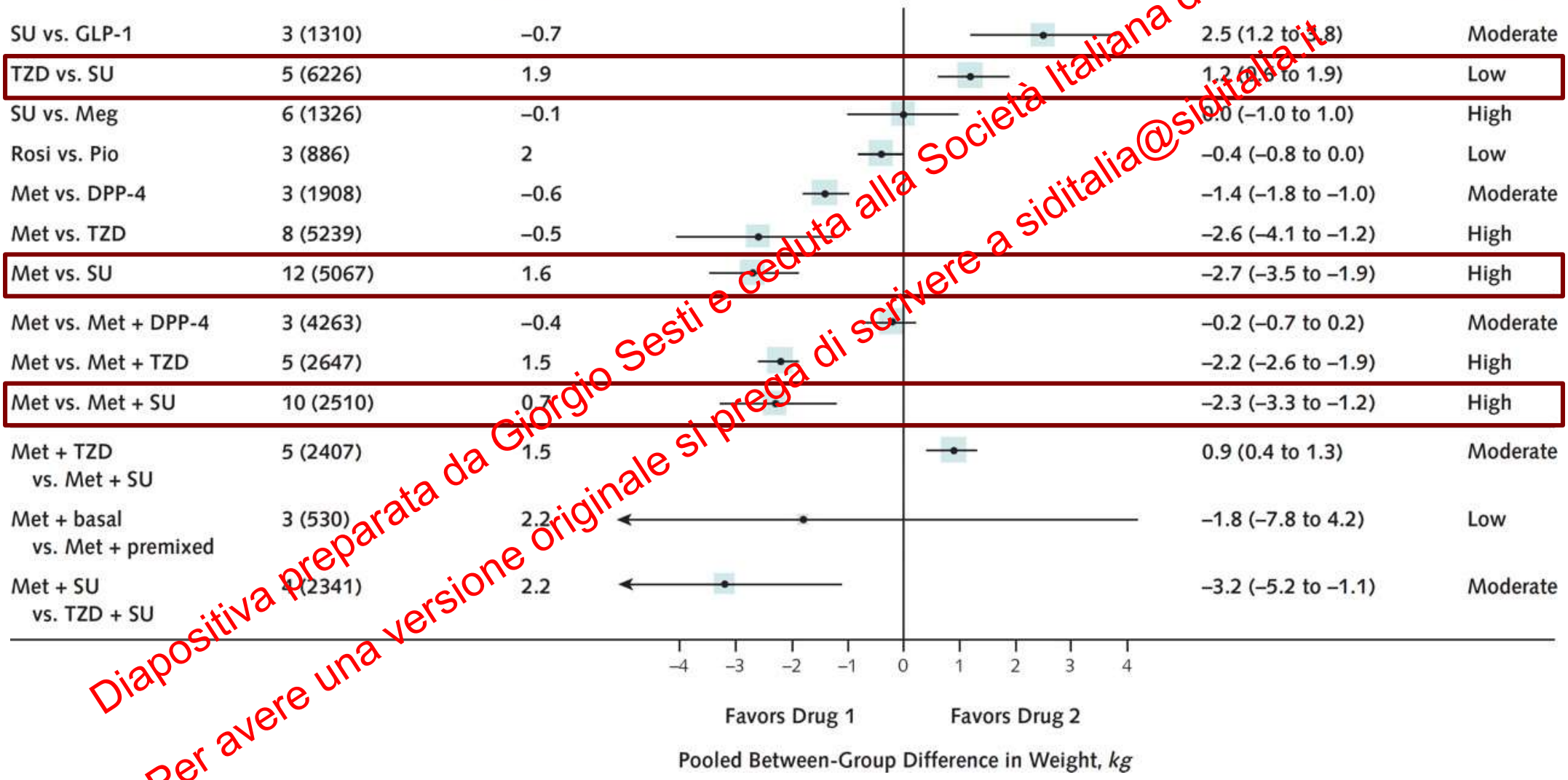
Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: Mean change from baseline in body weight



Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

Pooled between-group difference in body weight with monotherapy and combination therapies. A network meta-analysis of randomized trials at least 24 weeks in duration

Comparison (Drug 1 vs. Drug 2)	Studies (Participants), *n (n)*	Median Change From Baseline Weight With Drug 2, *kg*	Mean Difference in Weight (95% CI), *kg*	Strength of Evidence
SU vs. GLP-1	3 (1310)	–0.7	2.5 (1.2 to 3.8)	Moderate
TZD vs. SU	5 (6226)	1.9	1.2 (0.6 to 1.9)	Low
SU vs. Meg	6 (1326)	–0.1	0.0 (–1.0 to 1.0)	High
Rosi vs. Pio	3 (886)	2	–0.4 (–0.8 to 0.0)	Low
Met vs. DPP-4	3 (1908)	–0.6	–1.4 (–1.8 to –1.0)	Moderate
Met vs. TZD	8 (5239)	–0.5	–2.6 (–4.1 to –1.2)	High
Met vs. SU	12 (5067)	1.6	–2.7 (–3.5 to –1.9)	High
Met vs. Met + DPP-4	3 (4263)	–0.4	–0.2 (–0.7 to 0.2)	Moderate
Met vs. Met + TZD	5 (2647)	1.5	–2.2 (–2.6 to –1.9)	High
Met vs. Met + SU	10 (2510)	0.7	–2.3 (–3.3 to –1.2)	High
Met + TZD vs. Met + SU	5 (2407)	1.5	0.9 (0.4 to 1.3)	Moderate
Met + basal vs. Met + premixed	3 (530)	2.2	–1.8 (–7.8 to 4.2)	Low
Met + SU vs. TZD + SU	4 (2341)	2.2	–3.2 (–5.2 to –1.1)	Moderate



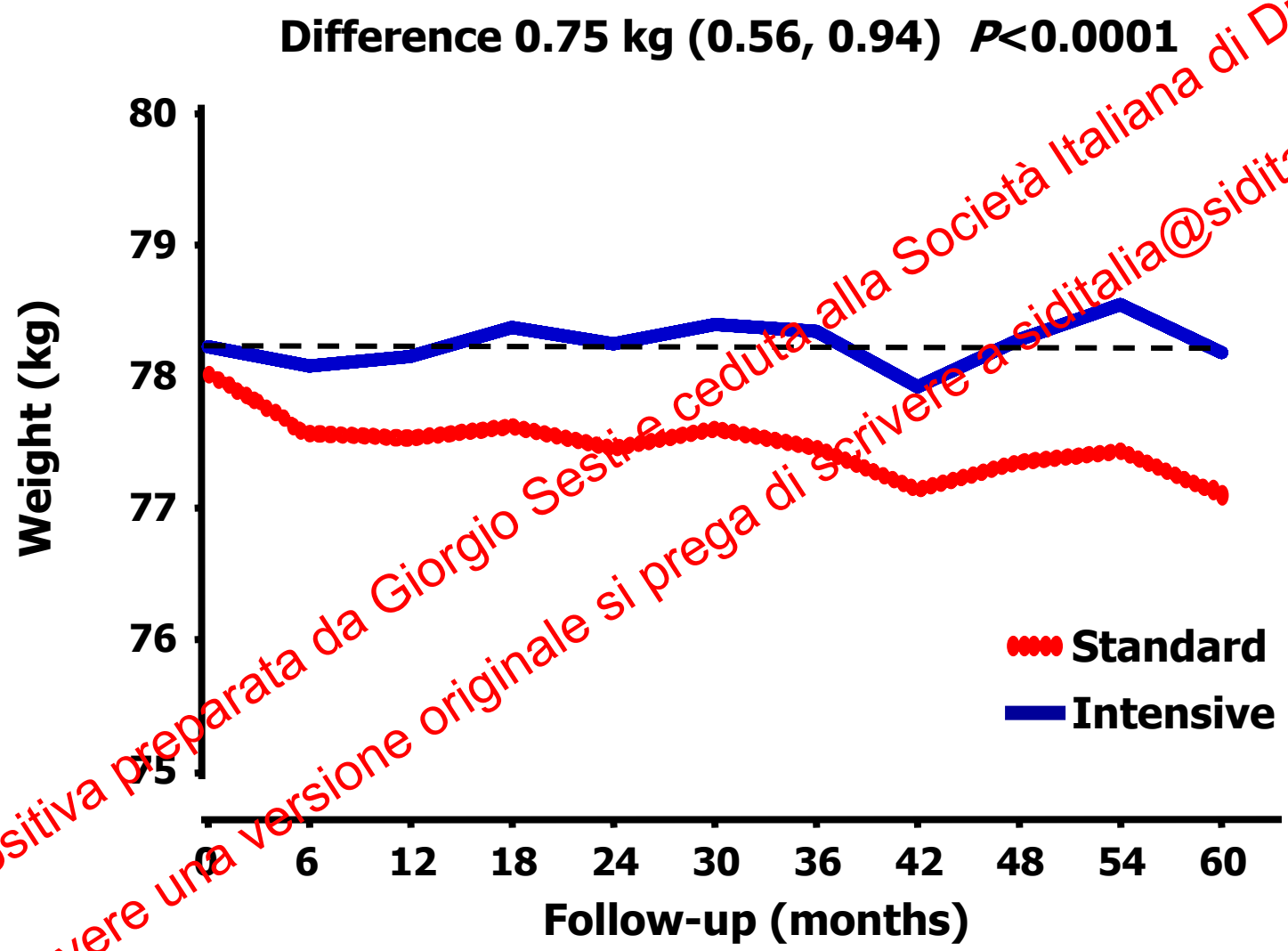
Bennett W L et al. Ann Intern Med 154 602-613, 2011

ADVANCE: Glucose control drugs at end of follow-up

	Randomized treatment	
	Intensive (n=4828)	Standard (n=4741)
Gliclazide MR	90.5%	1.6%
Other Sulfonylureas	1.9%	57.1%
Metformin	73.8%	67.0%
Thiazolidinediones	16.9%	10.9%
Acarbose	19.1%	12.9%
Glinides	1.2%	2.8%
Insulin	40.5%	24.1%

