



Terapia di combinazione con l'insulina

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Diapositiva preparata da CRISTINA BIANCHI e ceduta alla Società Italiana di Diabetologia.
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Dichiarazione Conflitto d'Interessi

La sottoscritta Dott.ssa Cristina Bianchi

DICHIARA

di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Boehringer Ingelheim Pharma
- Lilly Diabetes
- Novonordisk

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Insulin in combination with oral drugs



Insulin in combination with oral drugs



Insulin in combination with oral glucose-lowering agents

Insulin in combination with oral glucose-lowering agents can be used at either of two stages:



- an oral glucose-lowering agent may be added to insulin;
- insulin therapy may be added to oral glucose-lowering agents alone.

Insulin in combination with oral glucose-lowering agents

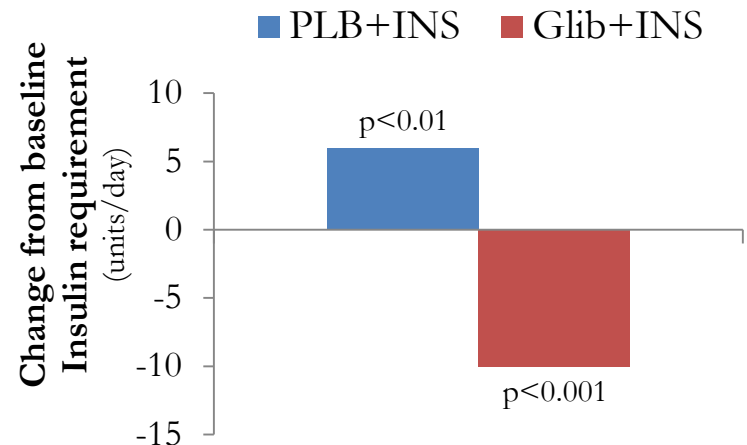
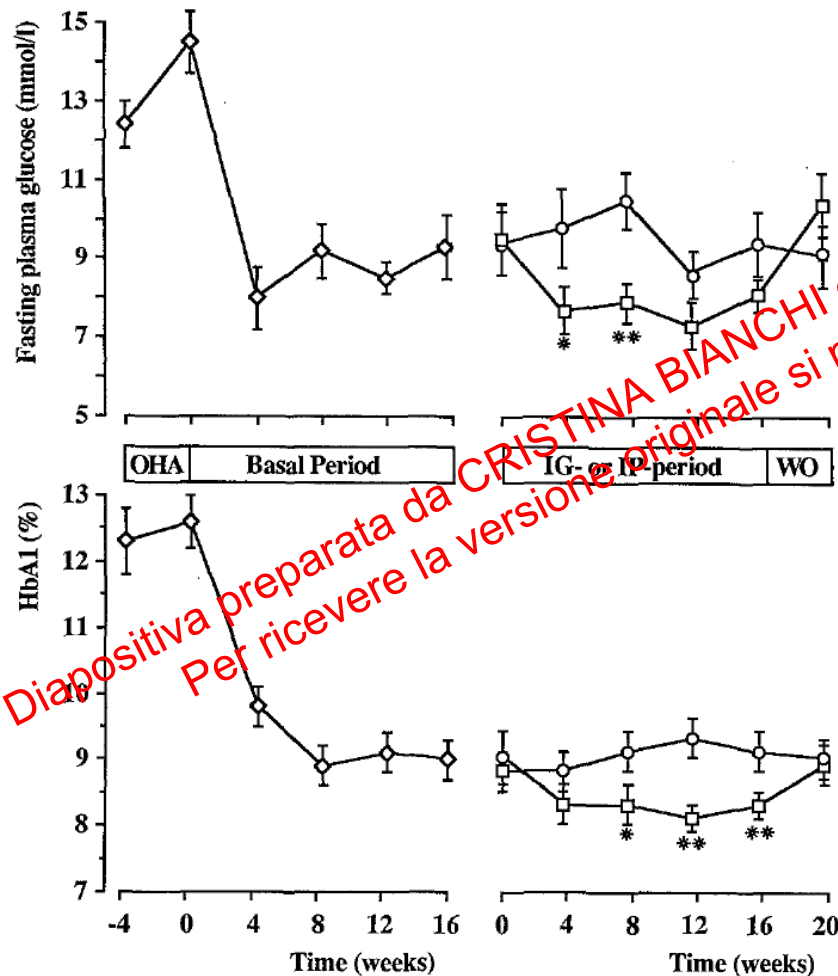
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Addition of Glibenclamide to Insulin treatment in type 2 Diabetes

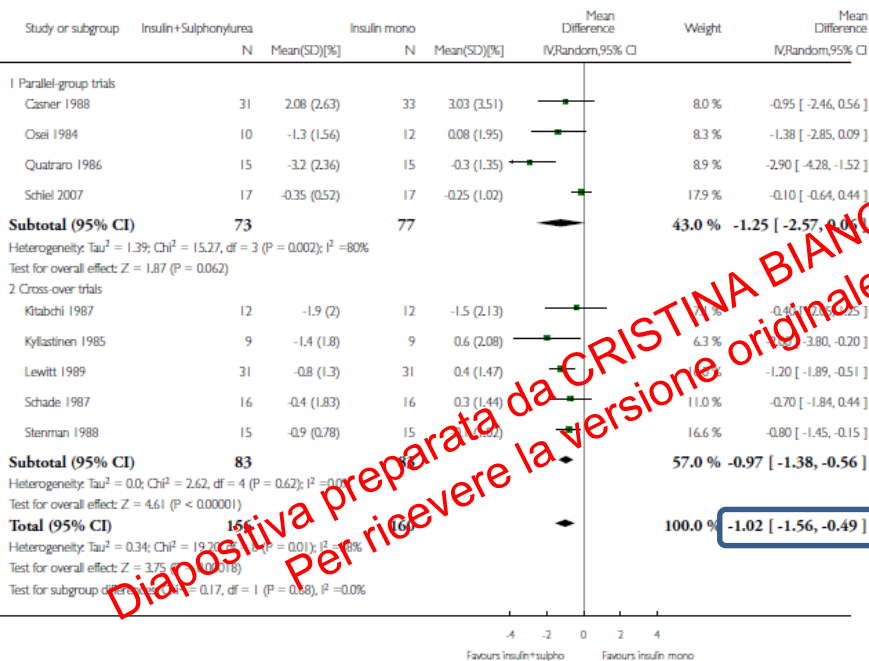
15 type 2 diabetic patients who had failed on treatment with oral hypoglycaemic agents



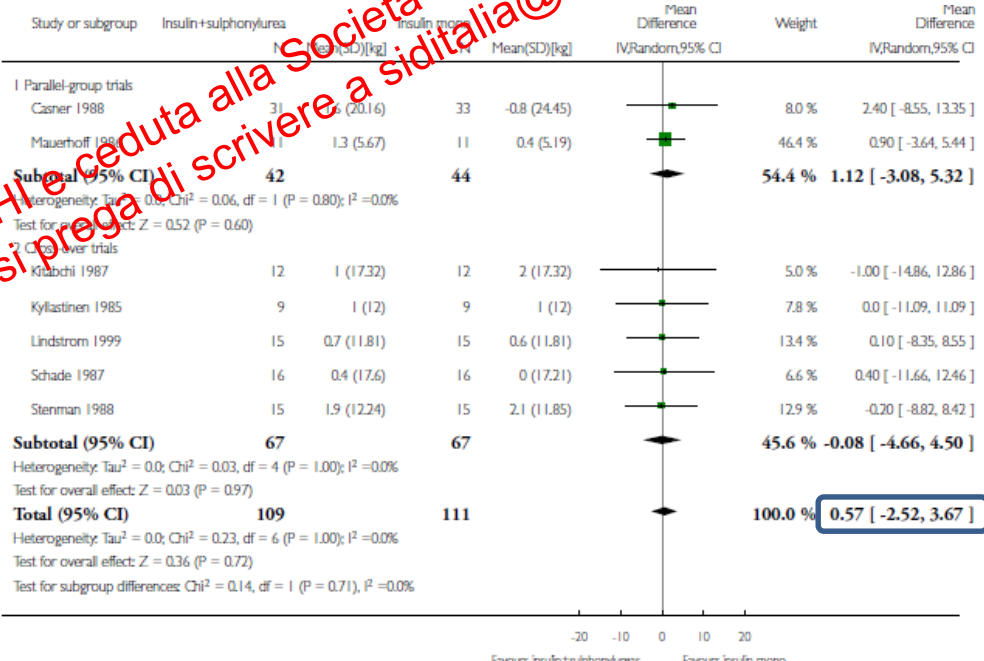
Insulin monotherapy vs. insulin plus sulphonylurea

- Cochrane meta-analysis -

Change in HbA1c from baseline

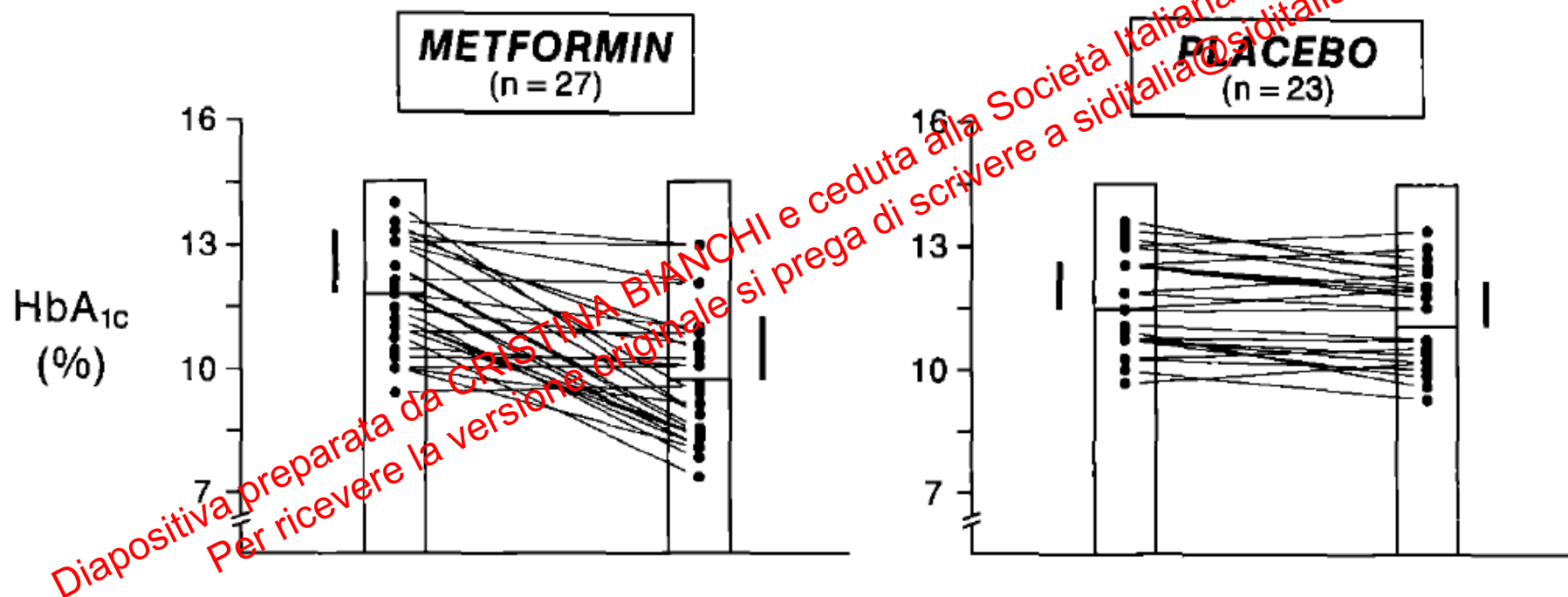


Change in body weight from baseline



Metformin for obese insulin-treated diabetic patients

50 insulin-treated, obese diabetics



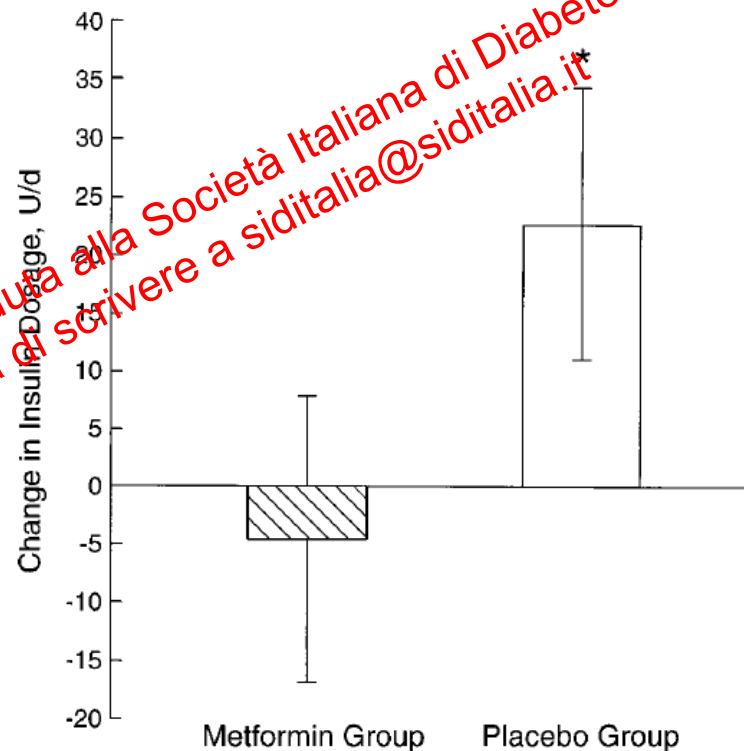
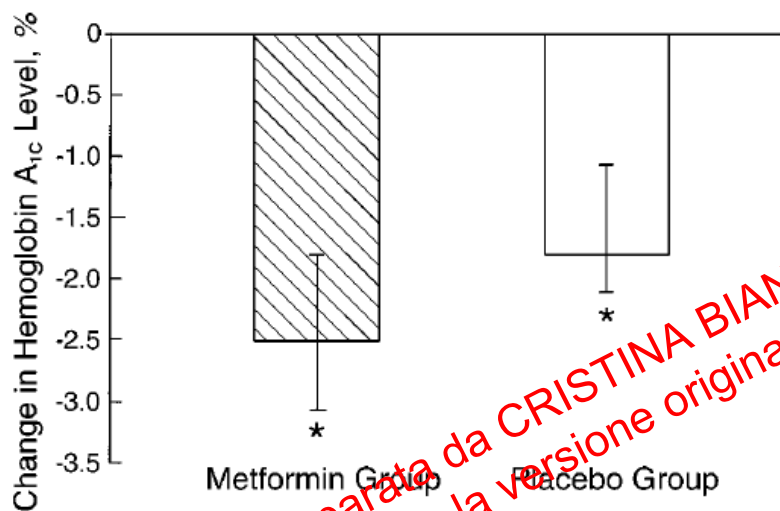
Adding Metformin to Insulin in type 2 Diabetes