N Engl J Med 358:2560-2572, 2008

ADVANCE: Difference in body weight at end of follow-up

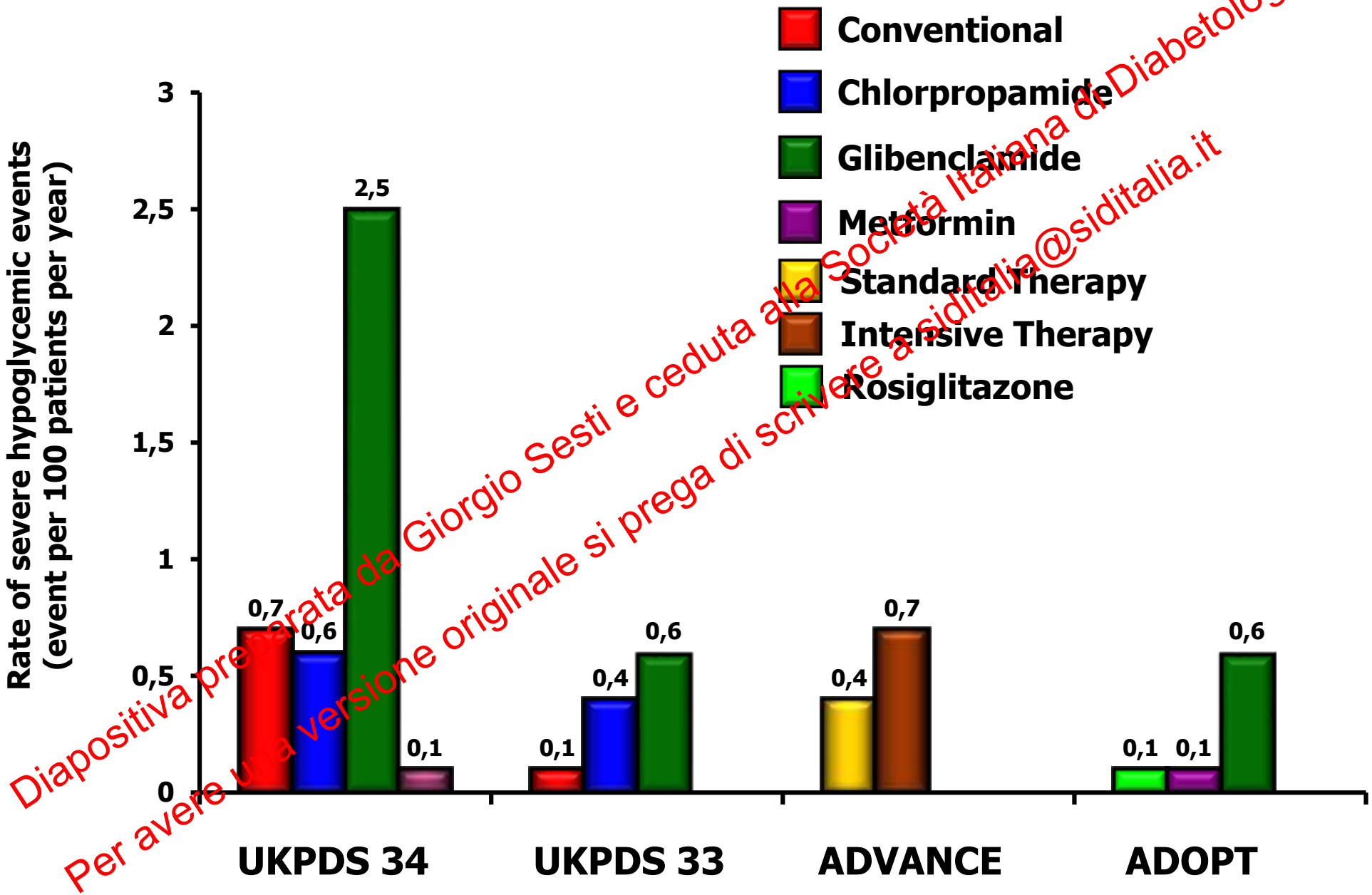


N Engl J Med 358:2560-2572, 2008

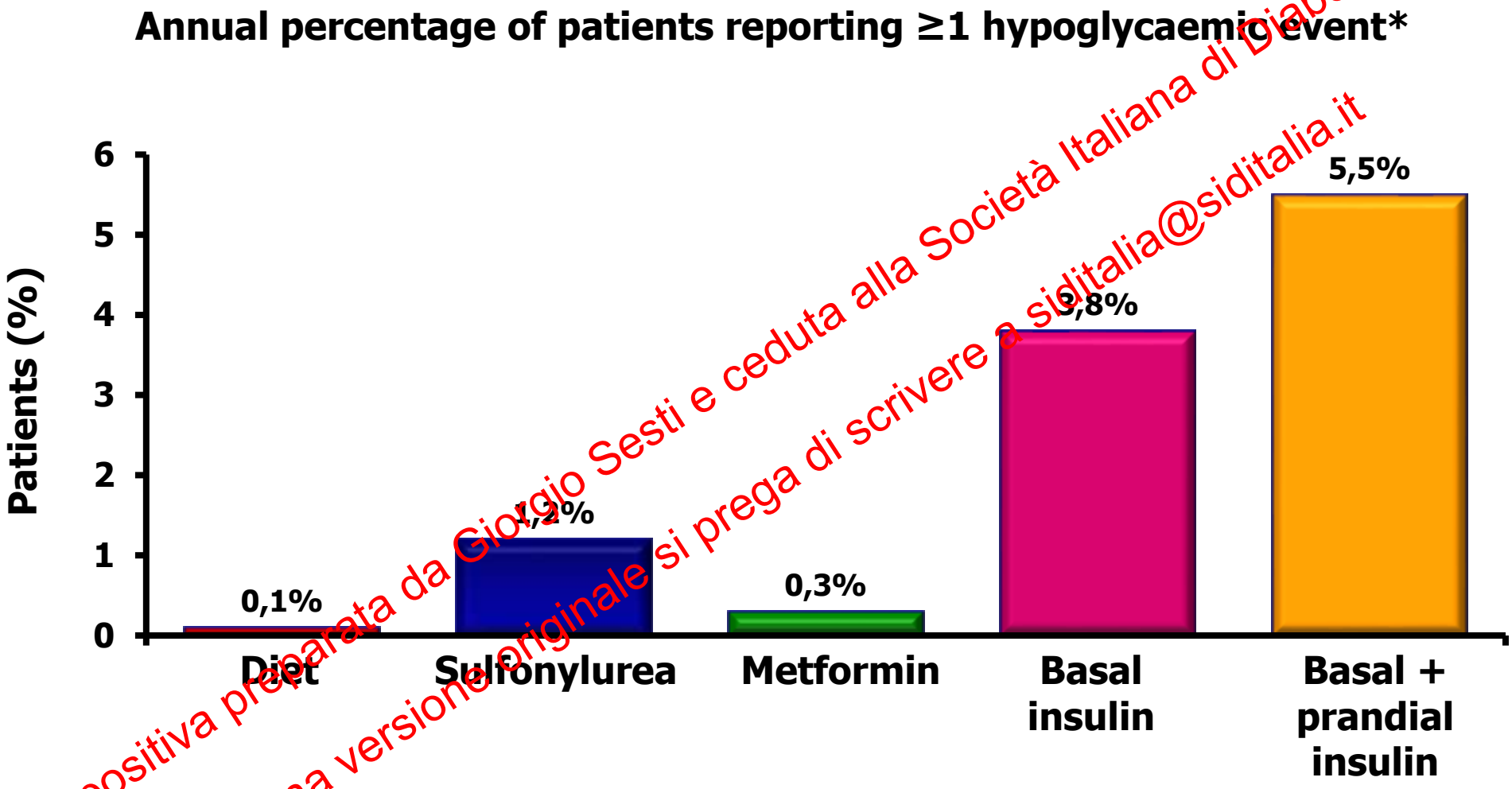
Sulfoniluree e glinidi:

1. Controllo Metabolico
2. Effetti sulla beta cellula
3. Durability
4. Effetti sul peso
5. **Ipoglicemie**
6. Complicanze micro-vascolari
7. Complicanze macro-vascolari

Rate of severe hypoglycemic events



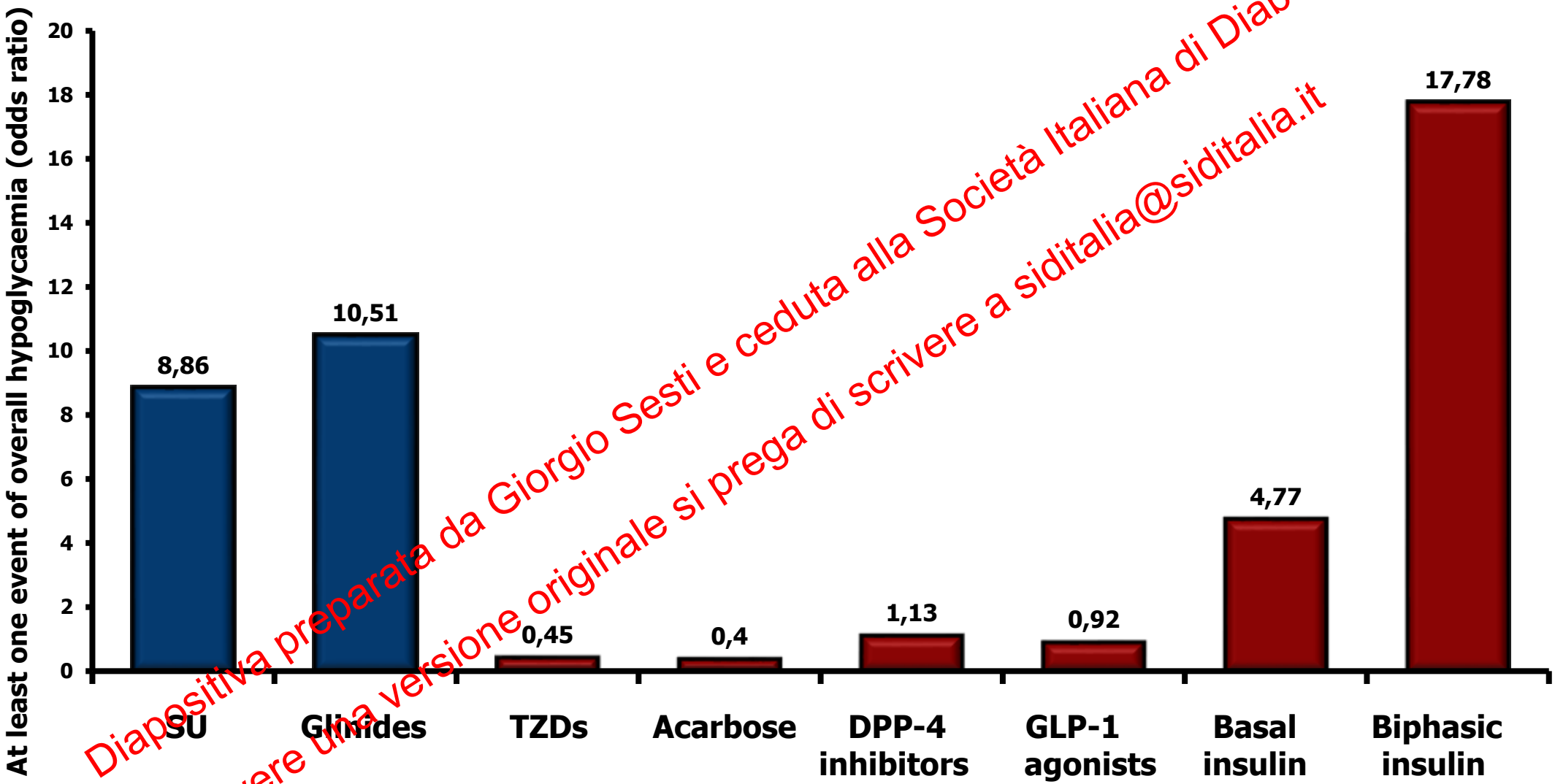
UKPDS: prevalence of hypoglycaemia in Type 2 diabetes



*Hypoglycaemia: temporary incapacity or requiring medical help

Wright AD et al. J Diabetes Complications.20:395-401, 2006

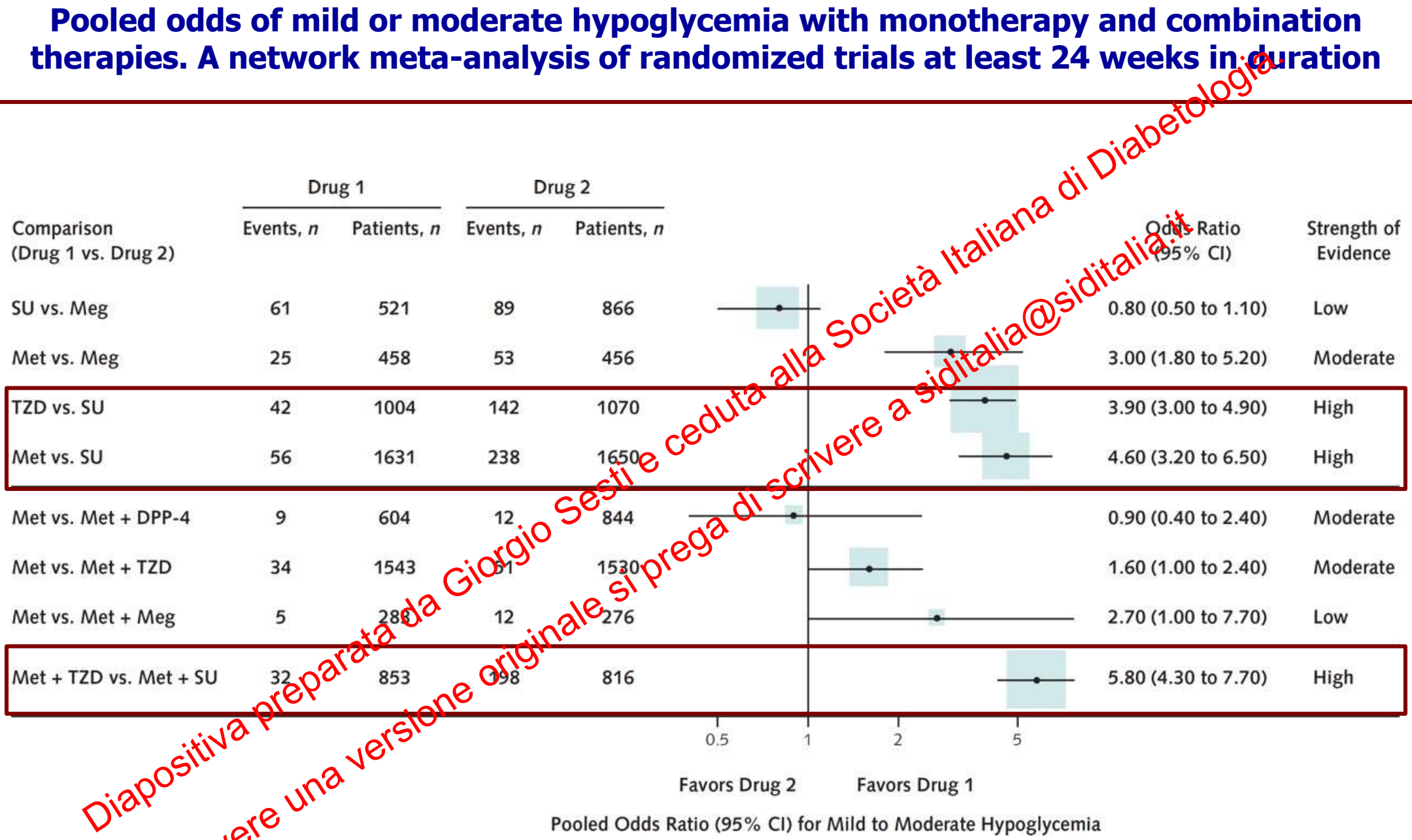
Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: At least one event of overall hypoglycaemia (odds ratio)



Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

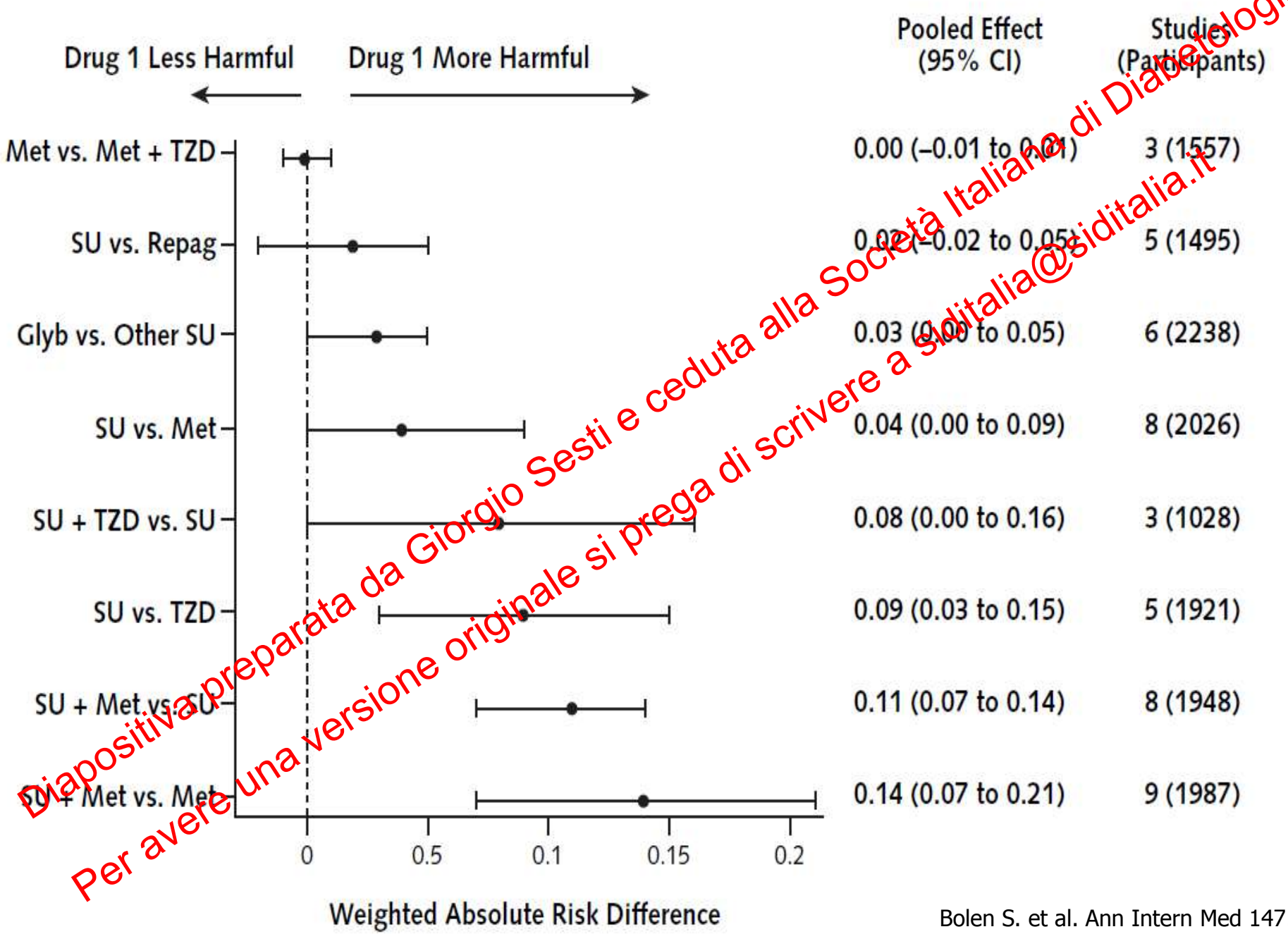
Pooled odds of mild or moderate hypoglycemia with monotherapy and combination therapies. A network meta-analysis of randomized trials at least 24 weeks in duration

Comparison (Drug 1 vs. Drug 2)	Drug 1 Events, *n*	Drug 1 Patients, *n*	Drug 2 Events, *n*	Drug 2 Patients, *n*	Odds Ratio (95% CI)	Strength of Evidence
SU vs. Meg	61	521	89	866	0.80 (0.50 to 1.10)	Low
Met vs. Meg	25	458	53	456	3.00 (1.80 to 5.20)	Moderate
TZD vs. SU	42	1004	142	1070	3.90 (3.00 to 4.90)	High
Met vs. SU	56	1631	238	1650	4.60 (3.20 to 6.50)	High
Met vs. Met + DPP-4	9	604	12	844	0.90 (0.40 to 2.40)	Moderate
Met vs. Met + TZD	34	1543	51	1530	1.60 (1.00 to 2.40)	Moderate
Met vs. Met + Meg	5	288	12	276	2.70 (1.00 to 7.70)	Low
Met + TZD vs. Met + SU	32	853	198	816	5.80 (4.30 to 7.70)	High



Bennett W L et al. Ann Intern Med 154 602-613, 2011

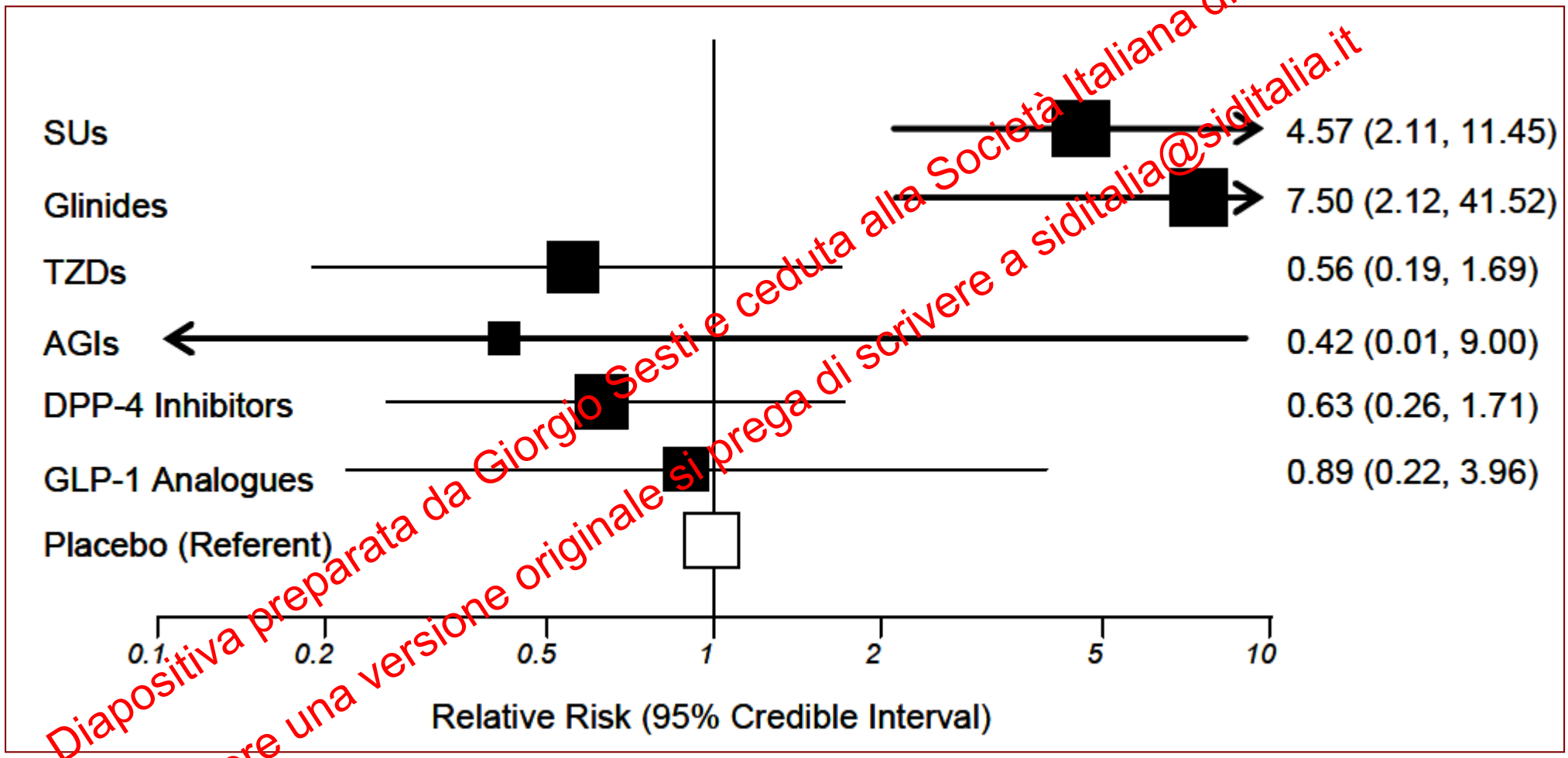
Pooled hypoglycemia results for randomized trials, by drug comparison



Bolen S. et al. Ann Intern Med 147:386-399, 2007

Meta-analysis of RCTs with at least 3 months' duration, evaluating antidiabetic drugs added to metformin

Change in Overall Hypoglycemia



Phung OJ et al. JAMA 303:1410-1418, 2010

Sulfoniluree e glinidi:

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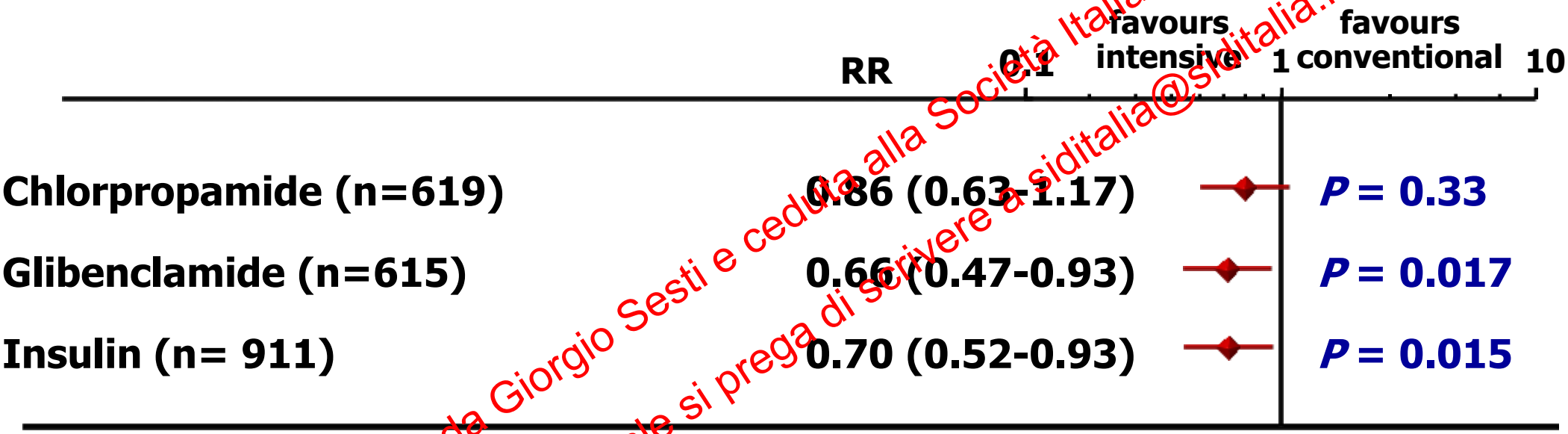
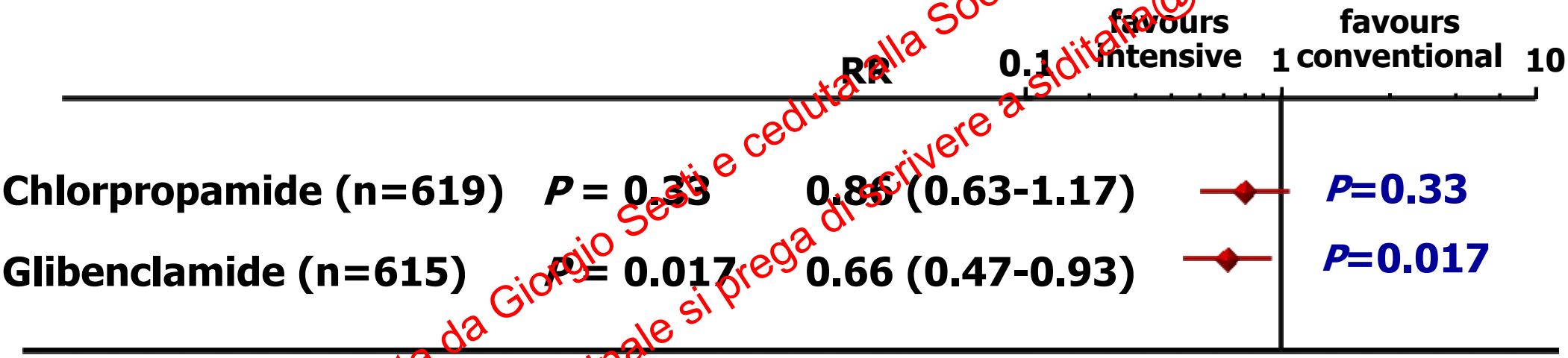
6. **Complicanze micro-vascolari**
7. Complicanze macro-vascolari