47 insulin-treated diabetics; follow-up: 4 months

Variable	Insulin+metformin	Insulin dose increase	p
Weight (kg)			
Baseline	76.8 ± 12.6	78.04 ± 12.9	ns
End	77.09 ± 11.7	79.2 ± 13.5	ns
Difference	0.3 ± 4.5	1.16 ± 1.9	<0.05
Body mass index (kg m ⁻²)			
Baseline	33 ± 4.7	31.9 ± 4.5	ns
End	33.06 ± 4.3	32.3 ± 4.6	ns
Difference	0.07 ± 1.97	0.45 ± 0.7	<0.05
Daily insulin dose (UI)			
Baseline	47.9 ± 10	51.8 ± 9	ns
End	45 ± 12.4	51 ± 11.2	<0.001
Difference	-2.9 ± 7.4	9.1 ± 5.1	<0.001
Fasting blood glucose (mmol l ⁻¹)			
Baseline	13.52 ± 3.69	14.12 ± 2.7	ns
End	10.6 ± 1.88	12.66 ± 3.47	= 0.09
Difference	-2.9 ± 4.45	-1.44 ± 3.45	ns
HbA _{1c} (%)			
Baseline	9.12 ± 1.42	9.57 ± 1.2	ns
End	7.76 ± 1.58	9.6 ± 1.79	<0.01
Difference	-1.87 ± 2.16	0.03 ± 1.68	<0.01
Total cholesterol (mmol l ⁻¹)			
Baseline	5.84 ± 0.99	5.92 ± 1.2	ns
End	5.28 ± 1.1	6.06 ± 1.24	<0.05
Difference	-0.56 ± 0.89	0.14 ± 0.72	<0.05
LDL cholesterol (mmol l ⁻¹)			
Baseline	3.84 ± 0.51	3.71 ± 1.15	ns
End	3.31 ± 0.79	3.9 ± 1.05	<0.05
Difference	-0.51 ± 0.73	0.19 ± 0.6	<0.01
HDL cholesterol (mmol l ⁻¹)			
Baseline	1.36 ± 0.18	1.26 ± 0.26	ns
End	1.36 ± 0.3	1.34 ± 0.35	ns
Difference	-0.003 ± 0.17	0.08 ± 0.25	ns
Triglycerides (mmol l ⁻¹)			
Baseline	2.01 ± 1.12	2.41 ± 1.53	ns
End	1.65 ± 0.75	2.32 ± 1.05	<0.05
Difference	-0.36 ± 0.7	-0.08 ± 1.18	ns

Adding Metformin to Insulin in type 2 Diabetes

43 insulin-treated diabetics; follow-up: 24 months

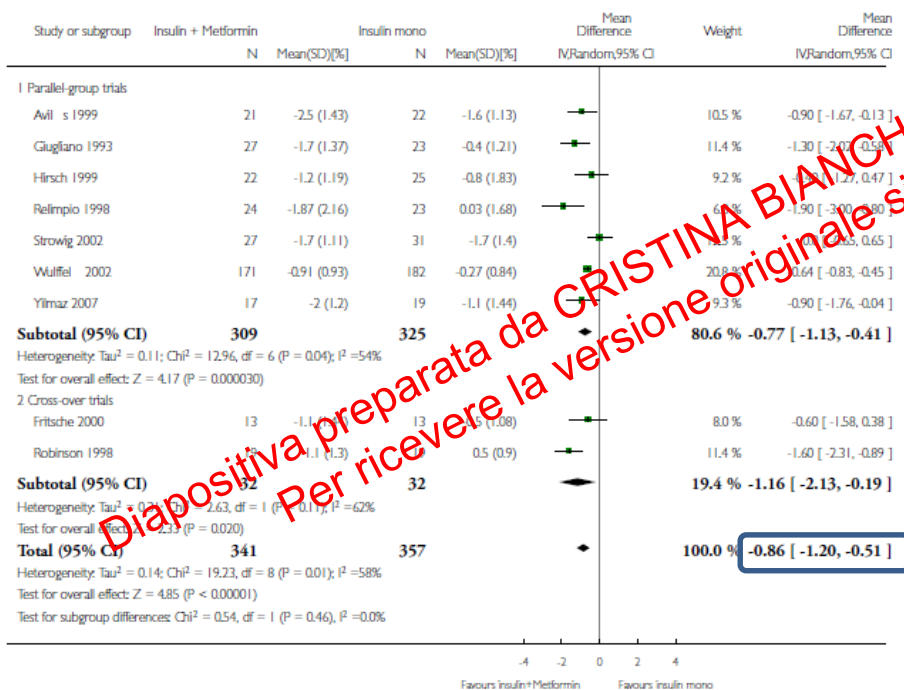


The addition of metformin to insulin therapy resulted in hemoglobin A_{1c} concentrations that were 10% lower than those achieved by insulin therapy alone. This improvement in glycemic control occurred with the use of 29% less insulin and without significant weight gain.

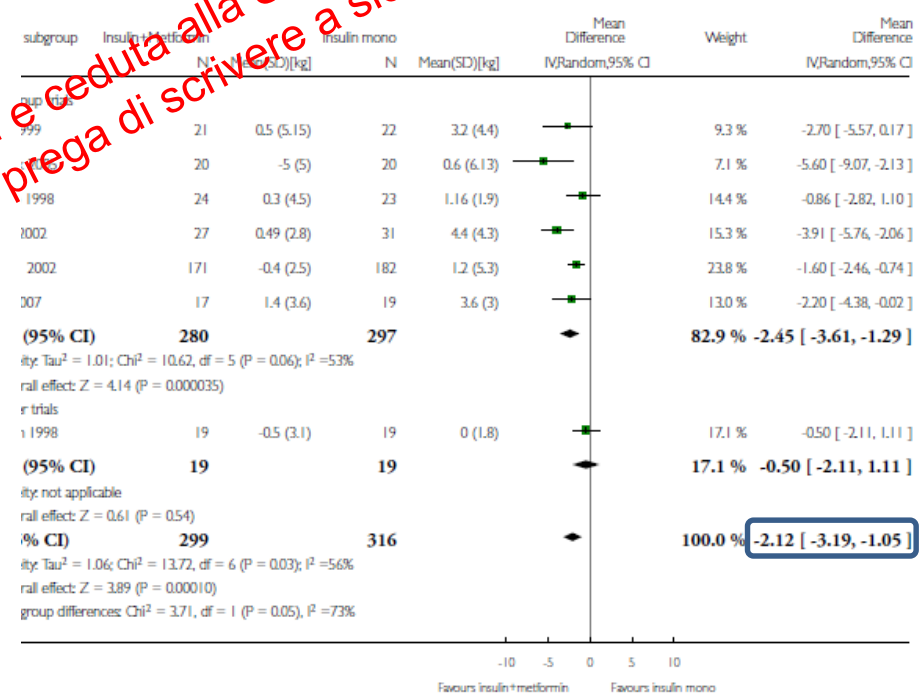
Insulin monotherapy *vs.* insulin plus metformin

- Cochrane meta-analysis -

Change in HbA1c from baseline

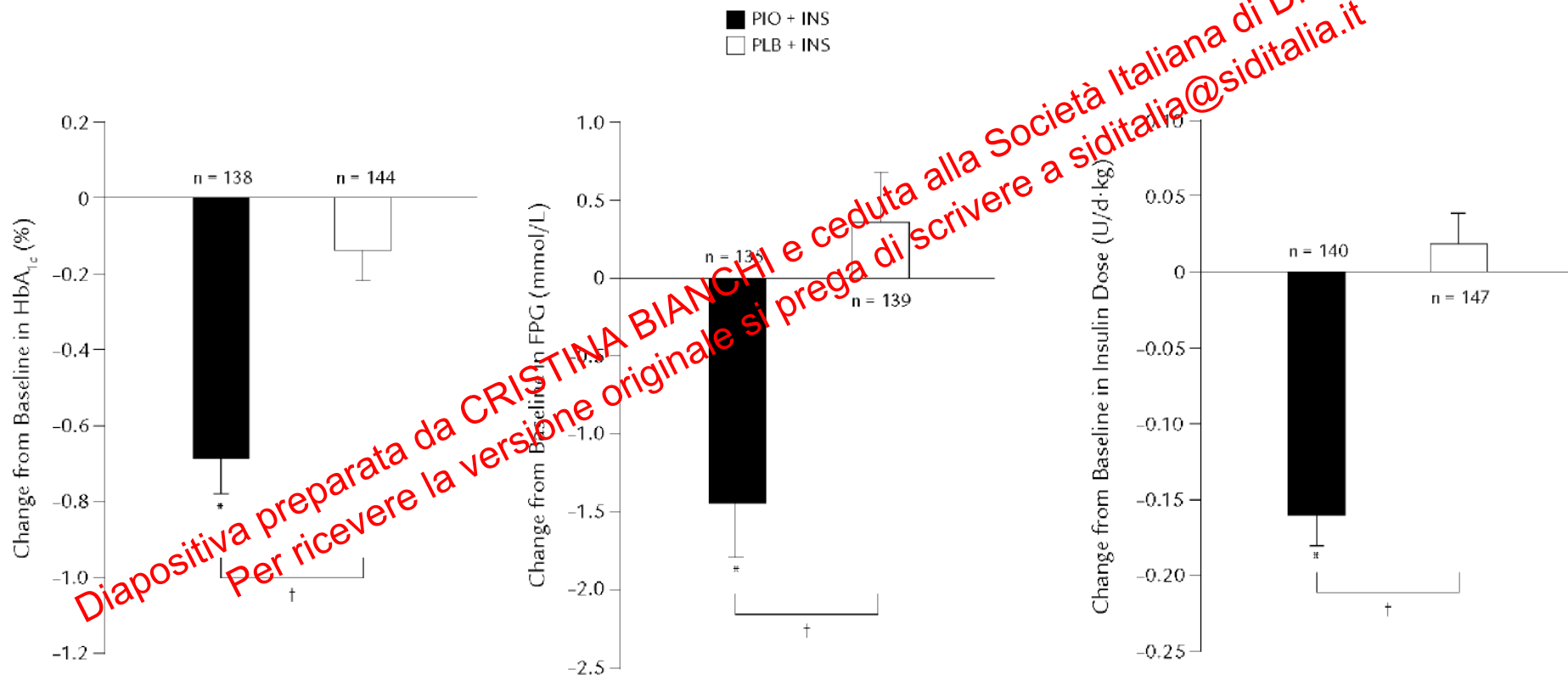


Change in body weight from baseline



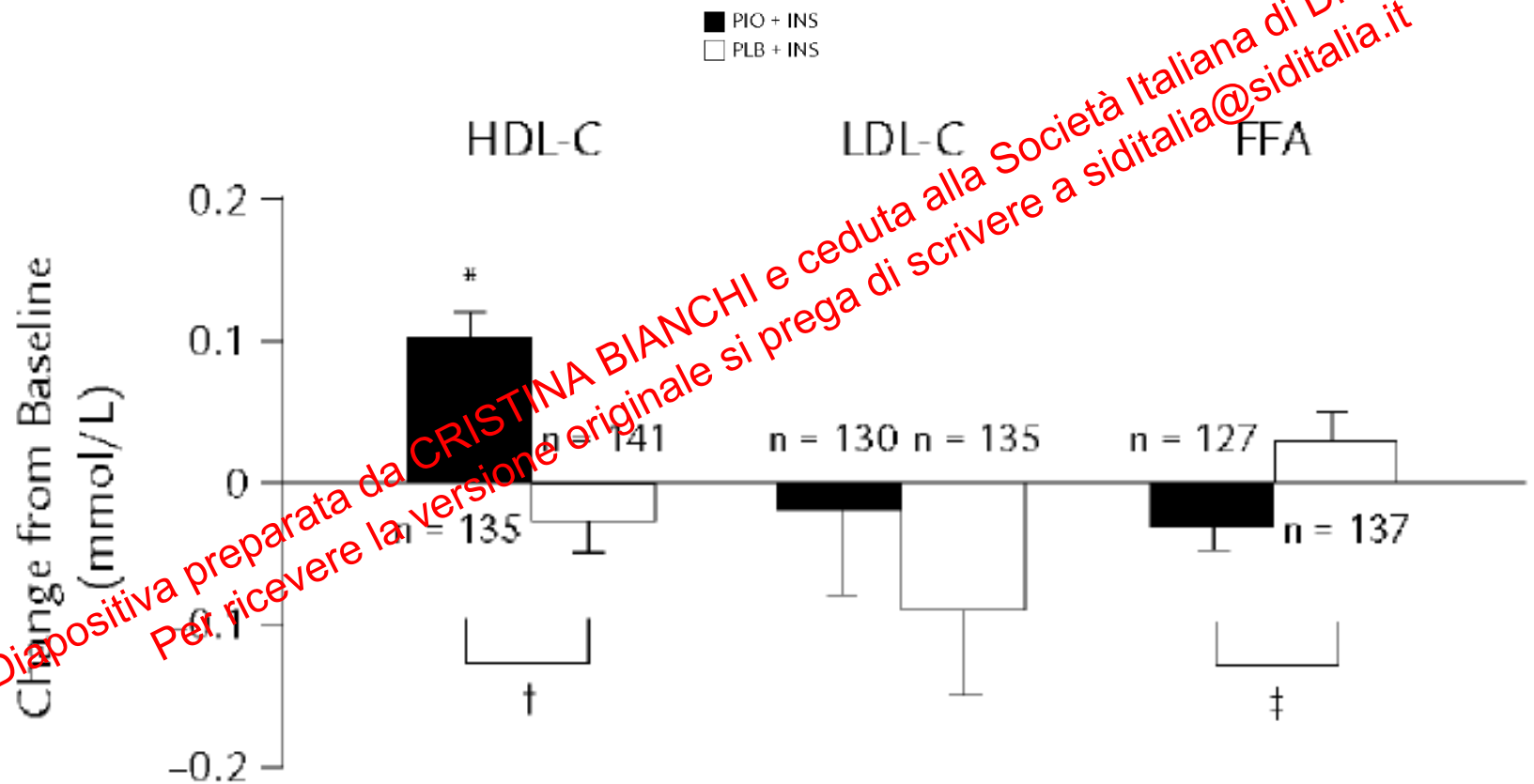
Pioglitazone add-on to insulin therapy in patients with type 2 Diabetes

289 type 2 diabetic patients inadequately controlled with insulin; follow-up: 6 months



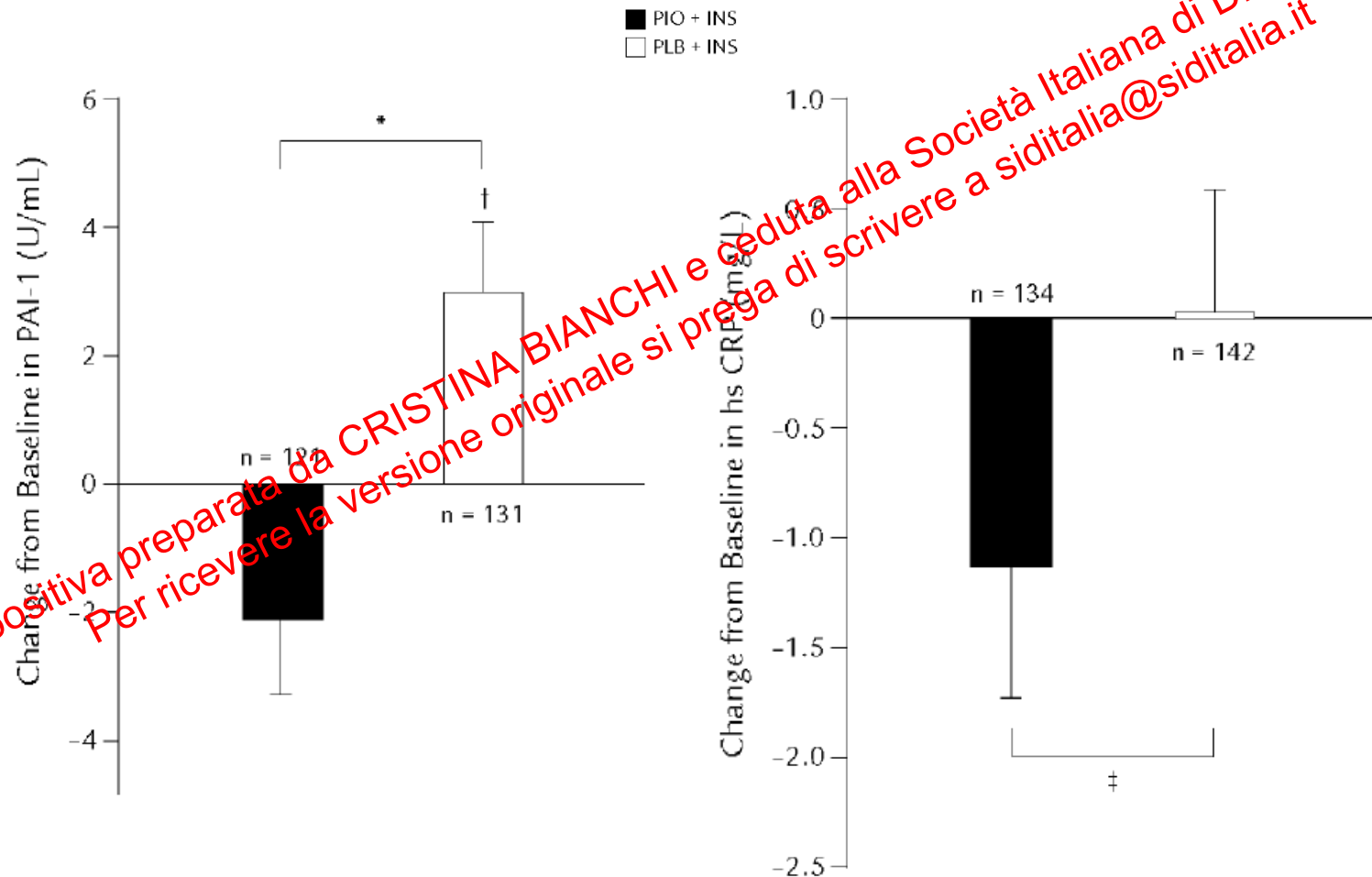
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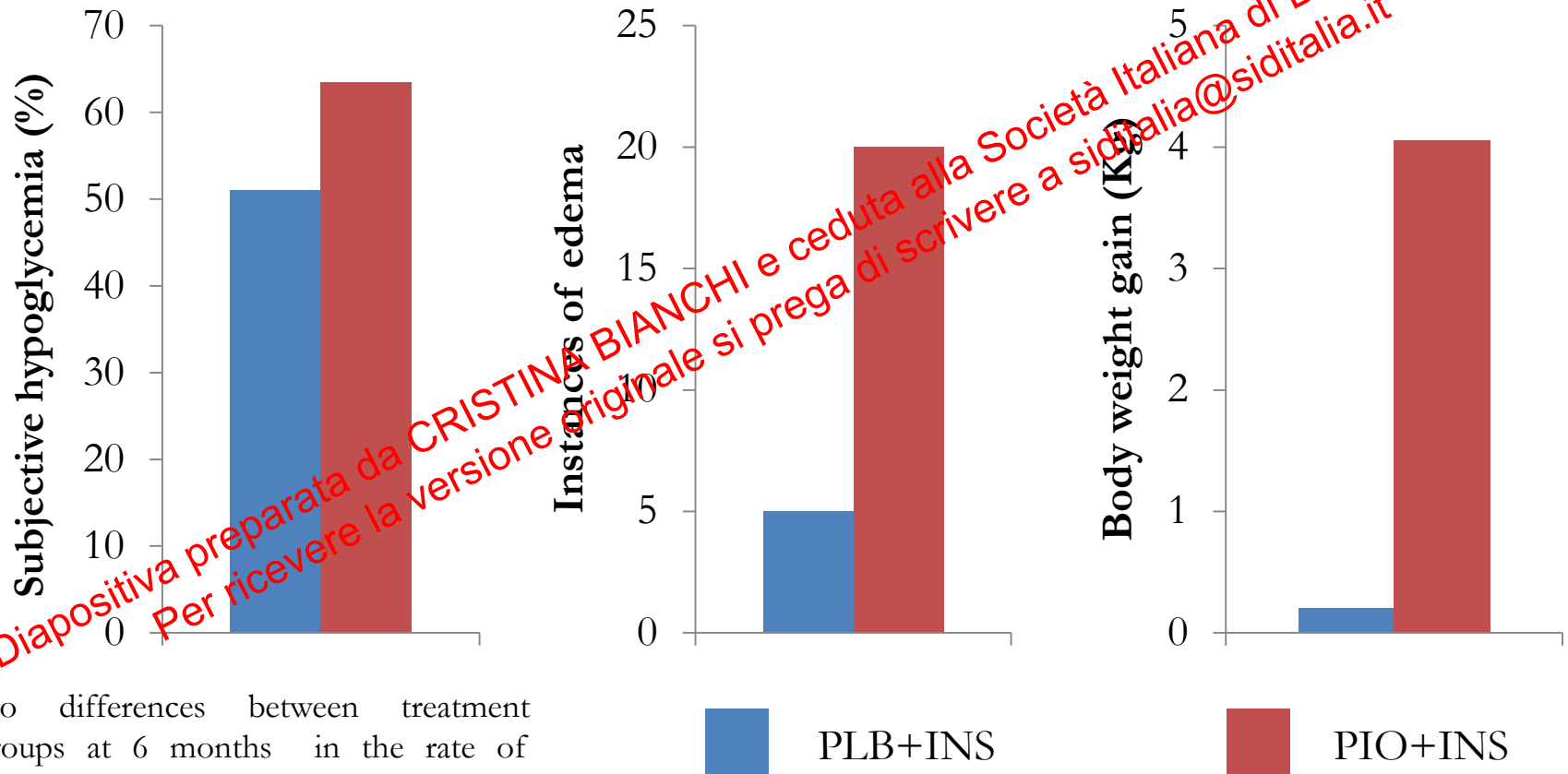
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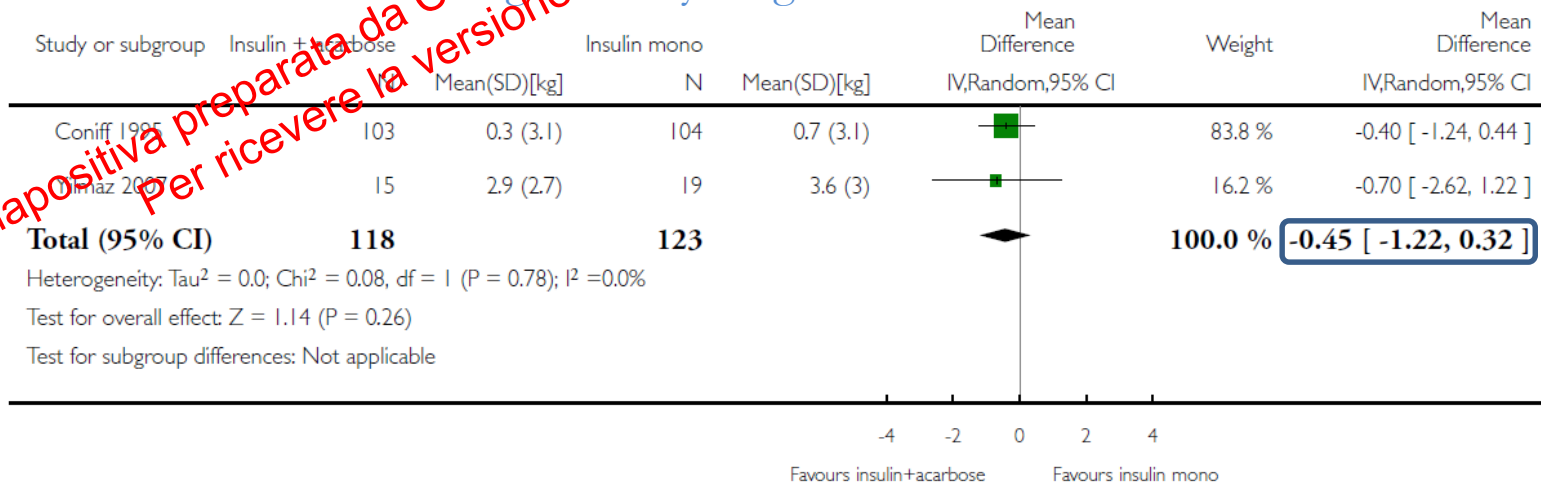
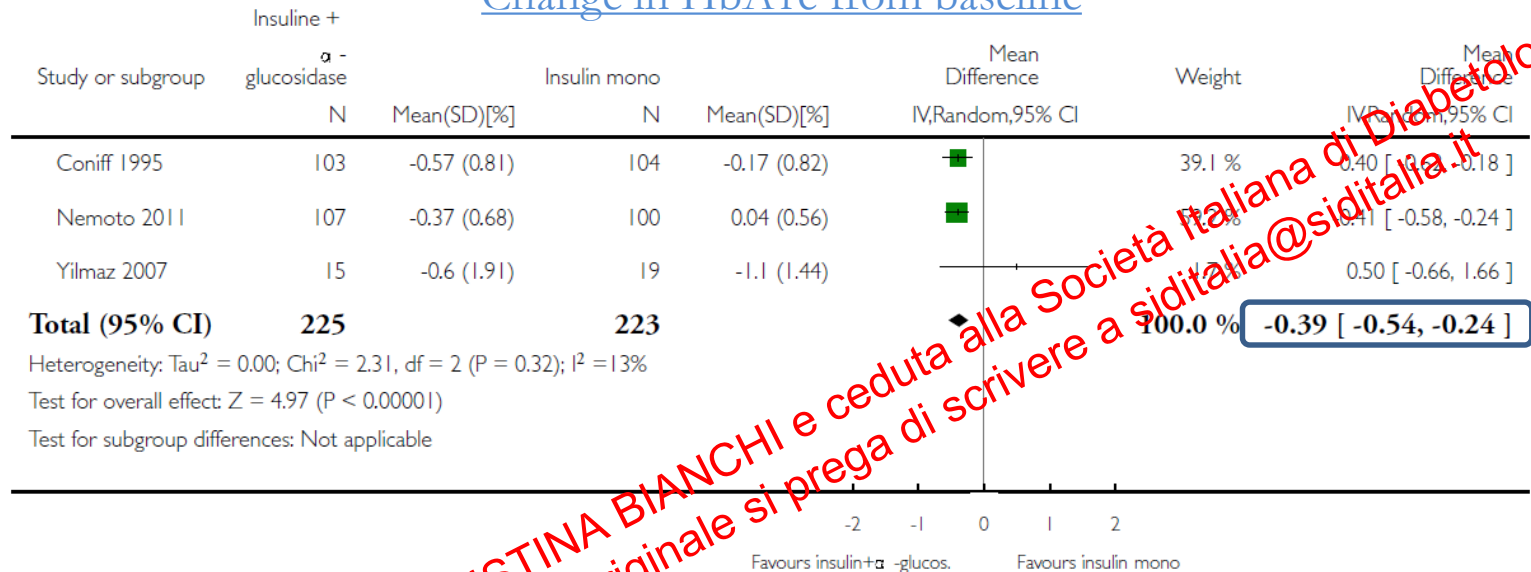


No differences between treatment groups at 6 months in the rate of hypoglycemic episodes per 30 days or the number of clinical hypoglycemic episodes (blood glucose <2.8 mmol/L).