UKPDS 33: Microvascular events (Retinopathy and nephropathy)



UKPDS 33 Lancet 352:837-853, 1998

UKPDS 33: Microvascular events (Retinopathy and nephropathy)

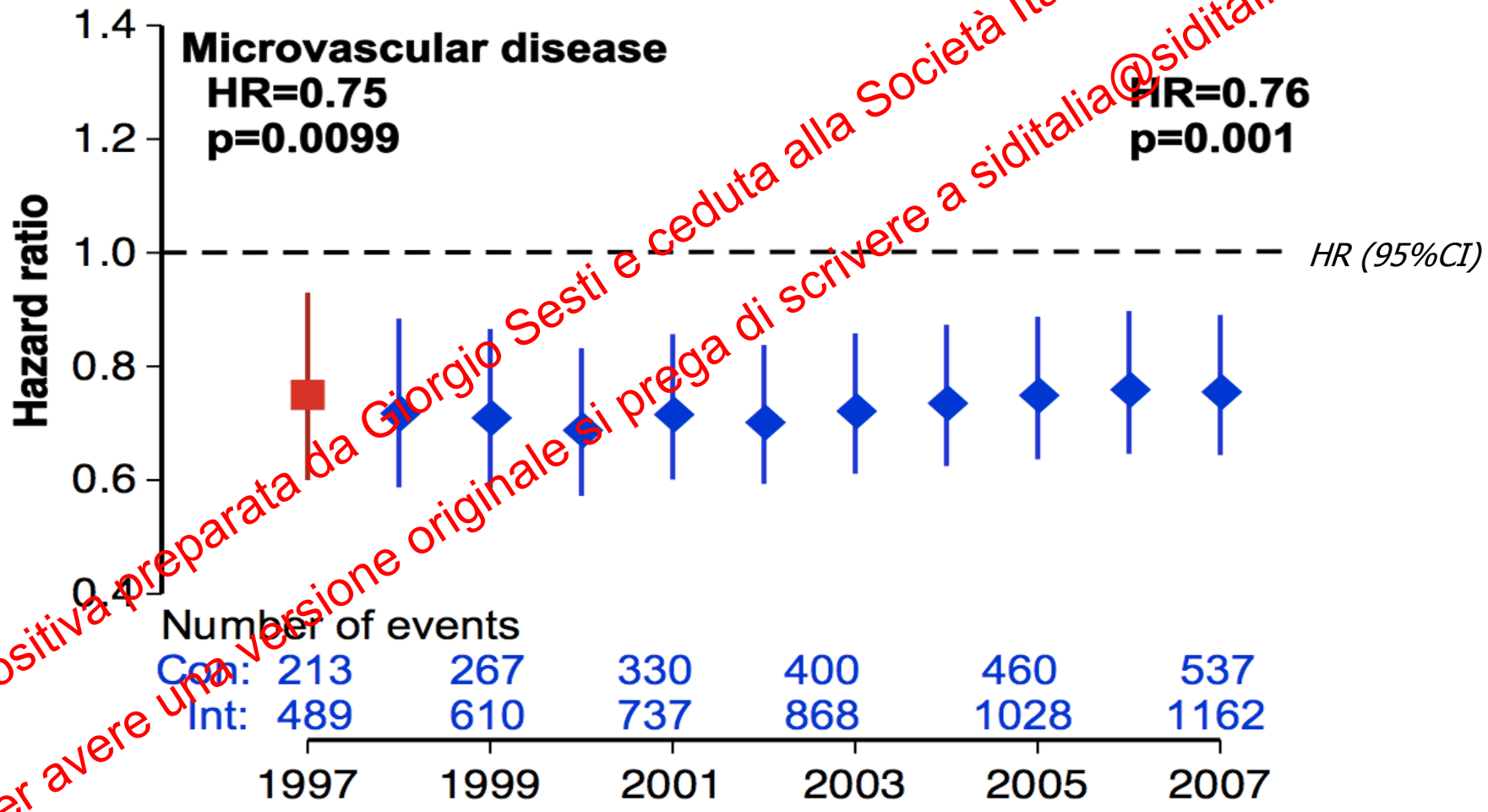


UKPDS 33 Lancet 352:837-853, 1998

UKPDS 80: Extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes- Microvascular Disease Hazard Ratio

(Photocoagulation, vitreous haemorrhage, renal failure)

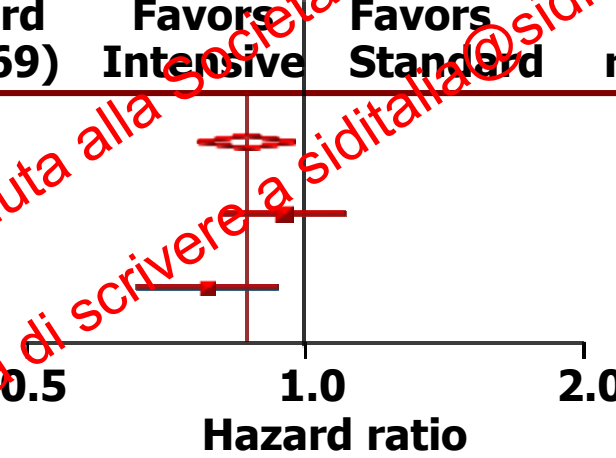
Intensive (SU/Ins) *vs.* Conventional glucose control



Holman R.R. et al. N Engl J Med 359:1577-1589, 2008

ADANCE: Major microvascular events

	Number of patients with event		Relative risk reduction (95% CI)
	Intensive (n=5,571)	Standard (n=5,569)	
Microvascular	526	605	14% (3 to 23) †
New or worsening retinopathy	332	349	5% (-10 to 18)
New or worsening nephropathy	230	292	21% (7 to 34) ‡



†*P*=0.01

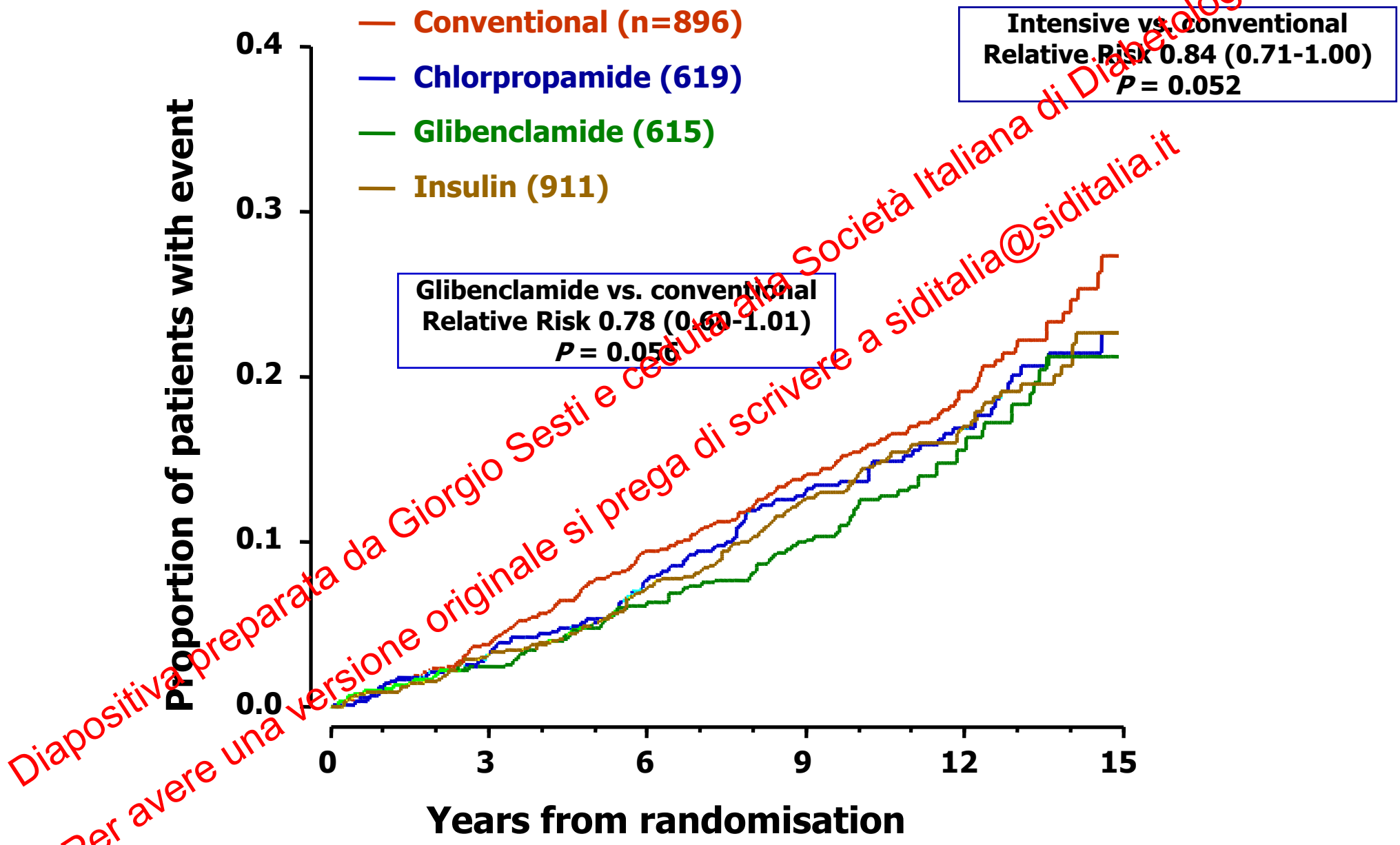
‡*P*=0.006

N Engl J Med 358:2560-2572, 2008

Sulfoniluree e glinidi:

1. Controllo Metabolico
2. Effetti sulla beta cellula
3. Durability
4. Effetti sul peso
5. Ipoglicemie
6. Complicanze micro-vascolari
7. **Complicanze macro-vascolari**
   a. **Randomized clinical trials (RCT)**
   b. Registry studies
   c. Meta-analisi

UKPDS 33: Myocardial Infarction

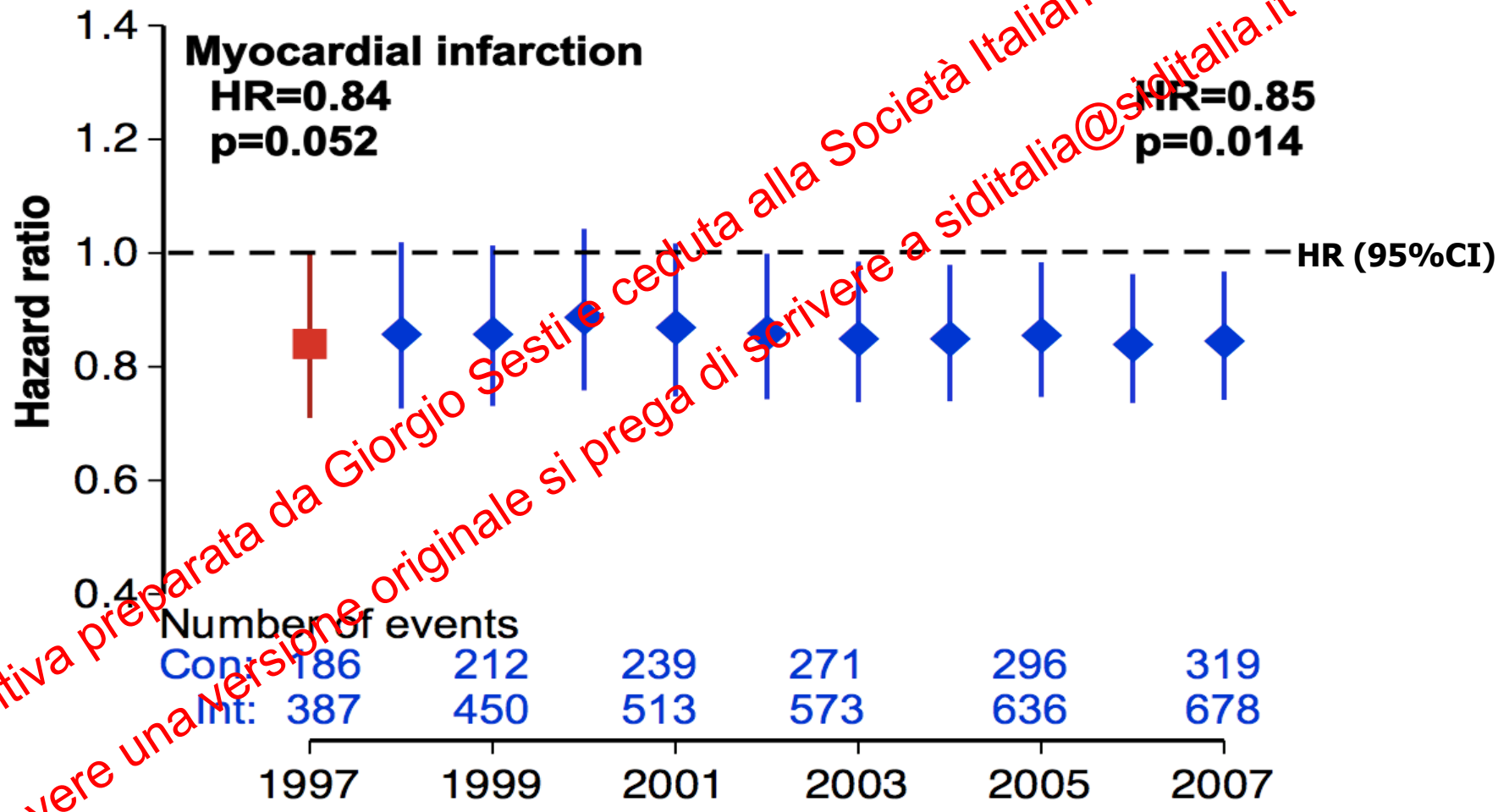


UKPDS 33 Lancet 352:837-853, 1998

Myocardial Infarction Hazard Ratio

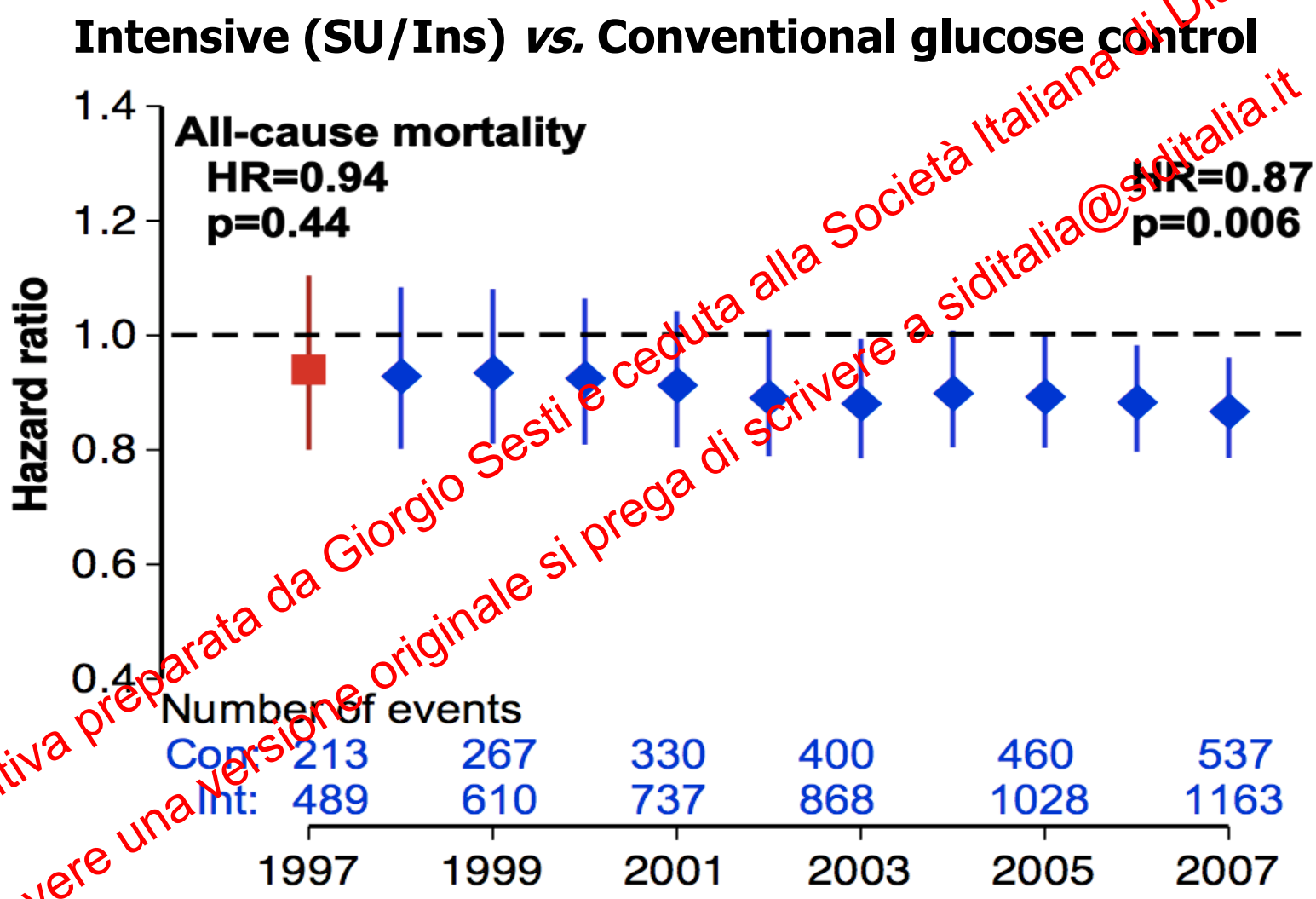
(Fatal or non-fatal myocardial infarction or sudden death)

Intensive (SU/Ins) vs. Conventional glucose control



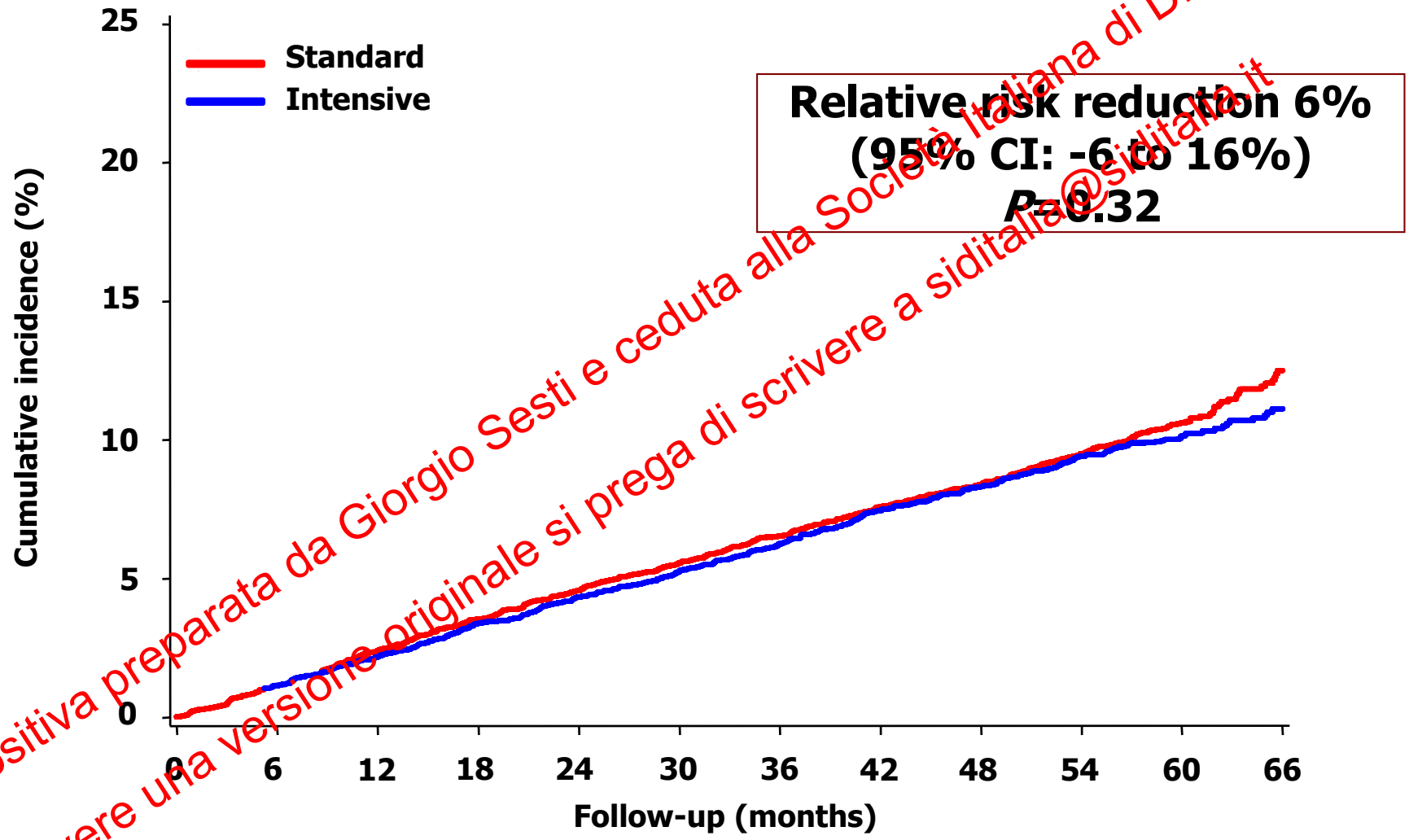
Holman R.R. et al. N Engl J Med 359:1577-1589, 2008

All-cause Mortality Hazard Ratio



Holman R.R. et al. N Engl J Med 359:1577-1589, 2008

Major macrovascular events defined as death from CV causes, nonfatal MI, or nonfatal stroke: ADVANCE



N Engl J Med 358:2560-2572, 2008

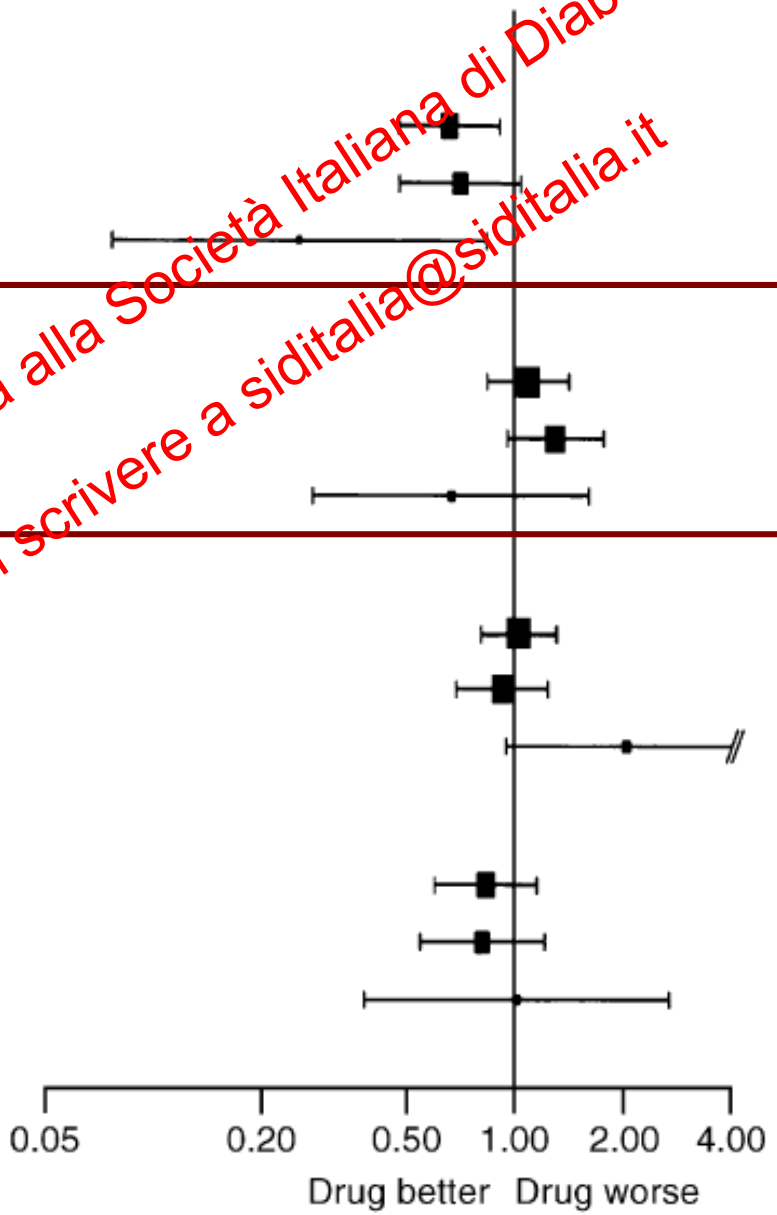
ADOPT: CV Adverse Events According to Treatment Group

Variable	Rosiglitazone (N = 1456)		Metformin (N = 1454)		Glyburide (N = 1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
Adverse events — no. of patients (%)						
Total events	346 (23.8)	1338 (91.9)	331 (22.8)	1341 (92.2)	308 (21.4)	1321 (91.7)
Cardiovascular disease	49 (3.4)	62 (4.3)	46 (3.2)	58 (4.0)	26 (1.8)†	41 (2.8)
Myocardial infarction						
Fatal	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.2)
Nonfatal	22 (1.5)	25 (1.7)	18 (1.2)	21 (1.4)	11 (0.8)	15 (1.0)
Congestive heart failure (investigator-reported)	12 (0.8)	22 (1.5)	12 (0.8)	19 (1.3)	3 (0.2)†	9 (0.6)†
Stroke	13 (0.9)	16 (1.1)	17 (1.2)	19 (1.3)	12 (0.8)	17 (1.2)