Insulin monotherapy *vs.* insulin plus acarbose

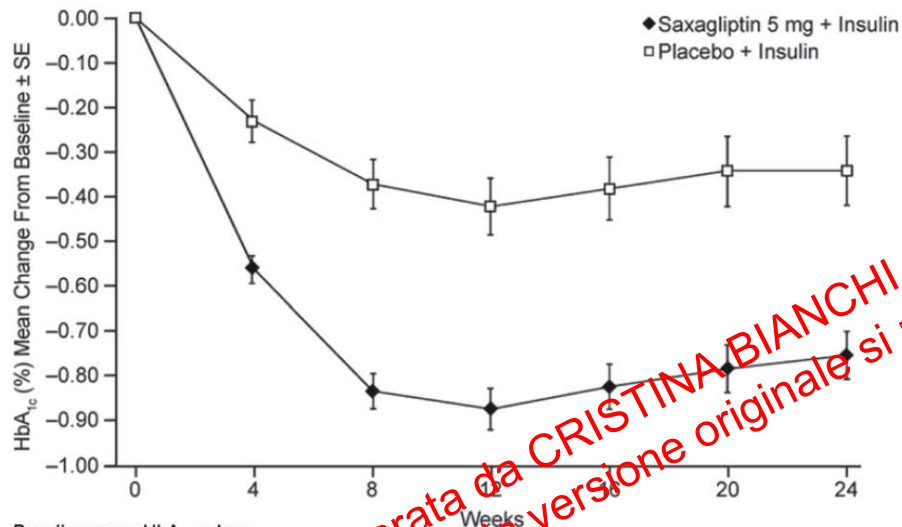
- *Cochrane meta-analysis* -

Change in HbA1c from baseline

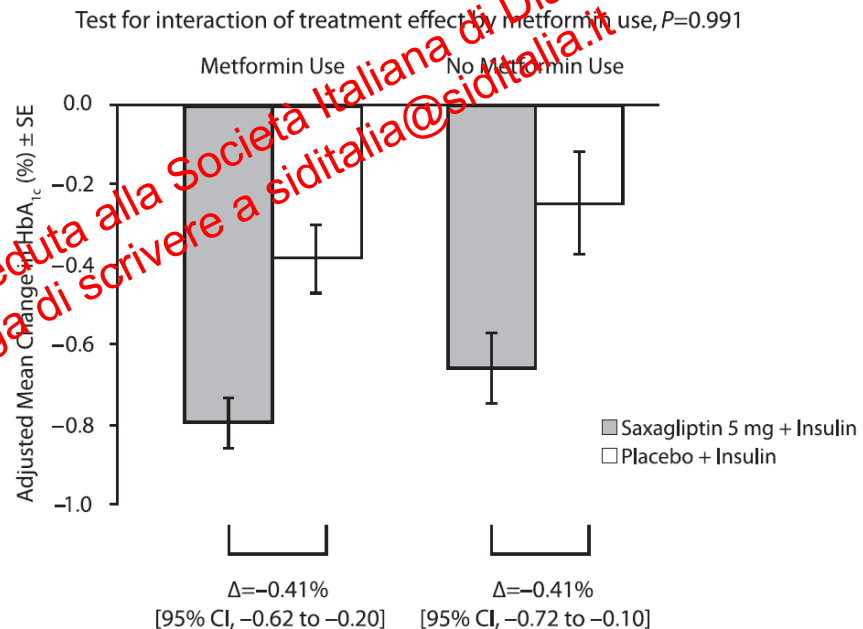


Saxagliptin added to insulin therapy in patients with type 2 diabetes

455 type 2 diabetic subjects using insulin $\pm$ metformin



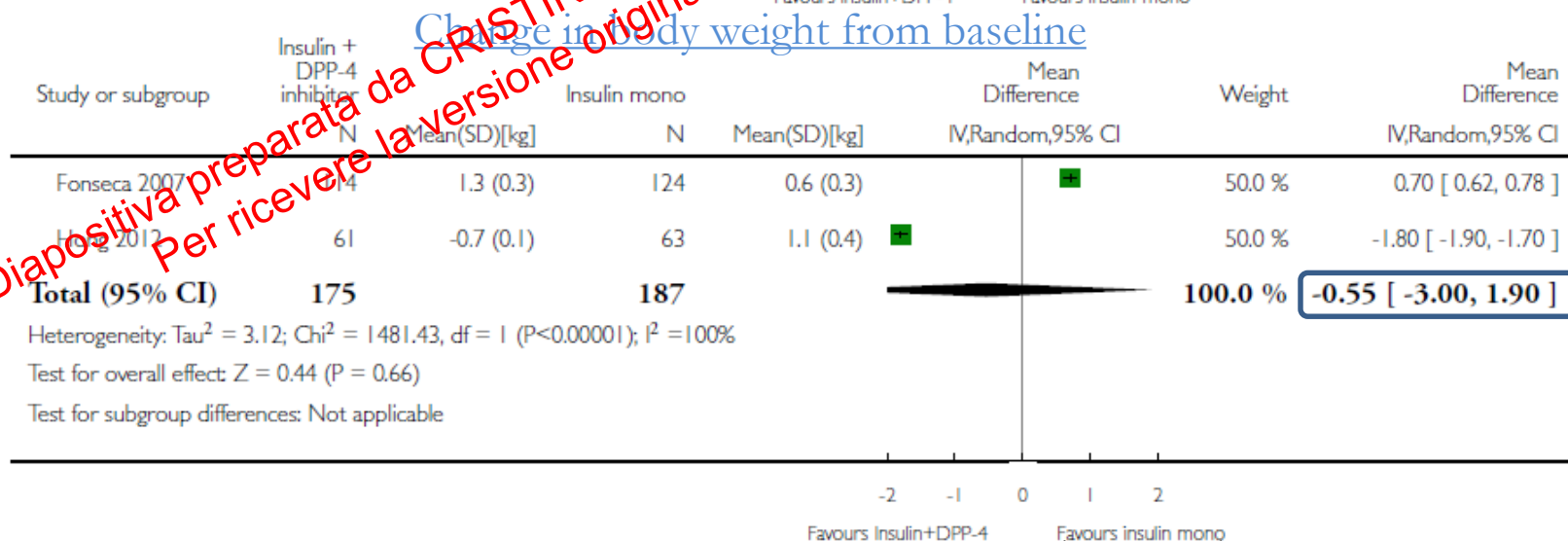
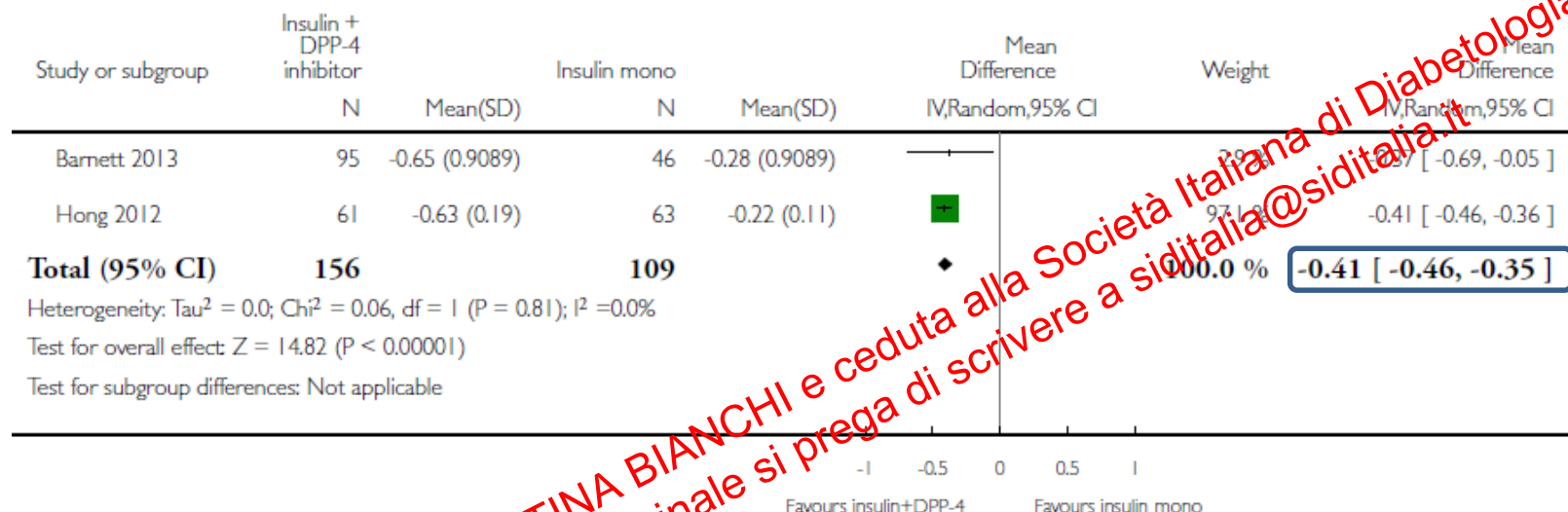
Baseline mean HbA_{1c} values
Saxagliptin: 8.67% (n=304)
Placebo: 8.64% (n=151)



- At 24 weeks, the mean increase in total daily insulin dose was smaller for the saxagliptin group than for the placebo group (difference: -3.3 U/day [95% CI: -5.6, -1.1]).
- Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo.
- Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively (confirmed hypoglycemia: 5.3%, 3.3%).

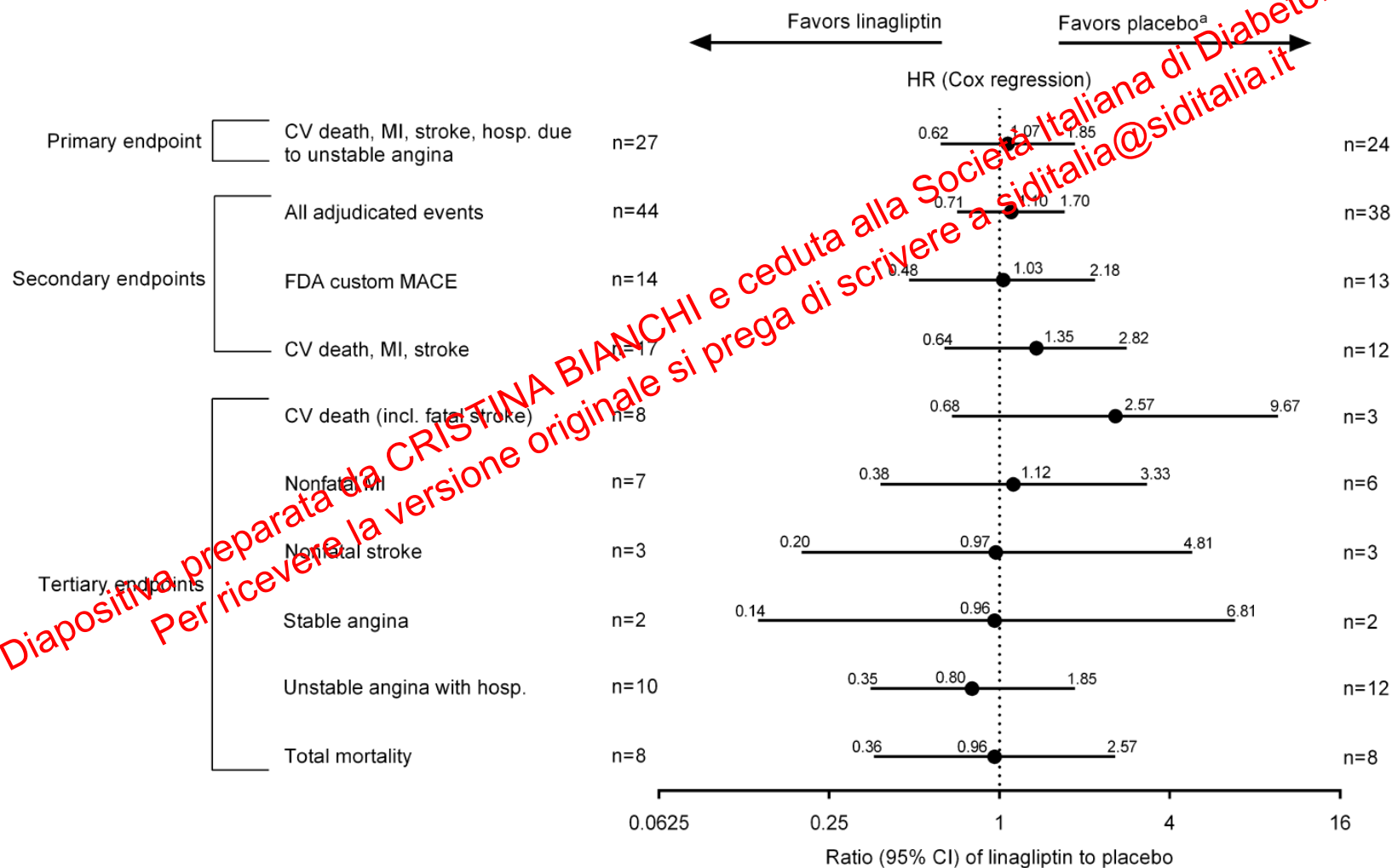
Insulin monotherapy *vs.* insulin plus DPP4-I

Cochrane meta-analysis - Change in HbA1c from baseline

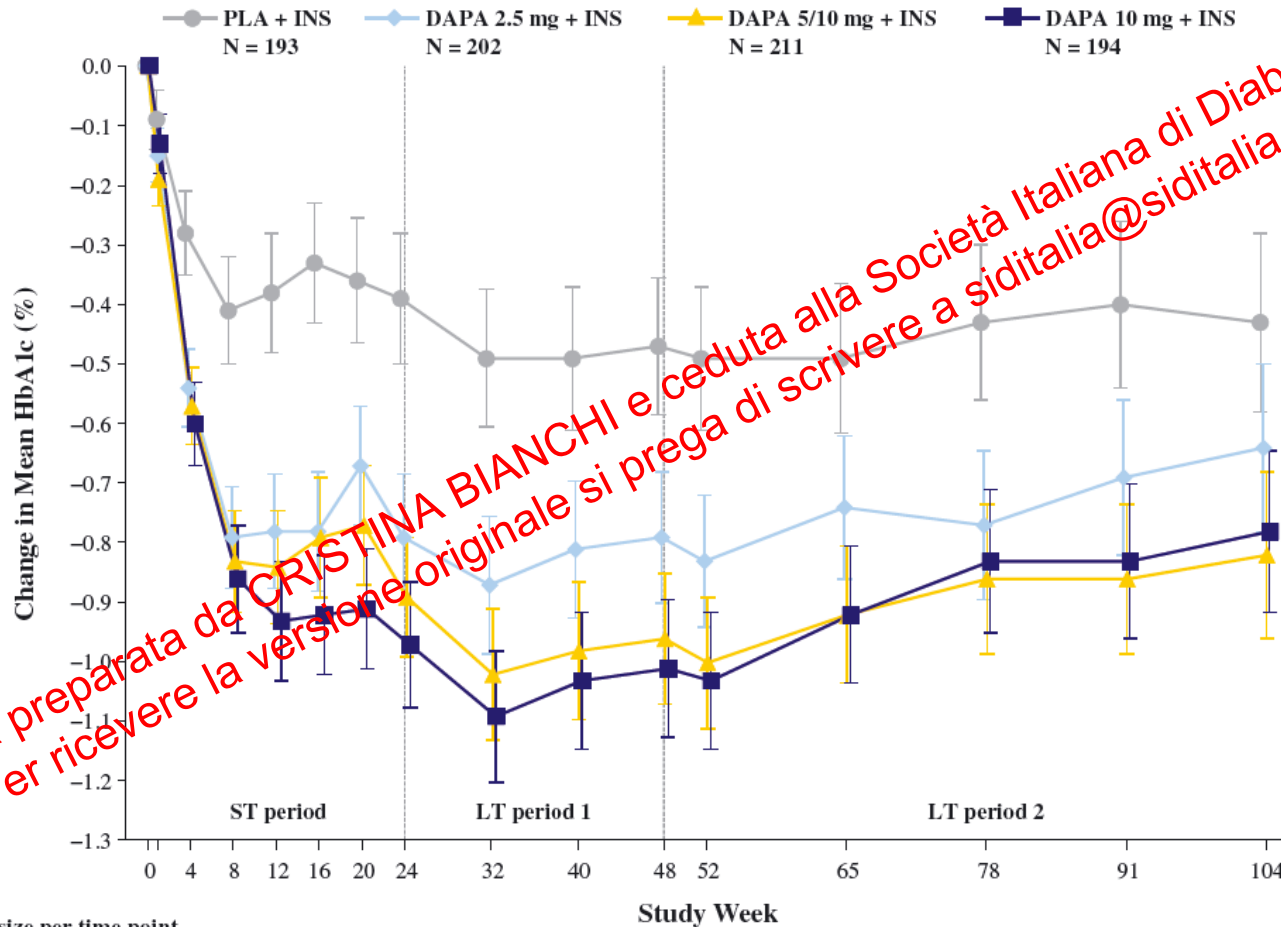


Cardiovascular safety of Linagliptin as add-on to Insulin in Type 2 Diabetes

- A Post-Hoc Analysis -



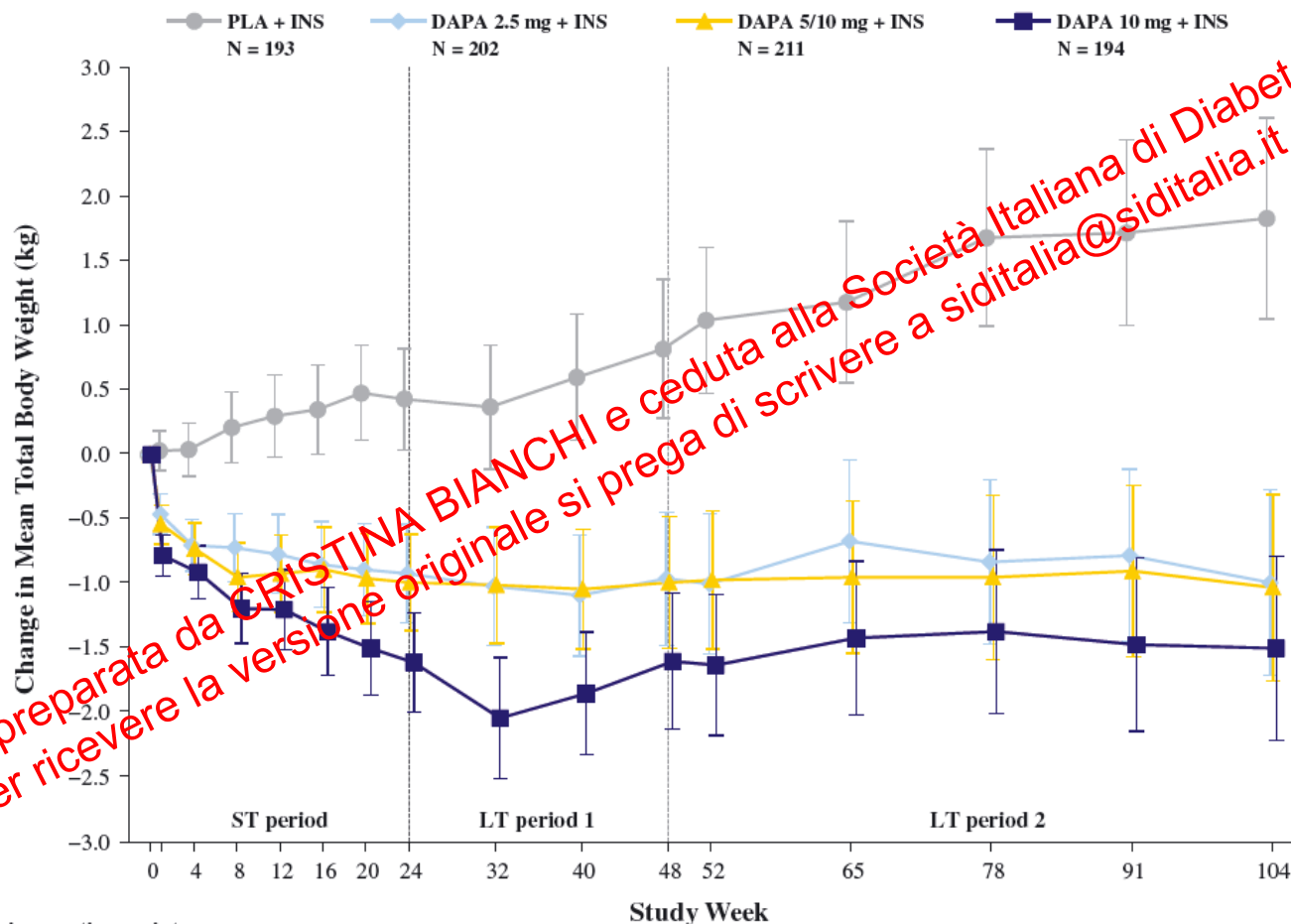
Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: change in HbA1c