Kahn et al. N Engl J Med 355:2427-2443, 2006

Prognostic implications of glucose-lowering treatment in patients with acute MI and T2DM : extended follow-up (median 4.1yrs) of the DIGAMI 2 Study

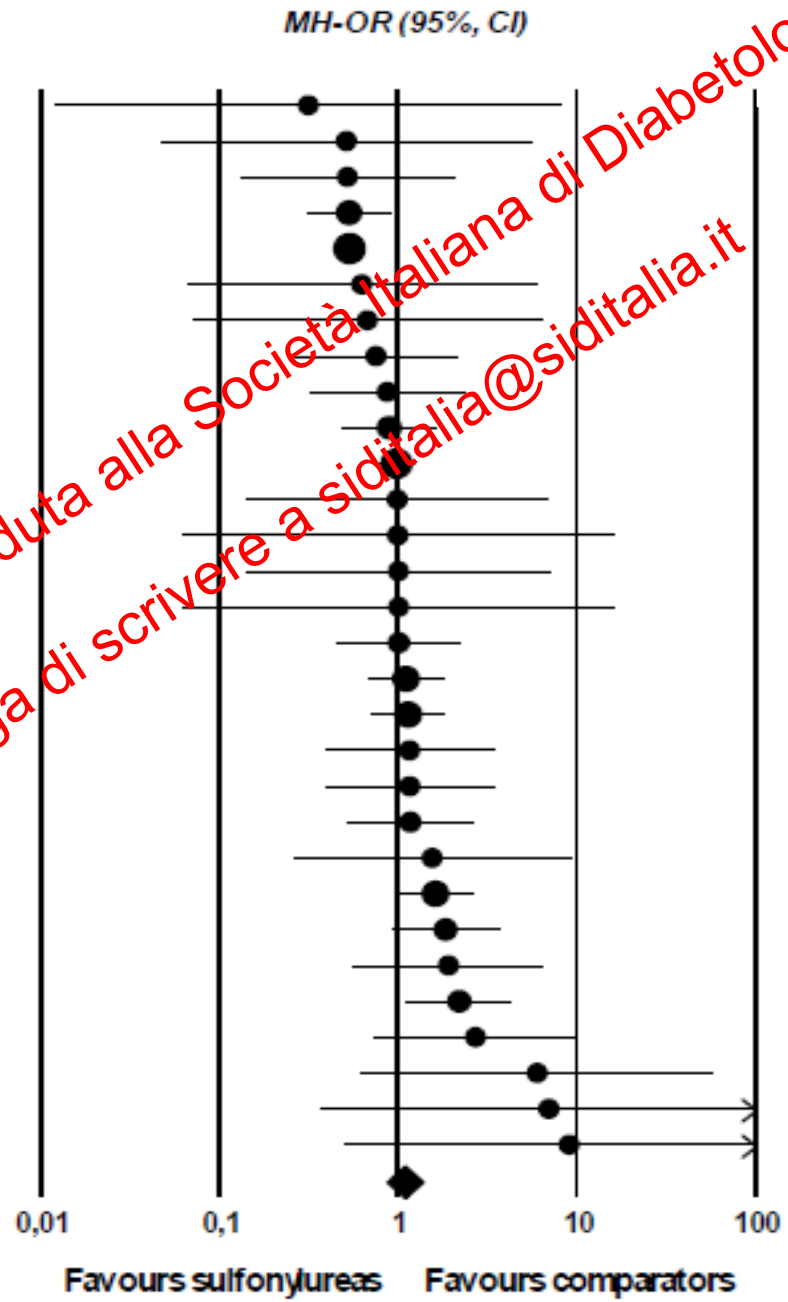
	Hazard ratio (95 % CI)	*p*-value
Metformin (185/888)[a]		
Death (47/271)[b]	0.65 (0.47–0.90)	0.0094
CV death (31/176)[b]	0.72 (0.49–1.06)	0.0995
Cancer death (6/31)[b]	0.25 (0.08–0.83)	0.0235
Sulfonylurea (250/823)[a]		
Death (79/239)[b]	1.09 (0.84–1.42)	0.5251
CV death (57/152)[b]	1.29 (0.94–1.76)	0.1145
Cancer death (11/26)[b]	0.67 (0.28–1.61)	0.3686
Insulin (631/442)[a]		
Death (208/110)[b]	1.03 (0.80–1.31)	0.9312
CV death (133/74)[b]	0.90 (0.67–1.21)	0.4726
Cancer death (27/10)[b]	2.05 (0.95–4.43)	0.0689
Any glucose-lowering drug (912/1610)[a]		
Death (276/42)[b]	0.83 (0.60–1.16)	0.2737
CV death (181/26)[b]	0.79 (0.53–1.17)	0.2398
Cancer death (33/4)[b]	1.01 (0.38–2.69)	0.9792



Mellbin LG et al. Diabetologia 54:1308–1317, 2011

Odds ratio for major CV events with SU: a meta-analysis of RCTs

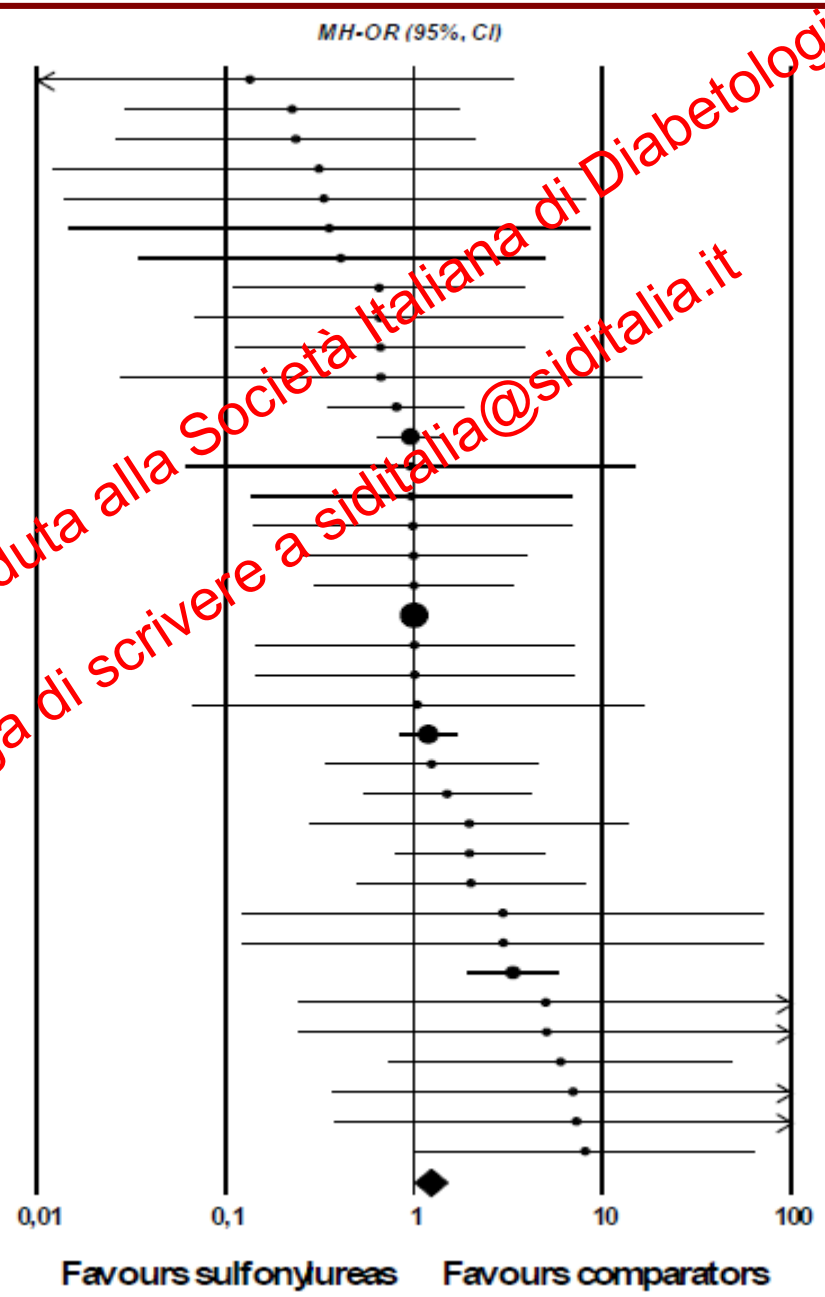
MH-OR	LL (95%. CI)	UL (95%. CI)	p
0.315	0.012	8.269	0.489
0.516	0.046	5.729	0.590
0.522	0.128	2.131	0.365
0.534	0.301	0.945	0.031
0.537	0.443	0.650	0.000
0.629	0.065	6.083	0.689
0.674	0.069	6.545	0.734
0.755	0.259	2.201	0.607
0.871	0.314	2.416	0.790
0.896	0.475	1.693	0.736
0.983	0.774	1.249	0.888
0.994	0.140	7.085	0.995
1.000	0.061	16.463	1.000
1.009	0.141	7.224	0.993
1.014	0.062	16.529	0.992
1.015	0.454	2.268	0.972
1.112	0.668	1.852	0.683
1.144	0.704	1.858	0.587
1.164	0.388	3.492	0.787
1.167	0.386	3.522	0.785
1.177	0.518	2.676	0.697
1.560	0.256	9.480	0.630
1.625	0.990	2.666	0.055
1.851	0.912	3.754	0.088
1.923	0.553	6.679	0.304
2.210	1.107	4.412	0.025
2.722	0.714	10.380	0.143
6.034	0.619	58.837	0.122
7.035	0.362	136.640	0.197
9.124	0.490	169.848	0.138
1.041	**0.825**	**1.312**	**0.736**



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

Odds ratio for all-cause mortality with SU: a meta-analysis of RCTs

First autor (Year)	MH-OR	LL (95%. CI)	UL (95%. CI)	p
Yki-Jarvinen 1999	0,14	0,01	3,48	0,23
Rubin 2008	0,23	0,03	1,80	0,16
Tan 1977	0,24	0,03	2,19	0,20
Birkeland 1996	0,32	0,01	8,27	0,49
Mazzone 2006	0,33	0,01	8,26	0,50
Bakris 2006	0,36	0,01	8,83	0,53
Alvarsson 2010	0,41	0,03	5,03	0,49
Nissen 2008	0,66	0,11	3,96	0,65
Marbury 1999	0,66	0,07	6,40	0,72
Ferrannini 2009	0,67	0,11	4,00	0,66
Seino 2010	0,67	0,03	16,63	0,81
Gerstein 2010	0,81	0,35	1,91	0,63
Kahn 2006	0,96	0,62	1,48	0,86
Filozof 2012	0,96	0,06	15,44	0,98
Hamann 2008	0,98	0,14	6,98	0,98
Goke 2010	1,00	0,14	7,10	1,00
Gallwitz 2012	1,00	0,25	4,02	1,00
Gallwitz 2012 (1)	1,01	0,29	3,50	0,98
UKPDS 33 1998	1,01	0,84	1,20	0,93
Charbonnel 2005	1,01	0,14	7,24	0,99
Giles 2010	1,01	0,14	7,29	0,99
Gerich 2005	1,05	0,07	16,07	0,97
Home 2009	1,20	0,83	1,73	0,32
Charbonnel 2004	1,25	0,33	4,67	0,74
Foley 2009	1,51	0,58	4,27	0,44
Johnston 1998	1,98	0,37	14,27	0,50
Hong 2012	1,99	0,78	5,07	0,15
Clarke 1977	2,02	0,49	8,39	0,33
Arechavaleta 2011	3,00	0,12	73,53	0,50
Garber 2009	3,00	0,12	74,00	0,50
UGDP Group 1982	3,37	1,20	5,98	0,00
Jain 2006	5,04	0,24	105,51	0,30
Matthews 2005	5,10	0,24	106,58	0,29
Tolvan 2009	6,06	0,73	50,40	0,10
Nauck 2011	7,34	0,36	136,64	0,20
Barnett 2006	7,34	0,38	142,83	0,19
Seck 2010	8,15	1,02	65,39	0,05
Overall	**1.22**	**1.01**	**1.49**	**0.047**



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

Sulfoniluree e glinidi:

1. Controllo Metabolico
2. Effetti sulla beta cellula
3. Durability
4. Effetti sul peso
5. Ipoglicemie
6. Complicanze micro-vascolari
7. **Complicanze macro-vascolari**
   a. Randomized clinical trials (RCT)
   b. **Registry studies**
   c. Meta-analisi

Impact of Preadmission Sulfonylureas on Mortality and CV Outcomes in Diabetic Patients with Acute Myocardial Infarction: The French registry on Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI)

Patients on SU had a lower risk of in-hospital mortality, compared with patients without sulfonylurea therapy before admission
OR= 0.50 (95% CI 0.27– 0.94); *P*=0.03