Sample size per time point

PLA + INS	193	183	173	169	167	164	166	163	159	157	122	116	114	109	107
DAPA 2.5 mg + INS	202	198	190	187	185	181	179	175	176	172	147	142	140	136	132
DAPA 5/10 mg + INS	211	201	195	191	187	187	185	184	180	173	150	143	133	131	128
DAPA 10 mg + INS	193	188	184	183	179	176	173	175	173	164	148	145	144	140	139

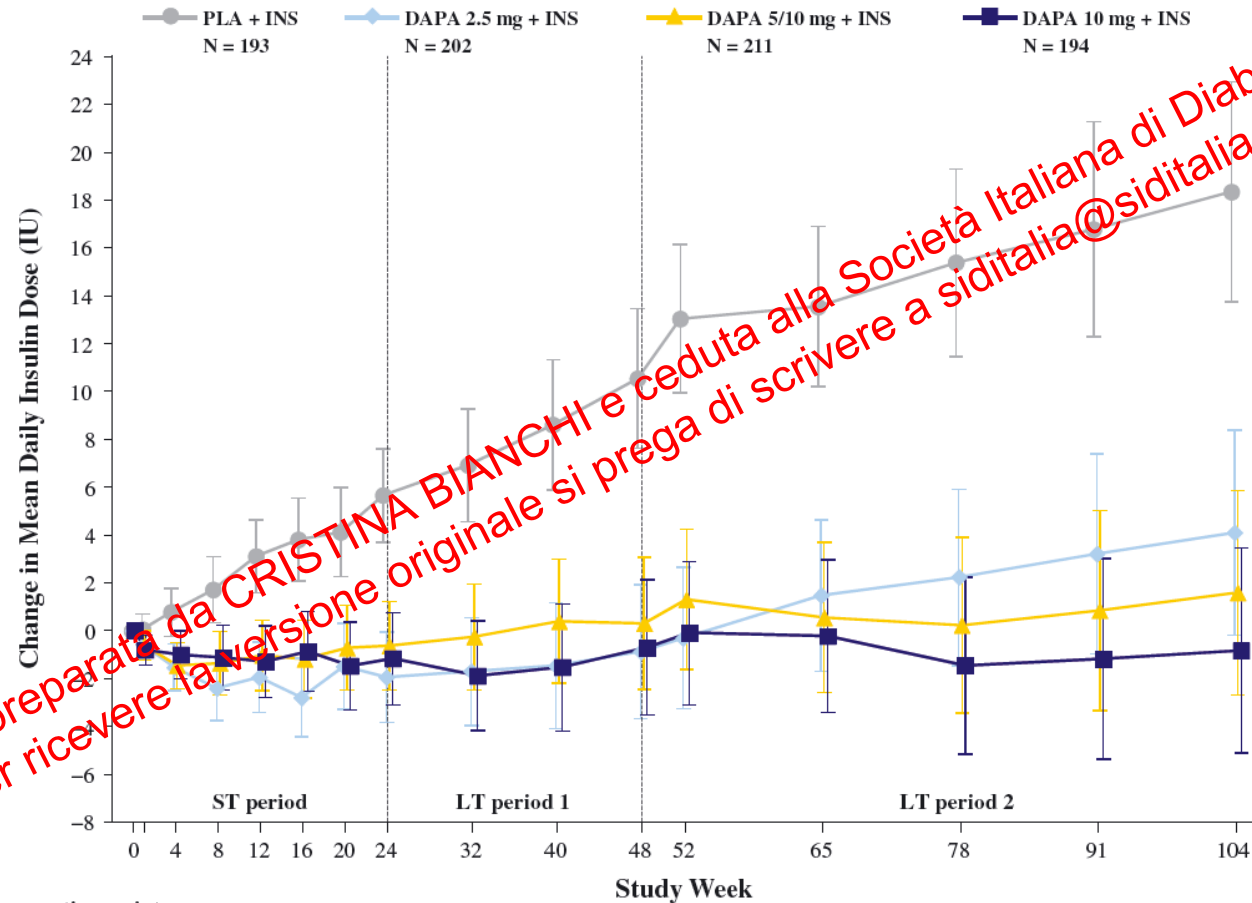
Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: change in body weight



Sample size per time point, n

PLA + INS	193	185	175	170	170	165	168	164	158	157	122	118	114	110	107
DAPA 2.5 mg + INS	202	198	191	188	188	182	180	176	176	174	147	142	140	136	132
DAPA 5/10 mg + INS	211	201	196	193	190	188	187	184	181	174	150	143	134	132	128
DAPA 10 mg + INS	193	190	186	183	180	178	177	176	174	166	148	146	144	142	141

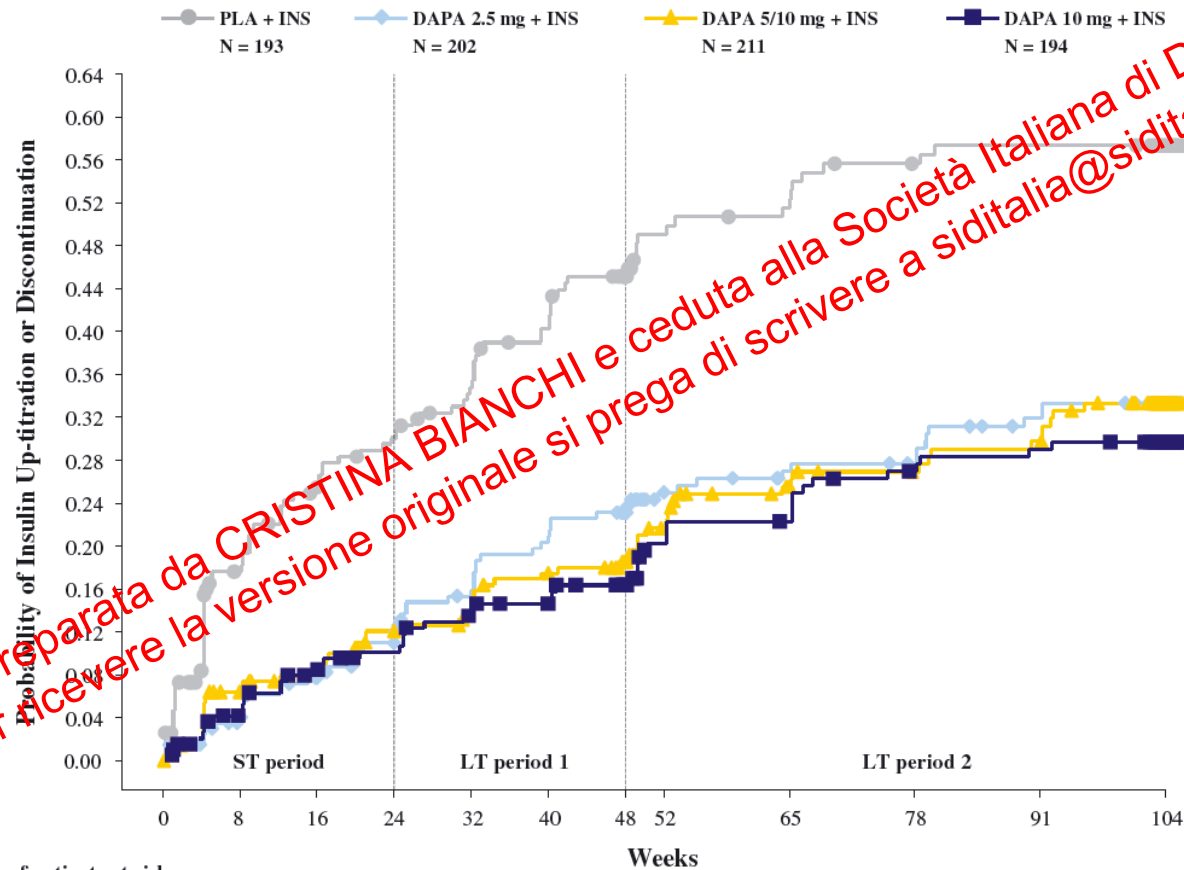
Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: change in daily insulin dose



Sample size per time point, n

PLA + INS	191	185	176	171	170	165	168	164	158	157	121	118	114	110	104
DAPA 2.5 mg + INS	200	197	189	187	186	181	180	174	176	173	144	142	140	136	130
DAPA 5/10 mg + INS	209	202	194	194	190	188	187	183	181	172	147	142	134	132	128
DAPA 10 mg + INS	194	189	185	183	180	178	177	175	173	166	145	146	144	142	140

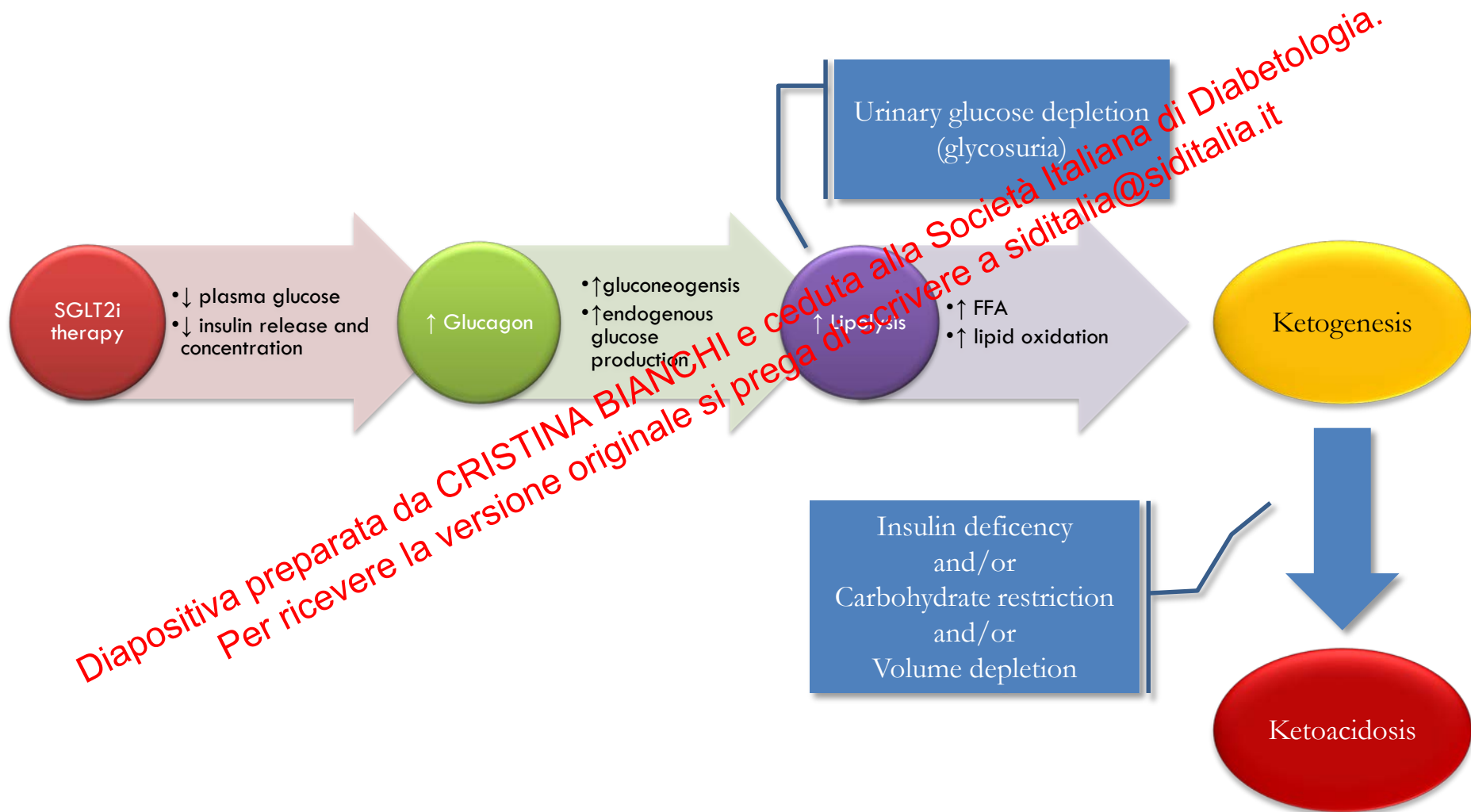
Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: probability of insulin up-titration or discontinuation



Number of patients at risk, n

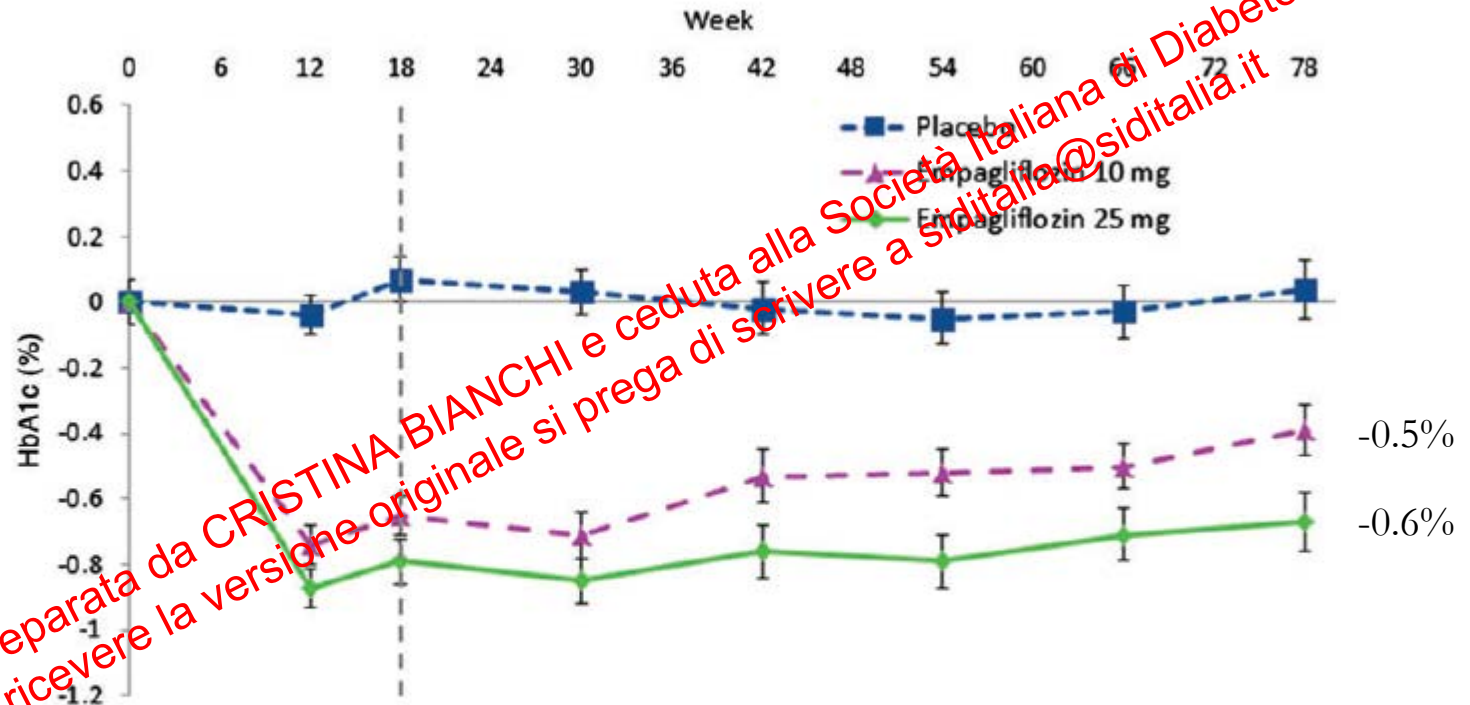
PLA + INS	193	148	131	121	109	98	82	63	59	52	50	37
DAPA 2.5 mg + INS	202	185	174	165	152	143	133	114	107	104	95	59
DAPA 5/10 mg + INS	211	186	178	167	162	153	144	123	110	103	99	60
DAPA 10 mg + INS	194	179	168	161	153	149	139	120	116	107	104	70