	No ADM (n = 215)	Insulin (n = 341)	Oral non-SU ADM (n = 295)	SU (n = 459)	*P* value
Death	18 (8.4)	32 (9.4)	19 (6.4)	18 (3.9)	0.014
Reinfarction	5 (2.3)	8 (2.3)	6 (2.0)	15 (3.3)	0.721
Stroke	3 (1.4)	5 (1.5)	2 (0.7)	3 (0.7)	0.579
Atrial fibrillation	13 (6.0)	27 (7.9)	14 (4.7)	26 (5.7)	0.382
Ventricular fibrillation	7 (3.3)	5 (1.5)	6 (2.0)	6 (1.3)	0.328
AV block	5 (2.3)	5 (1.5)	7 (2.4)	4 (0.9)	0.332
Sustained VT	10 (4.7)	8 (2.3)	5 (1.7)	12 (2.6)	0.215
Any of the above	45 (20.9)	73 (21.4)	46 (15.6)	70 (15.3)	0.058

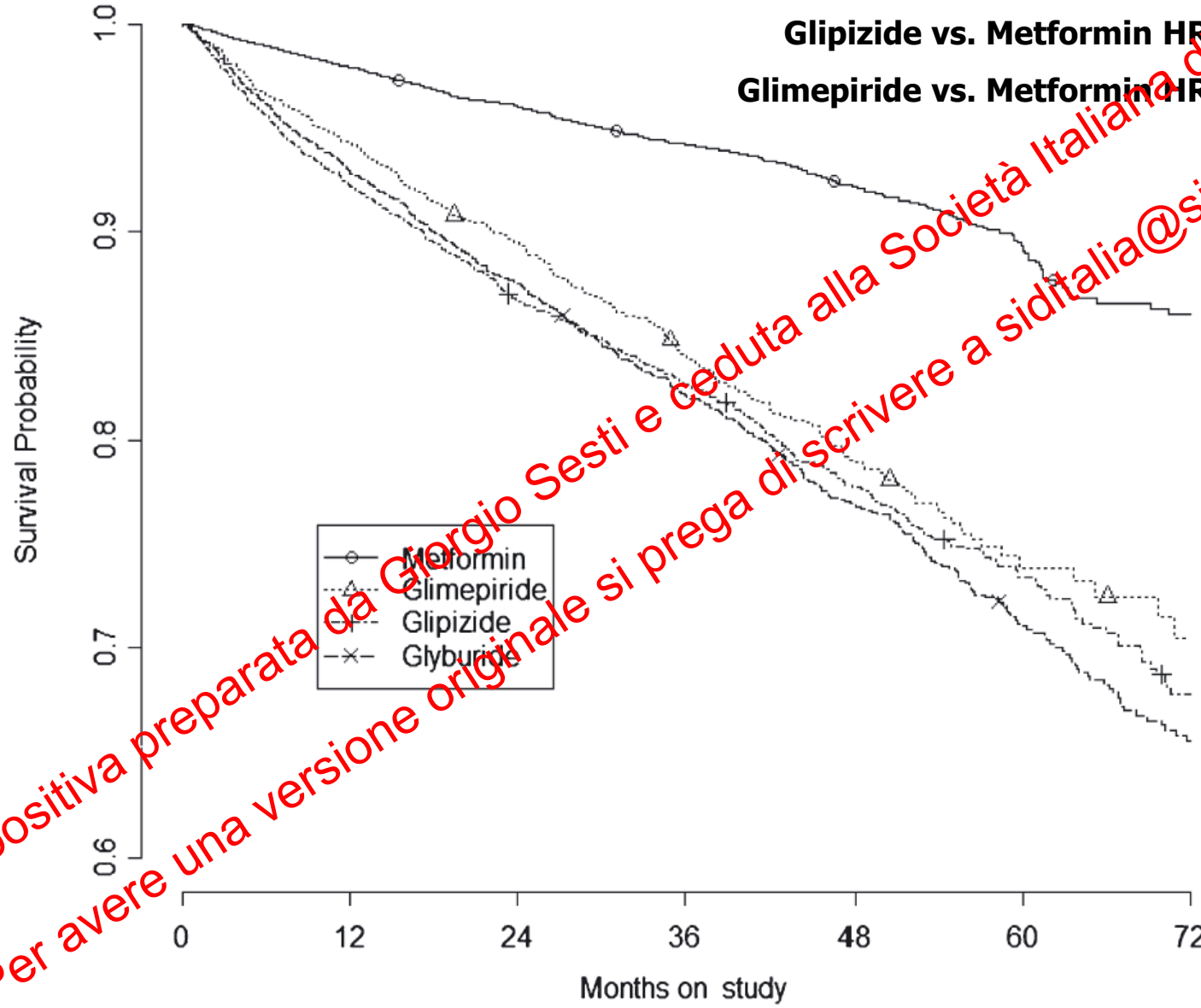
Zeller M et al. J Clin Endocrinol Metab 95: 4993–5002, 2010

Overall mortality in 23915 patients with type 2 diabetes initiators of monotherapy with metformin (12774), glipizide (4325), glyburide (4279) or glimepiride (2537)

Glyburide vs. Metformin HR: 1.59 (95%CI 1.35-1.88)

Glipizide vs. Metformin HR: 1.64 (95%CI 1.39-1.94)

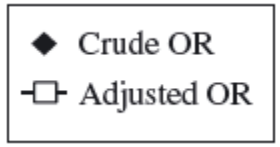
Glimepiride vs. Metformin HR: 1.68 (95%CI 1.37-2.06)



Metformin

Pantaleone K M et al. Diabetes Obes and Metab 14: 803–809, 2012

Risk of acute coronary events associated with glyburide compared with gliclazide use in patients with type 2 diabetes: a nested case–control study



Glyburide vs. Gliclazide	OR	95% CI	Glyburide *vs.* Gliclazide Cases (*n*)/Controls (*n*)		
Overall ACS Event					
All patients	1.12	1.04 – 1.20	2,920/11,204	*vs.*	1,319/5,519
	1.14	1.06 – 1.23			
Past Exposure	1.12	0.98 – 1.28	903/3,654	*vs.*	396/1,735
	1.16	1.01 – 1.33			
Recent Exposure	1.12	1.03 – 1.23	2,017/7,550	*vs.*	923/3,784
	1.13	1.04 – 1.24			

•Adjusted odds ratio for baseline drug use and co-morbidities;
• past exposure, a dispensation for glyburide or gliclazide more than 120 days of the event date;
• recent exposure: a dispensation for glyburide or gliclazide within 120 days of the event date.

Abdelmoneim As et al. Diabetes Obes and Metab 2013

Risk of coronary artery disease (CAD) using multivariable Cox models in a retrospective cohort of 20,450 T2DM patients from an electronic health record (EHR) derived clinical data repository at the Cleveland Clinic for the period 10/24/1998 to 10/12/2006

Hazard ratios and *P* values

Contrast	HR	95% CI		*P* value
		Lower	Upper	
CAD				
Pioglitazone versus metformin	1.11	0.91	1.34	0.32
Pioglitazone versus sulfonylurea	1.04	0.86	1.26	0.69
Rosiglitazone versus metformin	0.96	0.76	1.21	0.74
Rosiglitazone versus sulfonylurea	0.90	0.71	1.14	0.41
Metformin versus sulfonylurea	0.94	0.85	1.05	0.23
Pioglitazone versus rosiglitazone	1.15	0.87	1.53	0.32

Pantalone KM et al. Acta Diabetologica 46:145–154, 2009

First-time hospitalization for MI identified from the Hospital Discharge Registry and the Civil Registration System of North Jutland County, Denmark

Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for myocardial infarction according to prescriptions for antidiabetic drugs filled within 90 days before hospitalization compared with nondiabetic subjects.

	Cases* (N = 6636)	Controls* (N = 66,839)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Antidiabetic medication				
New sulphonylureas	56	322	1.96 (1.47–2.61)	1.36 (1.01–1.84)
Glimepiride	35	205	1.93 (1.34–2.77)	1.36 (0.93–1.99)
Gliclazide	21	117	2.01 (1.26–3.21)	1.37 (0.84–2.22)
Old sulphonylureas	305	1306	2.59 (2.28–2.95)	2.07 (1.81–2.37)
Glibenclamide	206	889	2.57 (2.20–3.01)	2.08 (1.77–2.45)
Glipizide	72	317	2.51 (1.94–3.25)	1.97 (1.50–2.58)
Tolbutamide	27	100	3.02 (1.97–4.64)	2.32 (1.48–3.64)
Nonsulphonylurea oral antidiabetic drugs	31	177	1.88 (1.25–2.82)	1.38 (0.90–2.11)
Insulin	235	737	3.55 (3.03–4.16)	2.56 (2.16–3.03)
Any combination	51	183	1.09 (0.77–1.55)	1.02 (0.70–1.47)
Diabetes without pharmacotherapy	189	423	4.96 (4.16–5.90)	3.51 (2.92–4.22)

*The total number of cases and controls is lower than in Table 1, because we excluded subjects using antidiabetic medication within 90 days to 3 years, but not in the 90 days before hospitalization.

†Adjusted for discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, and liver cirrhosis, and prescriptions for antihypertensive drugs, lipid-lowering agents, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, and nitrates before the date of hospitalization for myocardial infarction.

Johnsen SP et al Am J Ther 13:134–140, 2006

The general practice research database in the United Kingdom comprises clinical and prescribing data from anonymised patient based clinical records of about five million people.

Outcome: risk of myocardial infarction, congestive heart failure, and all cause mortality associated with prescription of different classes of oral anti-diabetes drugs among men and women with diabetes.

Mean follow-up was 7.1 years.

Tzoulaki, J et al. BMJ 339:b4731, 2009

Risk of a first episode of myocardial infarction among patients receiving rosiglitazone, pioglitazone, sulphonylureas, and other drugs and combinations compared with patients receiving metformin alone

Models and treatments	No of events	Hazard ratio (95% CI)	P value
Model 1 (2 761 889 intervals):			
First generation sulphonylureas	170	1.37 (1.15 to 1.62)	0.0003
Second generation sulphonylureas	1375	1.31 (1.21 to 1.43)	<0.001
Rosiglitazone	23	0.94 (0.62 to 1.43)	0.783
Rosiglitazone combination	83	1.08 (0.86 to 1.35)	0.524
Pioglitazone alone and combined	24	0.78 (0.52 to 1.17)	0.230
Other drugs and combinations	793	1.19 (1.08 to 1.31)	0.0007

Tzoulaki, J et al. BMJ 339:b4731, 2009

Risk for all cause mortality among patients receiving rosiglitazone, pioglitazone, sulphonylureas, and other drugs and combinations compared with patients receiving metformin alone

Models and treatments	No of events	Hazard ratio (95% CI)	P value
Model 1 (2 842 504 intervals):			
First generation sulphonylureas	1941	1.61 (1.49 to 1.74)	<0.001
Second generation sulphonylureas	9606	1.55 (1.48 to 1.62)	<0.001
Rosiglitazone	83	1.00 (0.78 to1.28)	0.990
Rosiglitazone combination	244	0.80 (0.70 to 0.93)	0.003
Pioglitazone alone and combined	71	0.61 (0.47 to 0.80)	0.0003
Other drugs and combinations	3291	1.03 (0.98 to 1.09)	0.271

Tzoulaki, J et al. BMJ 339:b4731, 2009

Annals of Internal Medicine | ORIGINAL RESEARCH

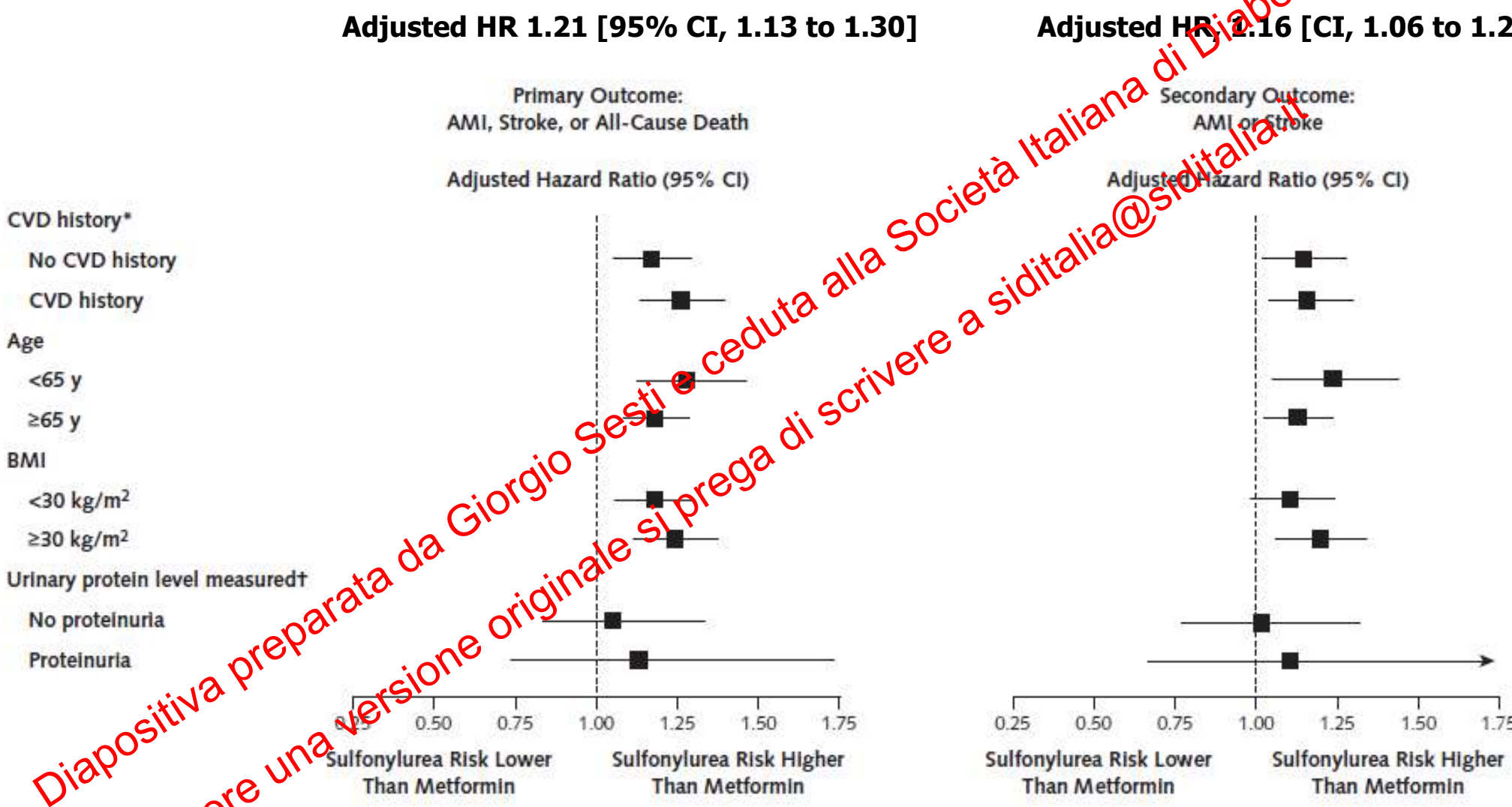
Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus

A Cohort Study

Retrospective cohort study from National Veterans Health Administration databases linked to Medicare files.

Characteristic	Full Cohort		
	Metformin (n = 155 025)	Sulfonylureas (n = 98 665)	Standardized Difference*†
Median age (IQR), y	62 (56–71)	67 (57–76)	0.33
Men, %	95	97	0.12
Race, %			
White	74	75	0.04
Black	12	13	0.04
Hispanic/other	6	6	0.03
Available§	91	95	0.13
HbA_{1c}			
Median level (IQR), %	7.0 (6.4–7.8)	7.3 (6.6–8.2)	0.17
Available§	67	61	0.14

Adjusted hazard ratios for the primary composite outcome (CVD or death) and secondary outcome (CVD alone), stratified by CVD history, age, and BMI



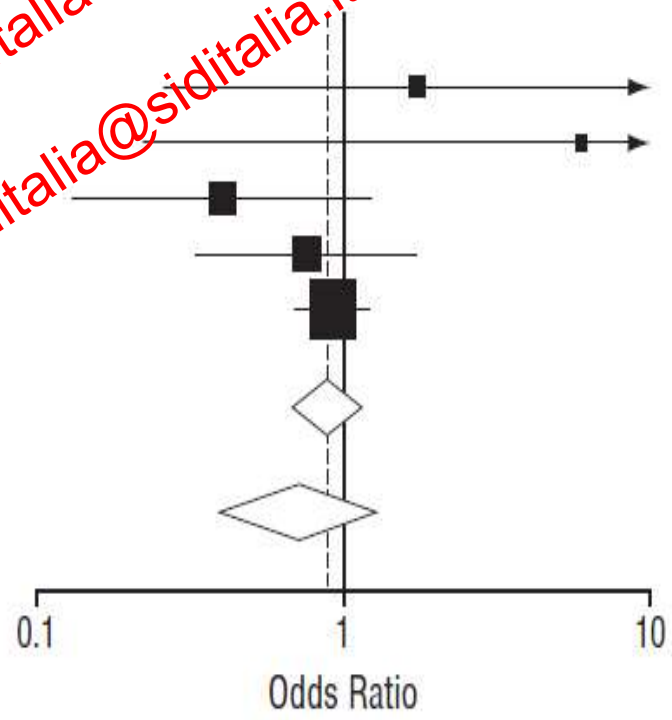
Roumie CL et al. Ann Intern Med157:601-610, 2012

Sulfoniluree e glinidi:

1. Controllo Metabolico
2. Effetti sulla beta cellula
3. Durability
4. Effetti sul peso
5. Ipoglicemie
6. Complicanze micro-vascolari
7. **Complicanze macro-vascolari**
   a. Randomized clinical trials (RCT)
   b. Registry studies
   c. **Meta-analisi**

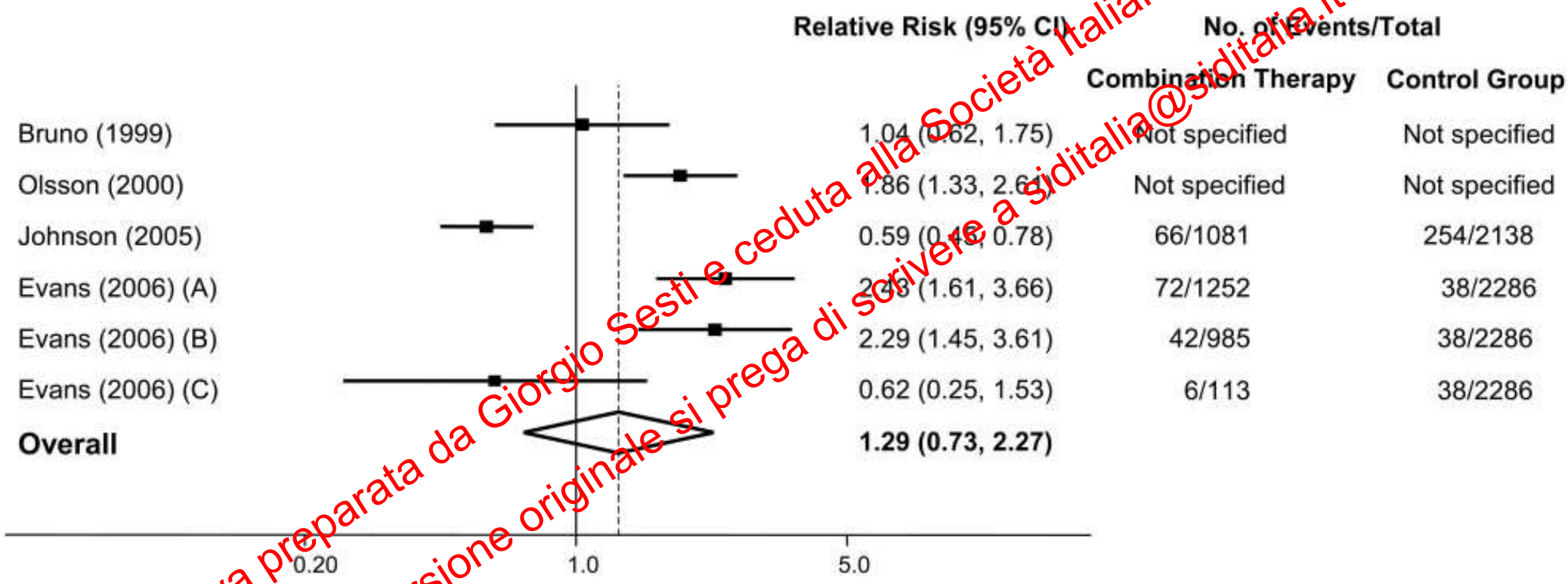
Comparative effects of any Sulfonylurea vs. any comparator on cardiovascular morbidity: meta-analysis of five RCT (n=2.795)

Source	OR (95% CI)	Weight, %
Hermann et al,[41] 1994	1.74 (0.27-11.11)	1.07
Lawrence et al,[44] 2005	5.93 (0.23-151.78)	0.20
Marbury et al,[45] 1999	0.41 (0.14-1.21)	7.72
St John Sutton et al,[53] 2002	0.76 (0.34-1.70)	8.52
UKPDS Group,[1] 1998 (UKPDS 33)	0.92 (0.72-1.18)	82.48
Overall pooled OR	0.89 (0.71-1.11)	100.00
Pooled OR, excluding UKPDS 33	0.72 (0.41-1.28)	



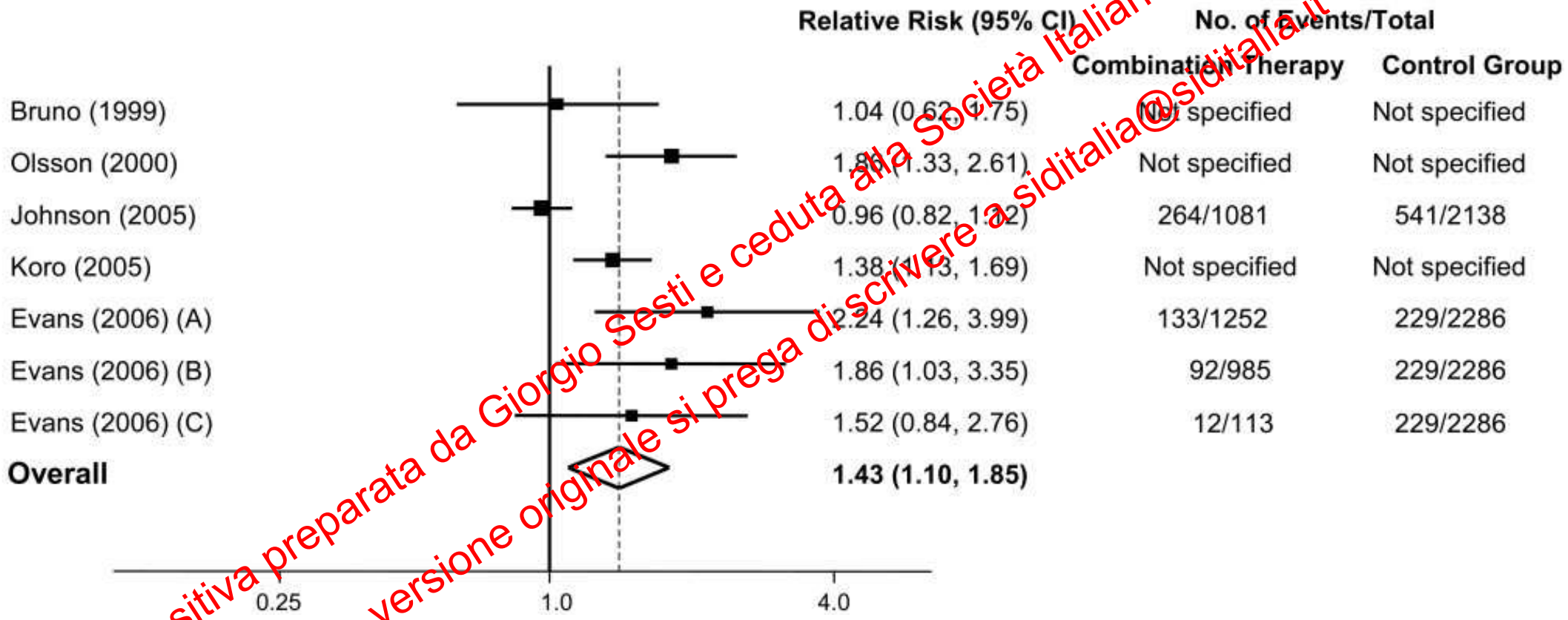
Selvin E et a. Arch Intern Med 168:2070-2080, 2008

RR estimates for CVD mortality associated with combination therapy of metformin and sulfonylurea: a meta-analysis of observational studies



Rao AD et al. Diabetes Care 31:1672–1678, 2008

RR estimates for a composite end point of CVD hospitalizations (the first CV event fatal or nonfatal), or mortality associated with combination therapy of metformin and sulfonylurea: a meta-analysis of observational studies



Rao AD et al. Diabetes Care 31:1672–1678, 2008

Flow-chart per la terapia del diabete mellito di tipo 2

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico)

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2 g die

↓

Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti G.I.	Costo
Gliptina	1A	1B	Rari	1A	1B	2B	1A	elevato
A. R. GLP-1	1A	1A	Non indicato in IRC	2B	1A	2B	1C	elevato
Sulfonilurea o Repaglinide	1D	1D	Non indicato in IRC[2]	3C[3]	1B	1B	1A	basso
Pioglitazone	1A	1D	Fratture	1A	1A	1E	1A	medio
Acarbosio	1A	1C	Rari	2B	2B	3C	1C	basso
Gliflozina	1A	1A	Infezioni G.U.	3C	2B	2B	1A	???
Insulina Basale	1D	1D	Rari	1B	1A	1B	1A	medio

note:
[1]: solo per saxagliptin, possibile rischio per scompenso cardiaco
[2]: alcuni farmaci di questa classe non sono a metabolismo renale, ma non sono comunque indicati
[3]: solo per glibenclamide, possibili rischi cardiaci