SGLT2i & Euglycemic Diabetic Ketoacidosis



Empagliflozin in insulin treated type 2 diabetes

494 type 2 diabetic subjects on basal insulin (glargine, detemir, NPH) – follow-up: 78 weeks

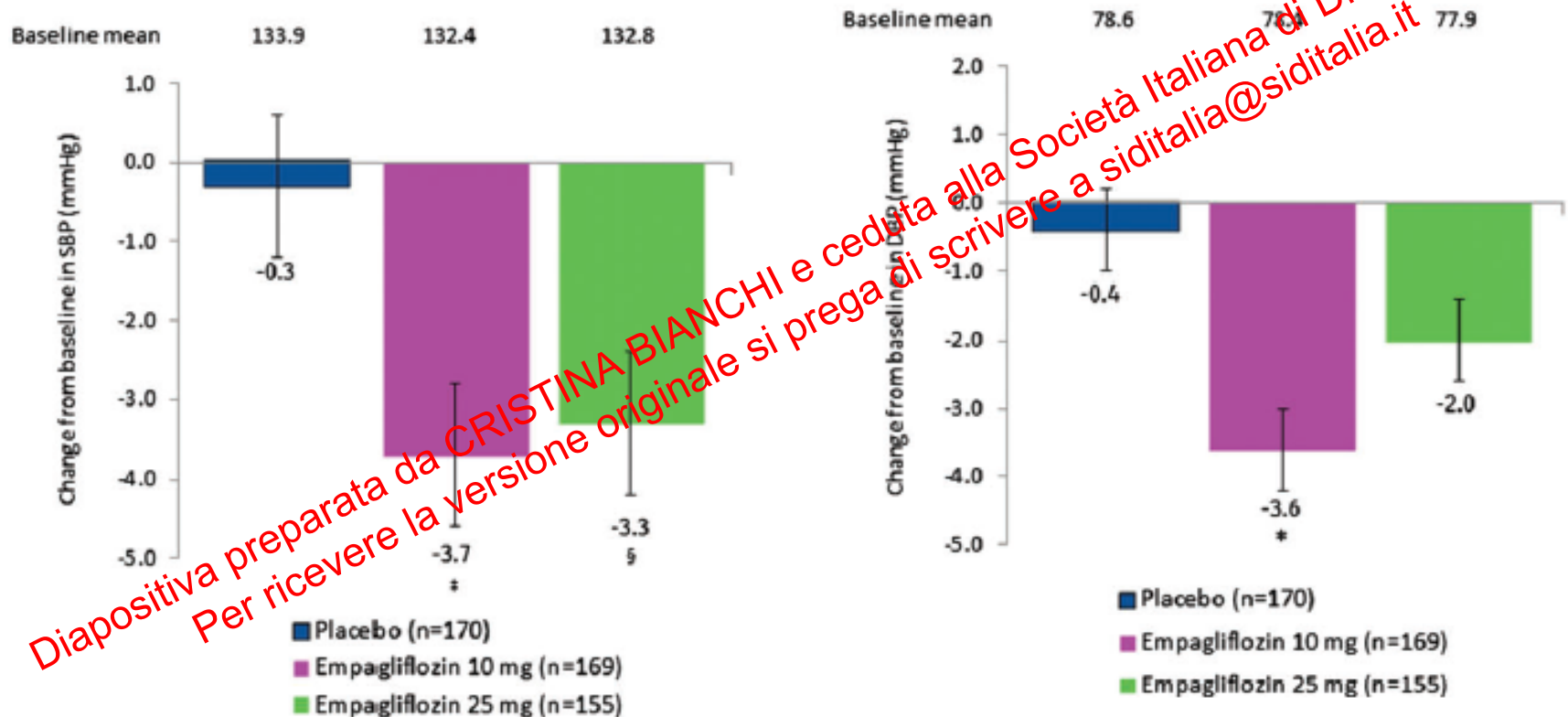


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Number of analysed patients	Placebo	156	129	141	132	119	113	105	98
	Empagliflozin 10 mg	160	132	148	137	123	121	115	114
	Empagliflozin 25 mg	137	120	123	114	110	107	98	96

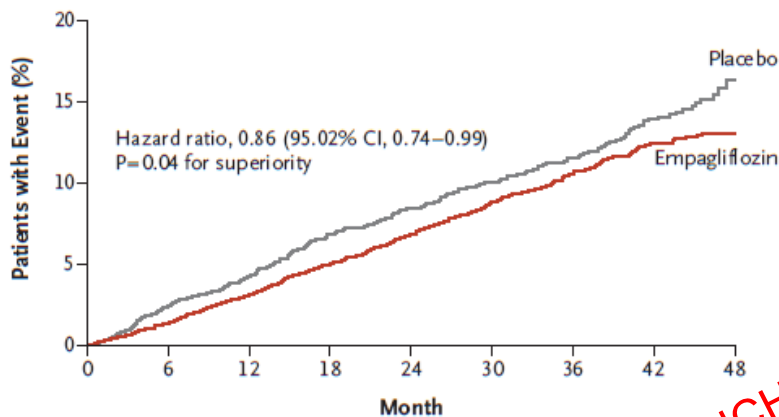
Empagliflozin in insulin treated type 2 diabetes: change in Blood Pressure

494 type 2 diabetic subjects on basal insulin (glargine, detemir, NPH) – follow-up: 18 weeks



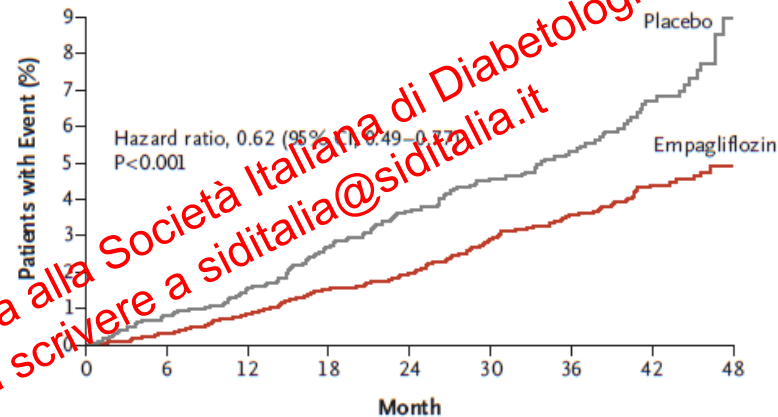
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Primary Outcome

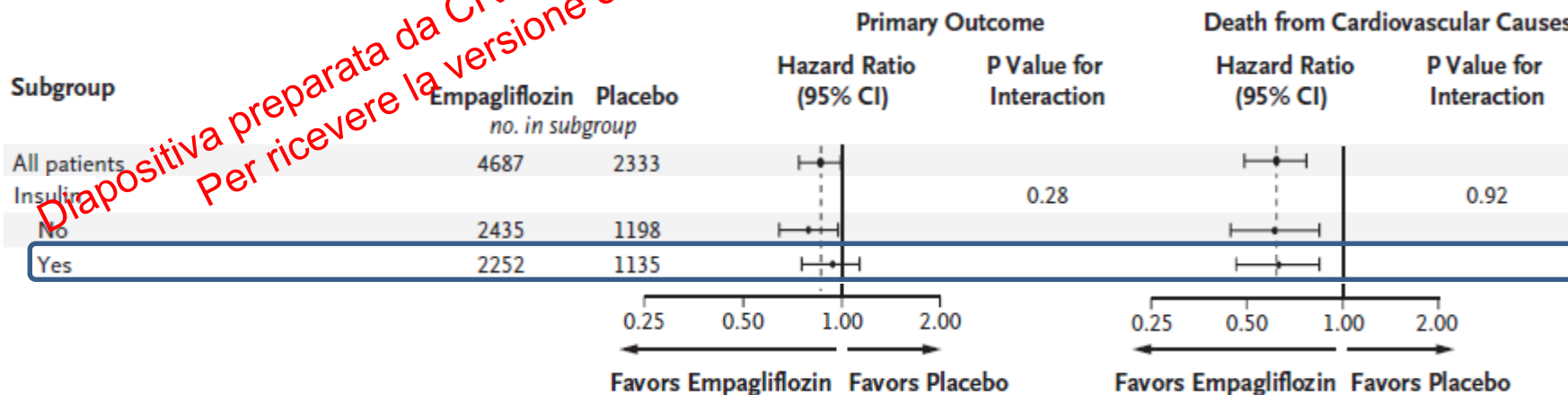


No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1604	876
Placebo	2333	2256	2194	2112	1875	1380	1004	741	466

Death from Cardiovascular Causes



No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177



Factors governing choice of oral agent to use in combination with basal insulin

Clinical factor	SU/Glinides	MET	Pioglitazone	Acarbose	DPP4-I	SGLT2-I
Efficacy	High	High	High	Low	Low	Moderate
Cost	Low	Low	Low	Low	High	High
Weight	Gain	Slight loss	Gain	Neutral	Neutral	Loss
Risk of Hypos	Increased	Low	Low	Low	Low	Low
Chronic kidney disease	Increased risk of Hypos	Caution if eGFR <30 ml/min/1.73 m ²	Increased risk of fluid retention	Not known	DPP4-I dose adjustment	Reduced efficacy
Heart failure	Not known	Neutral	Increased risk of HF	Not known	Increased risk (?)	Benefit
Cardiovascular disease/mortality	Increased with I-II generation	Benefit	Potential benefit	Neutral	Neutral	Benefit



Take-home messages (I)

- ✓ The addition of all oral glucose-lowering agents in people with type 2 diabetes and inadequate glycemic control who are on insulin therapy has positive effects on glycemic control and insulin requirements.
- ✓ Additional weight gain can only be avoided by adding metformin or a SGLT-2 inhibitor to insulin.
- ✓ The addition of sulphonylureas results in more hypoglycaemic events.
- ✓ The addition of pioglitazone results in more fluid retention and risk of heart failure.
- ✓ Other well-known adverse effects of oral glucose-lowering agents, as well as all proven or potential positive non-glycemic effects that may reduce cardiovascular risk, have to be taken into account when prescribing oral glucose-lowering agents in addition to insulin therapy.

Insulin in combination with oral glucose-lowering agents

Insulin in combination with oral glucose-lowering agents can be used at either of two stages:



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Antihyperglycemic therapy in type 2 diabetes: ADA general recommendations

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy**.

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy

Metformin

Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy

Metformin +

Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy

Metformin +

Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin*	or GLP-1-RA	or Insulin*	or GLP-1-RA
or Insulin*	or Insulin*		or Insulin*		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy

(See Figure 8.2)

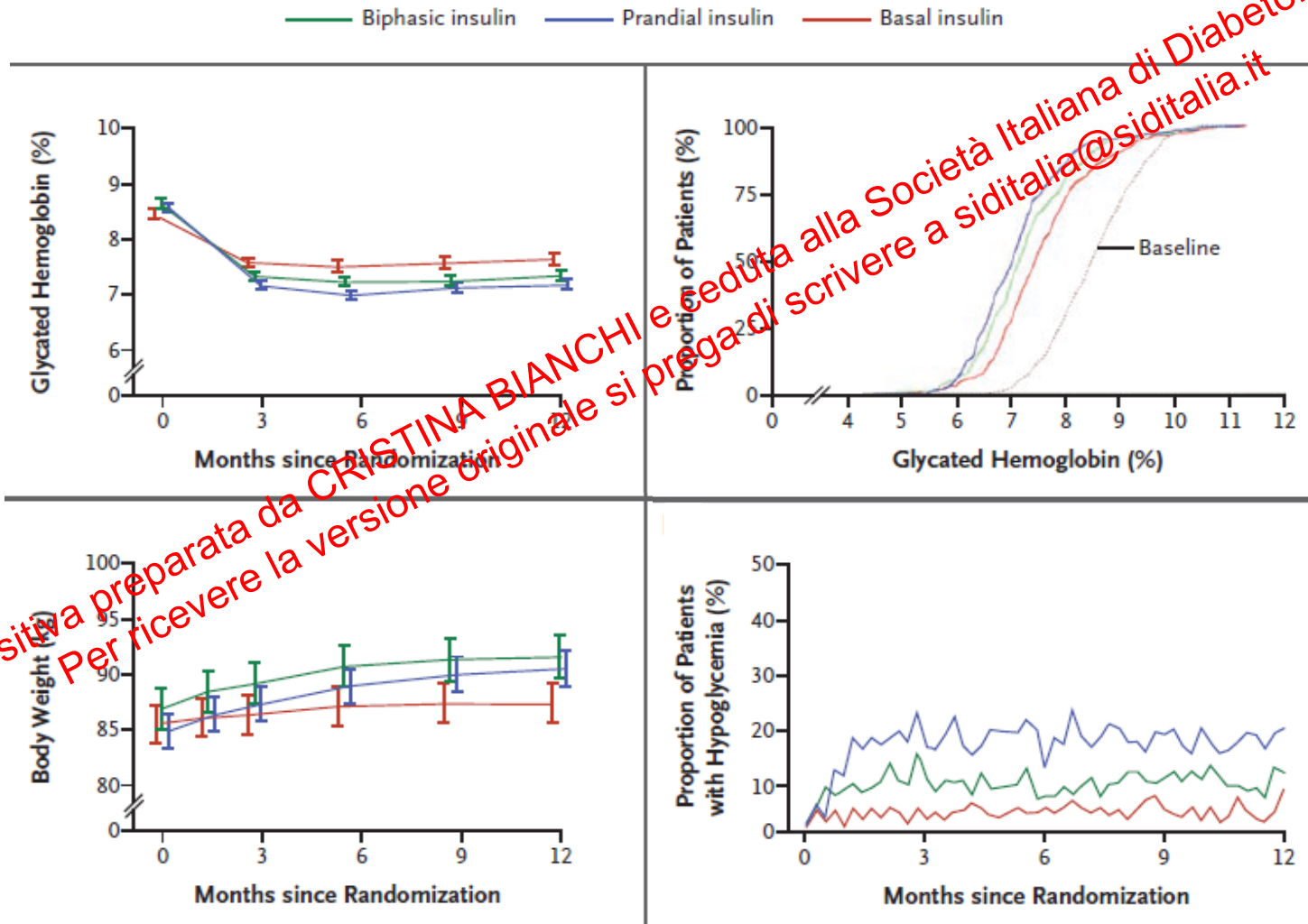
Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

-Treating to Target in Type 2 Diabetes (4-T) Study -

Characteristic	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	All Patients (N=708)
Demographic				
Male sex — no. (%)	159 (67.7)	152 (63.6)	143 (61.1)	454 (64.1)
Age — yr	61.7±8.9	61.6±10.5	61.9±10.0	61.7±9.8
Duration of diabetes — yr				
Median	9	9	9	9
Interquartile range	6–12	6–14	6–12	6–13
Clinical				
Use of oral antidiabetic medication — no.				
Metformin only	4	0	2	6
Sulfonylurea only	10	12	8	30
Both metformin and sulfonylurea	221	227	224	672

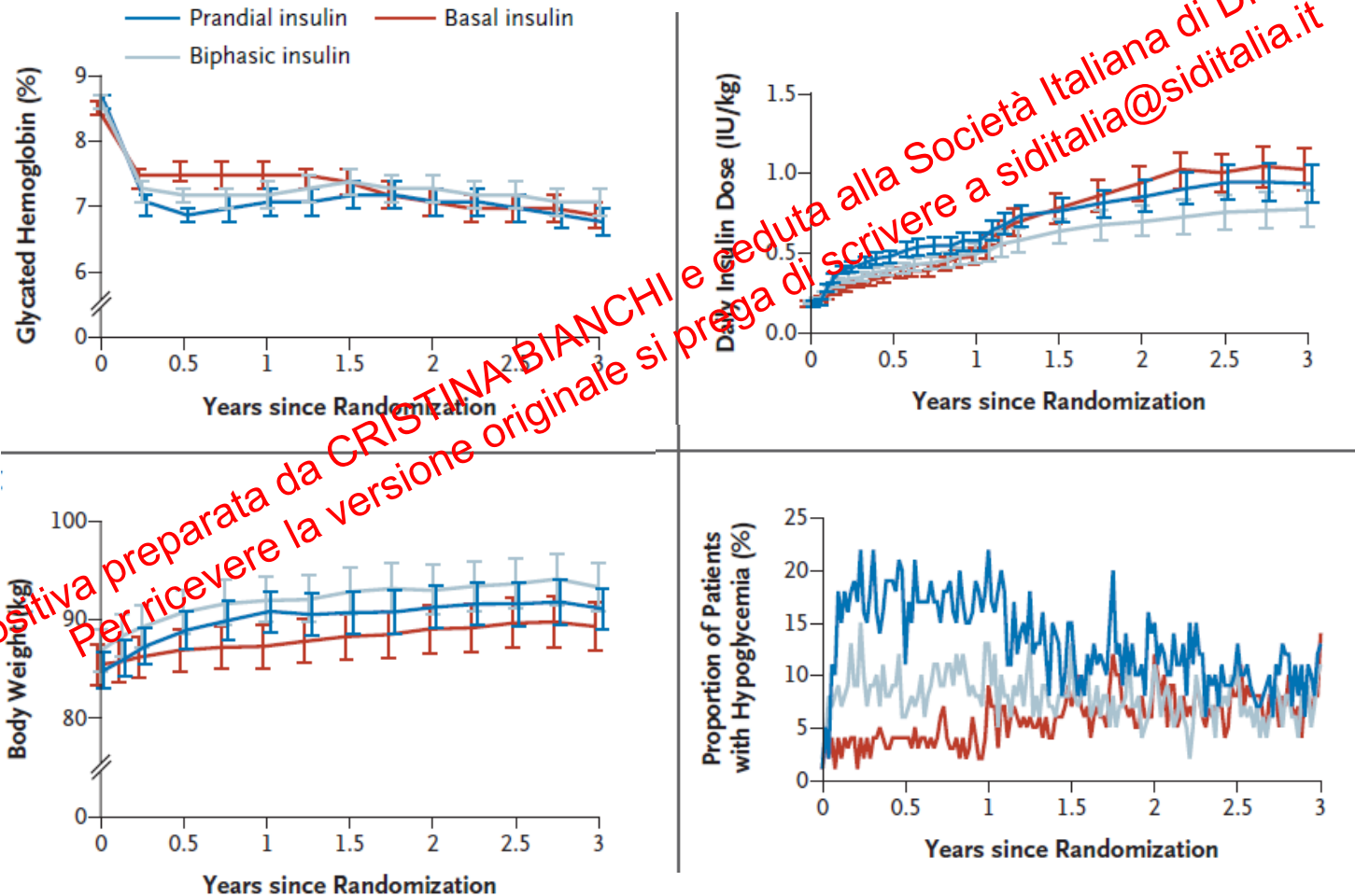
Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

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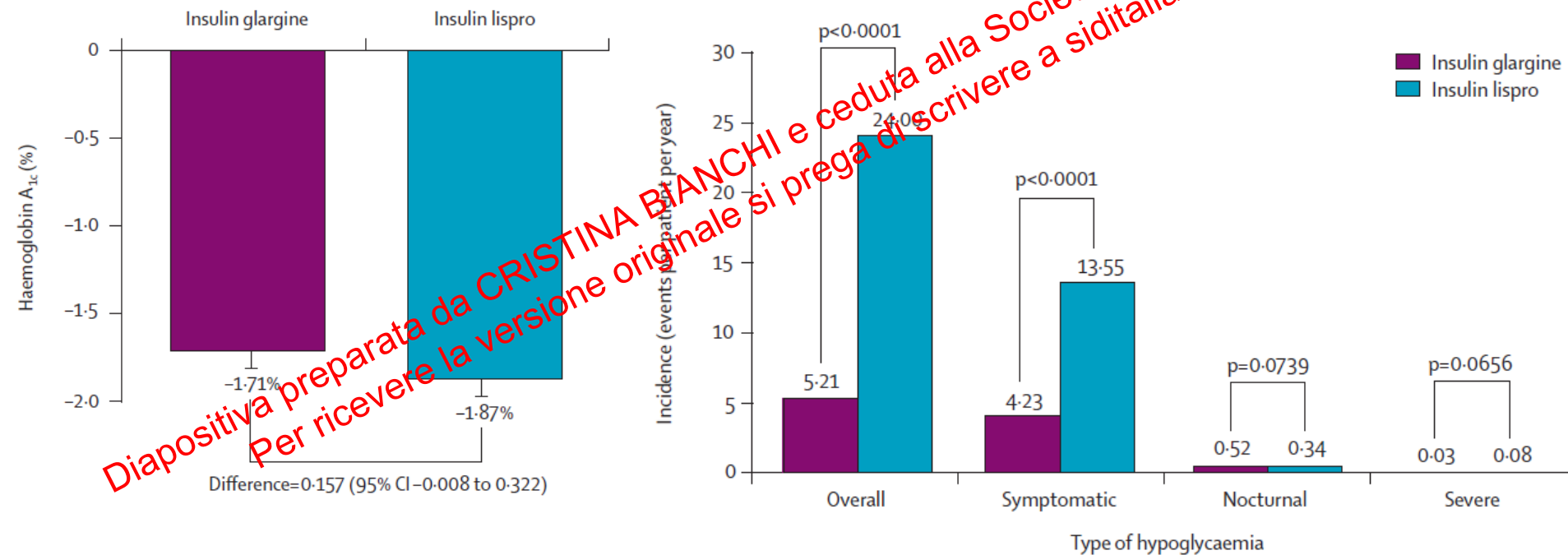
Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

-Treating to Target in Type 2 Diabetes (4-T) Study -



Basal Insulin *vs.* Prandial Insulin in type 2 Diabetes on oral hypoglycaemic agents - *APOLLO Study* -

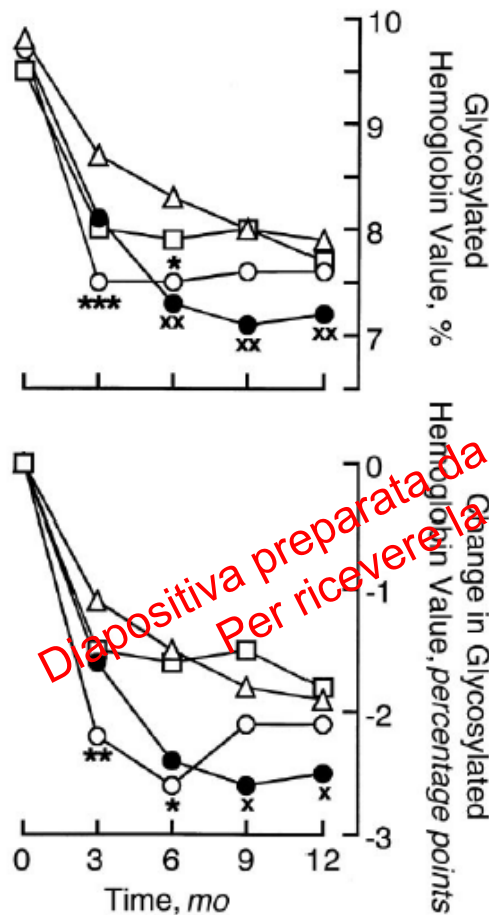
418 patients with type 2 diabetes; follow-up: 44 weeks



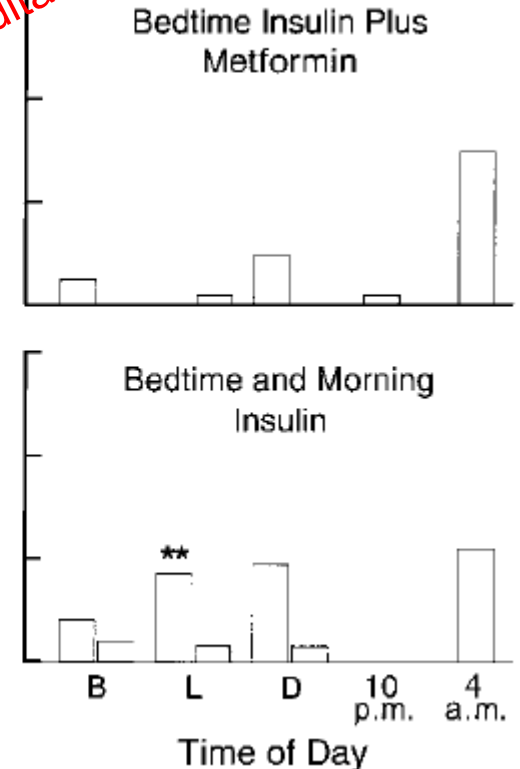
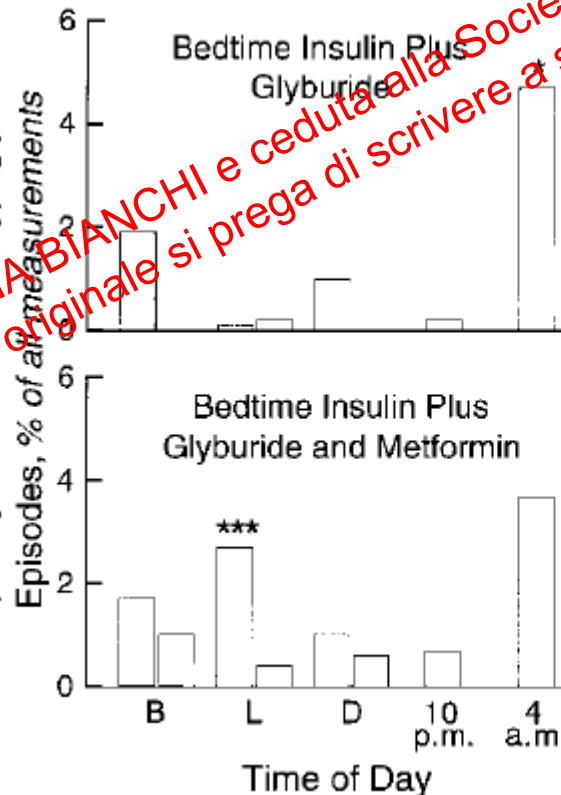
Combination therapy with bed-time insulin and oral hypoglycemic agents in type 2 Diabetes

96 patients poorly controlled with sulfonylurea therapy (mean HbA1c 9.9%)

● Bed-time insulin+metformin □ Bed-time insulin+glyburide ○ Bed-time insulin+both oral agents △ Bed-time+morning insulin



Frequency of Biochemical Hypoglycemic Episodes, % of all measurements



Continuation *vs.* discontinuation of secretagogues when initiating insulin

964 patients with type 2 diabetes - combination of metformin and/or secretagogues with basal insulin

	Continuation (<i>n</i> = 498)	Discontinuation (<i>n</i> = 367)	p value
Glycaemic control			
Reduction in HbA1c level from baseline to week 12 (%)	-1.53 ± 0.92	-1.05 ± 1.04	<0.001
Reduction in HbA1c level from baseline to study endpoint (%)	-1.59 ± 1.08	-1.30 ± 1.14	0.382
Patients attaining HbA1c < 7% at study endpoint	208 (41.6)	156 (42.5)	0.705
Reduction in fasting PG from baseline to study endpoint (mmol/l)	-2.7 ± 2.7	-3.2 ± 2.4	0.589
Reduction in predinner PG from baseline to study endpoint (mmol/l)	-2.5 ± 3.2	-1.6 ± 3.4	<0.001
Hypoglycaemia*			
Patients with at least one hypoglycaemic event during the study	199 (40.0)	90 (24.5)	<0.001
Hypoglycaemia event rate per patient-year	3.2 ± 7.6	1.6 ± 5.1	<0.001
Patients attaining HbA1c < 7% at study endpoint without hypoglycaemia* during the study	99 (19.9)	97 (26.4)	0.018
Daily insulin dose			
Units	52.5 ± 39.8	67.0 ± 44.8	<0.001
Units per kg	0.6 ± 0.4	0.8 ± 0.4	<0.001
Weight gain (kg)	1.44 ± 3.04	0.43 ± 3.00	<0.001

Data are mean ± standard deviation or *n* (%). PG, plasma glucose.

*Hypoglycaemia was defined as symptomatic hypoglycaemia confirmed by a home plasma glucose measurement ≤ 3.1 mmol/l.

Sulfonylurea+Insulin vs. Metformin+Insulins: mortality rate

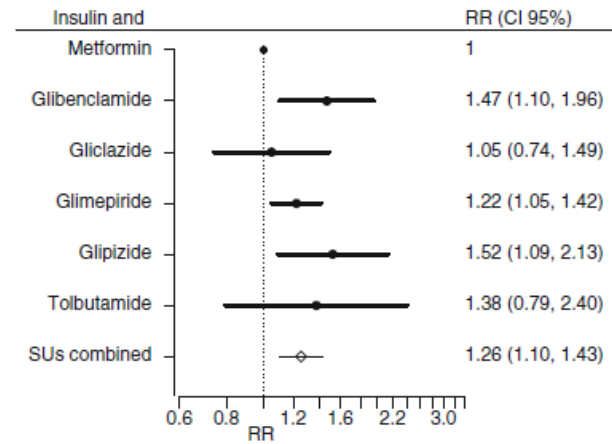
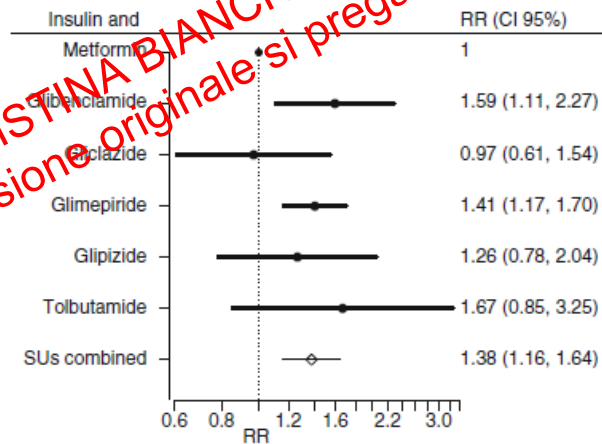
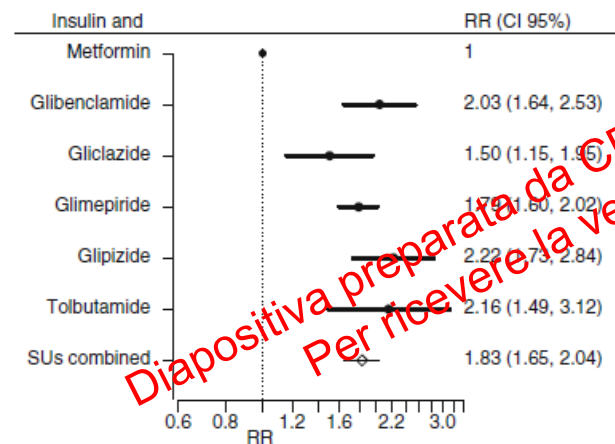
- *A retrospective Danish nationwide study* -

11,081 patients used SU + insulin and 16,910 used metformin + insulin
followed from 1 January 1997 to 31 December 2009

All cause-mortality

Cardiovascular death

Acute MI-Stroke-Cardiovascular death



Insulin in combination with oral drugs: some concerns

Initiating or intensifying insulin therapy is associated with some concerns about:

- Weight gain
- Hypoglycemia
- Complexity of regimens



Insulin in combination with oral drugs: some concerns

Initiating or intensifying insulin therapy is associated with some concerns about:

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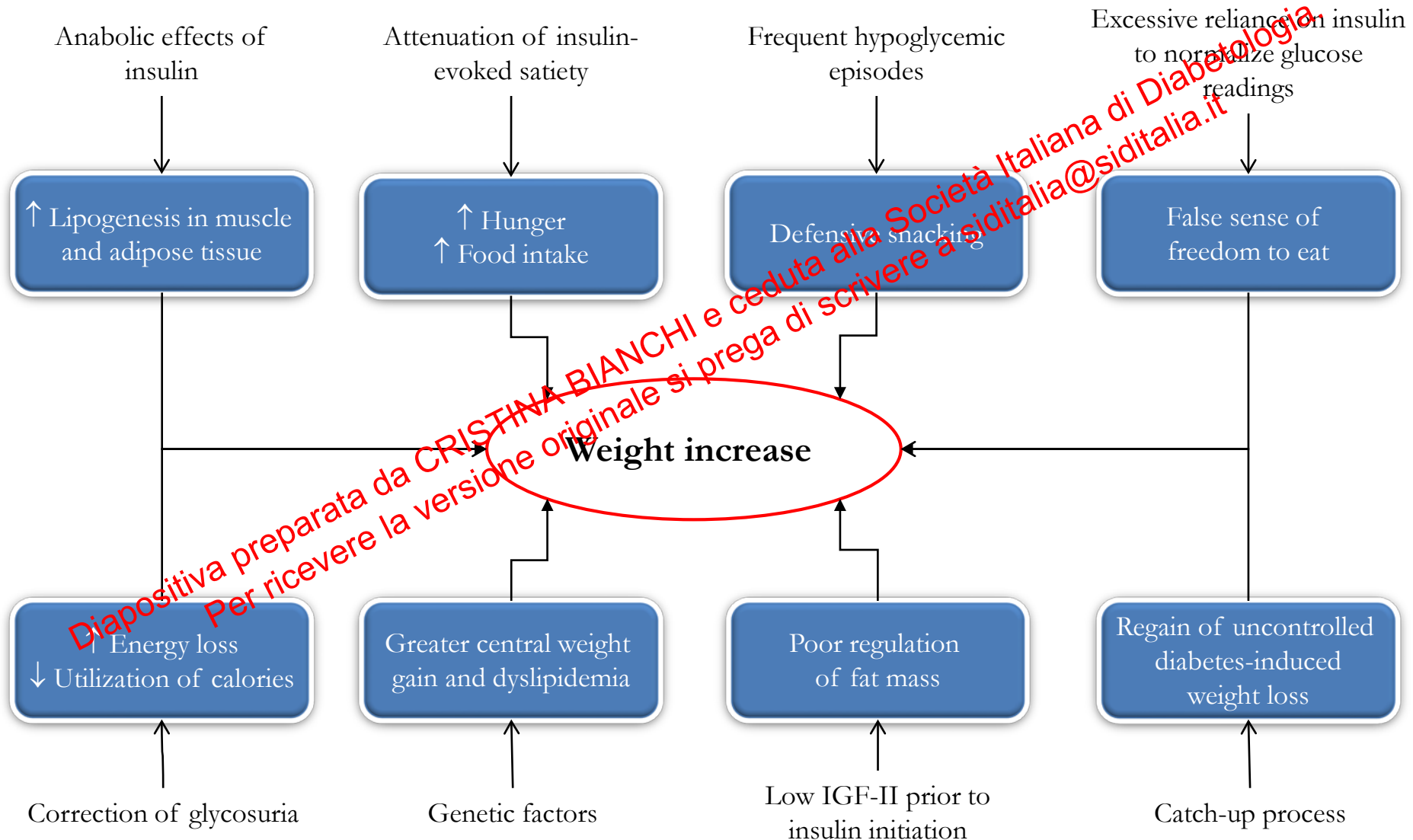
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- Complexity of regimens



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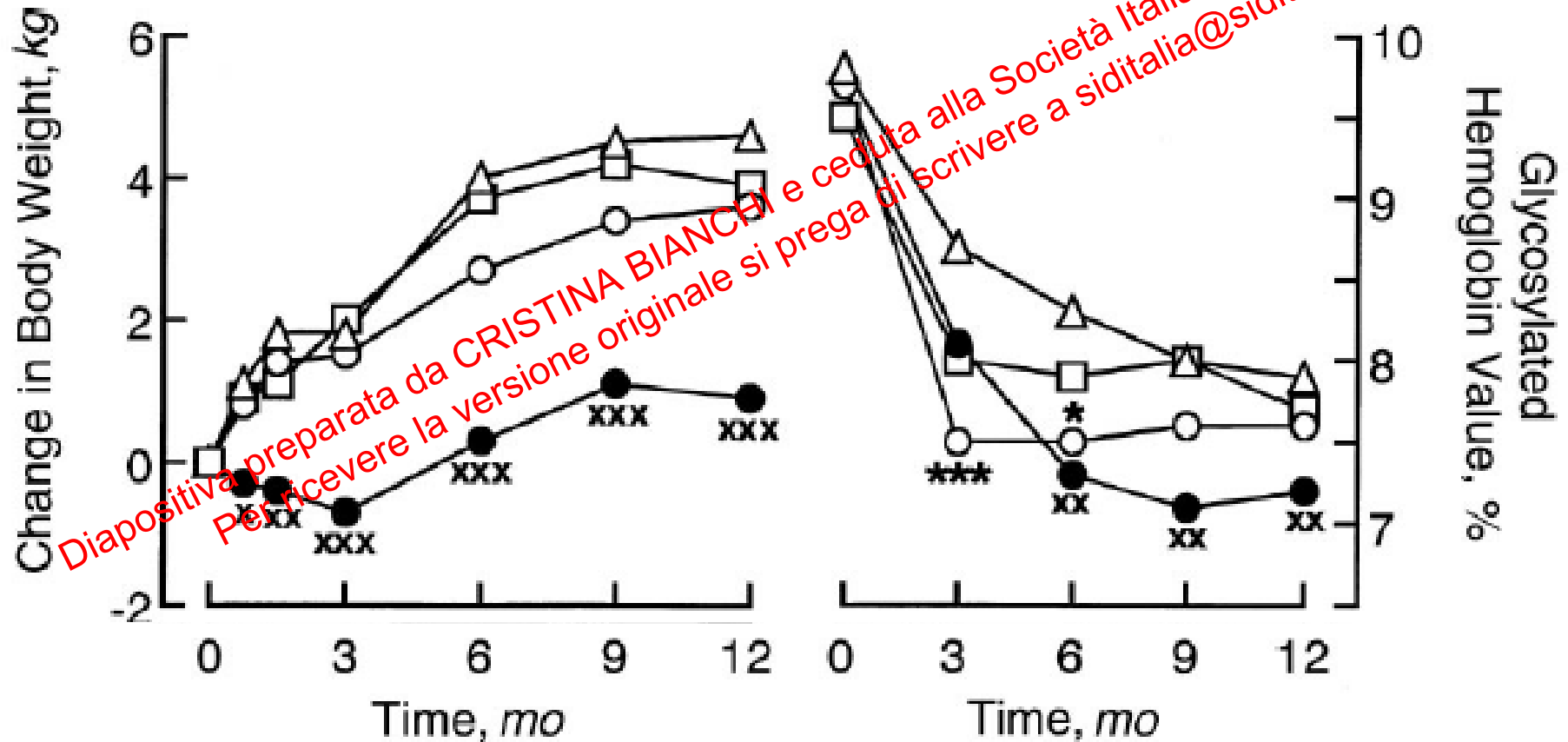
Factors explaining body weight increase in T2D on insulin treatment



Combination therapy with bed-time insulin and oral hypoglycemic agents in type 2 Diabetes

96 patients poorly controlled with sulfonylurea therapy (mean HbA1c 9.9%)

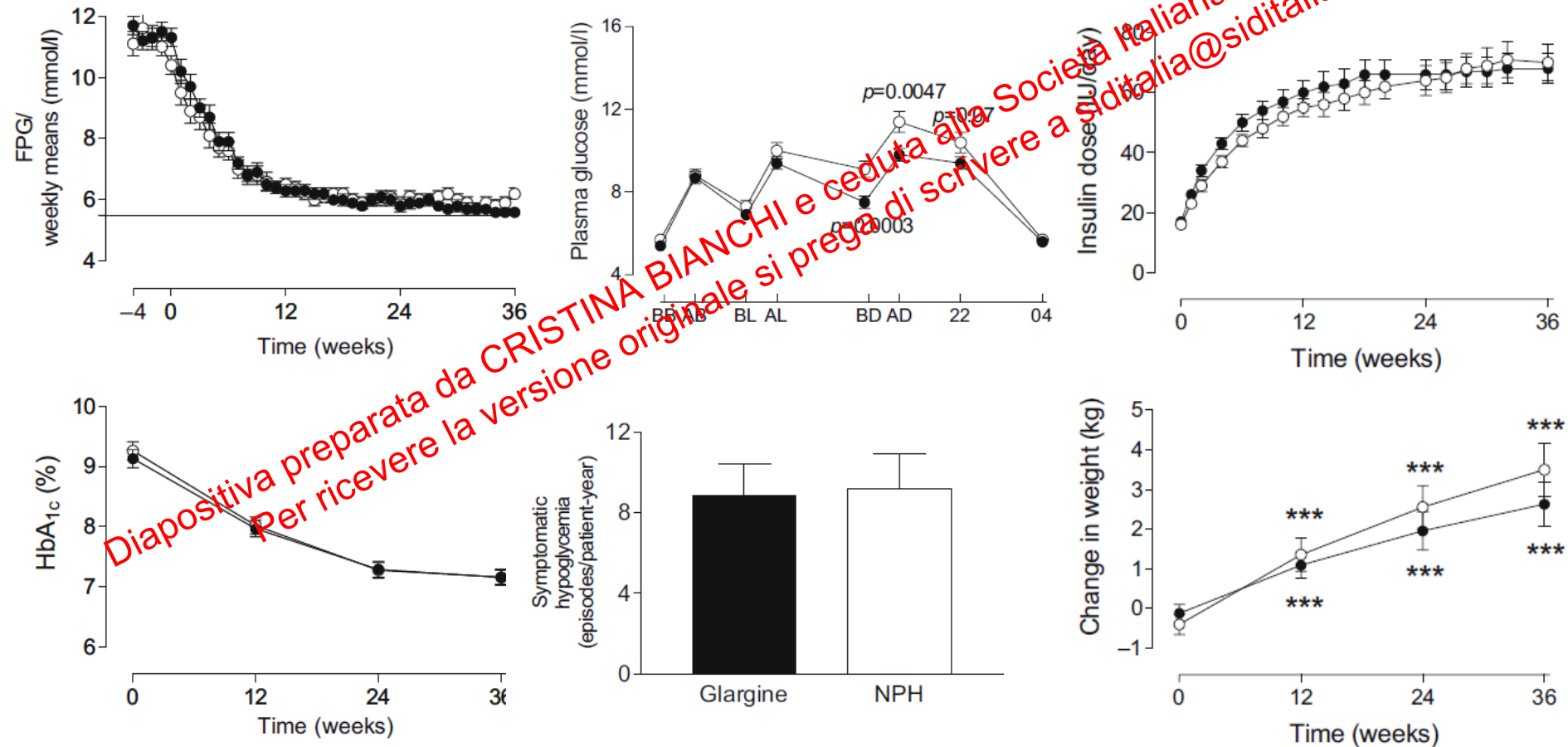
● Bed-time insulin+metformin □ Bed-time insulin+glyburide ○ Bed-time insulin+both oral agents △ Bed-time insulin+morning insulin



Insulin glargine or NPH combined with metformin in type 2 diabetes

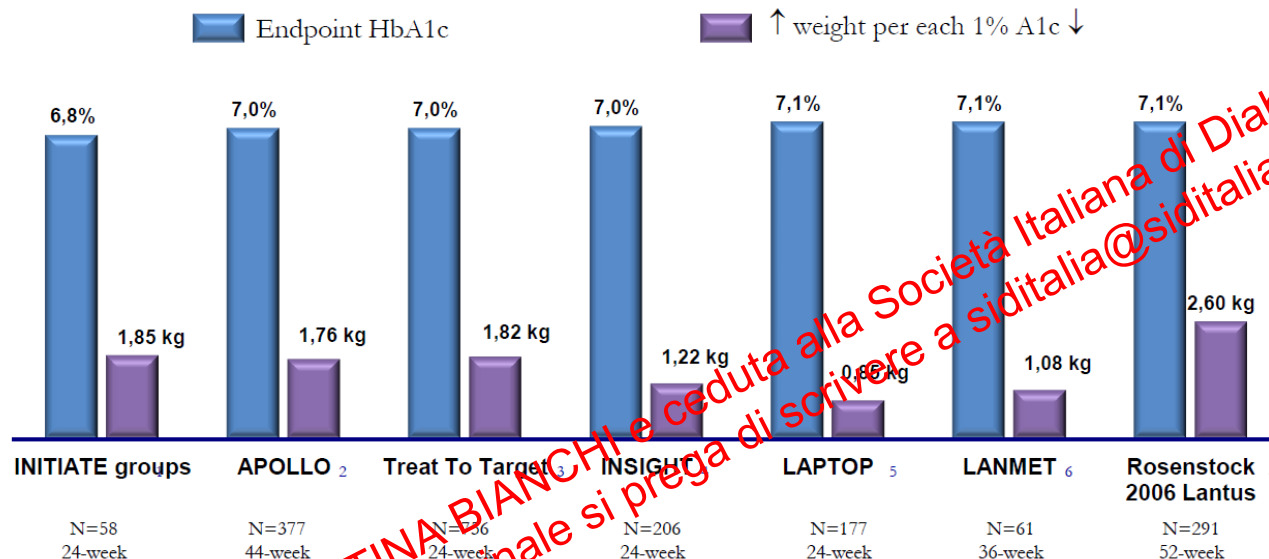
- The LANMET study -

○ NPH + MET ● Glargine + MET

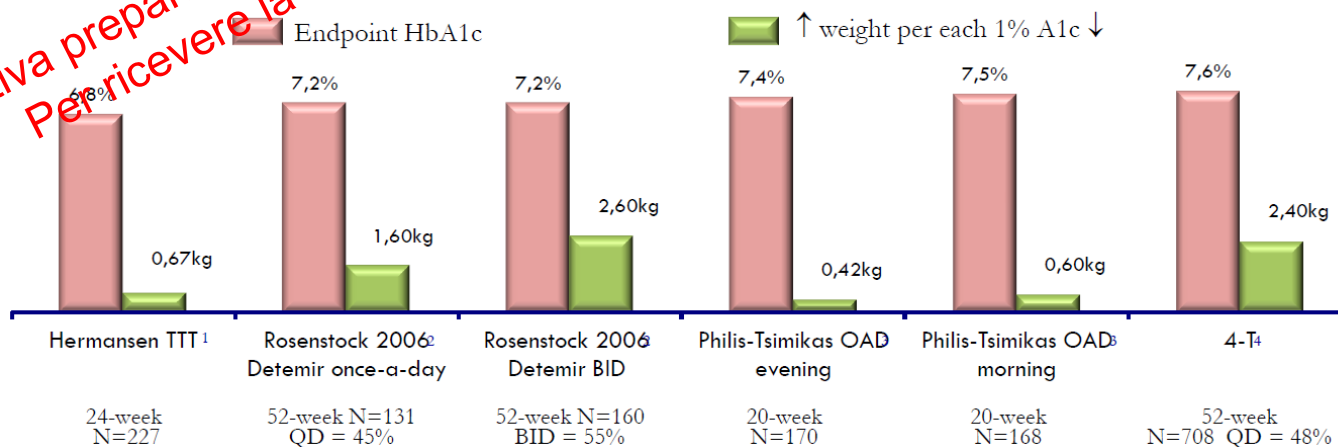


Glargine and Detemir weight impact in RCTs

Glargine 0.8 to 2.6 kg body weight increase for each 1% decrease in HbA1c



Detemir 0.7 to 2.6 kg body weight increase for each 1% decrease in HbA1c



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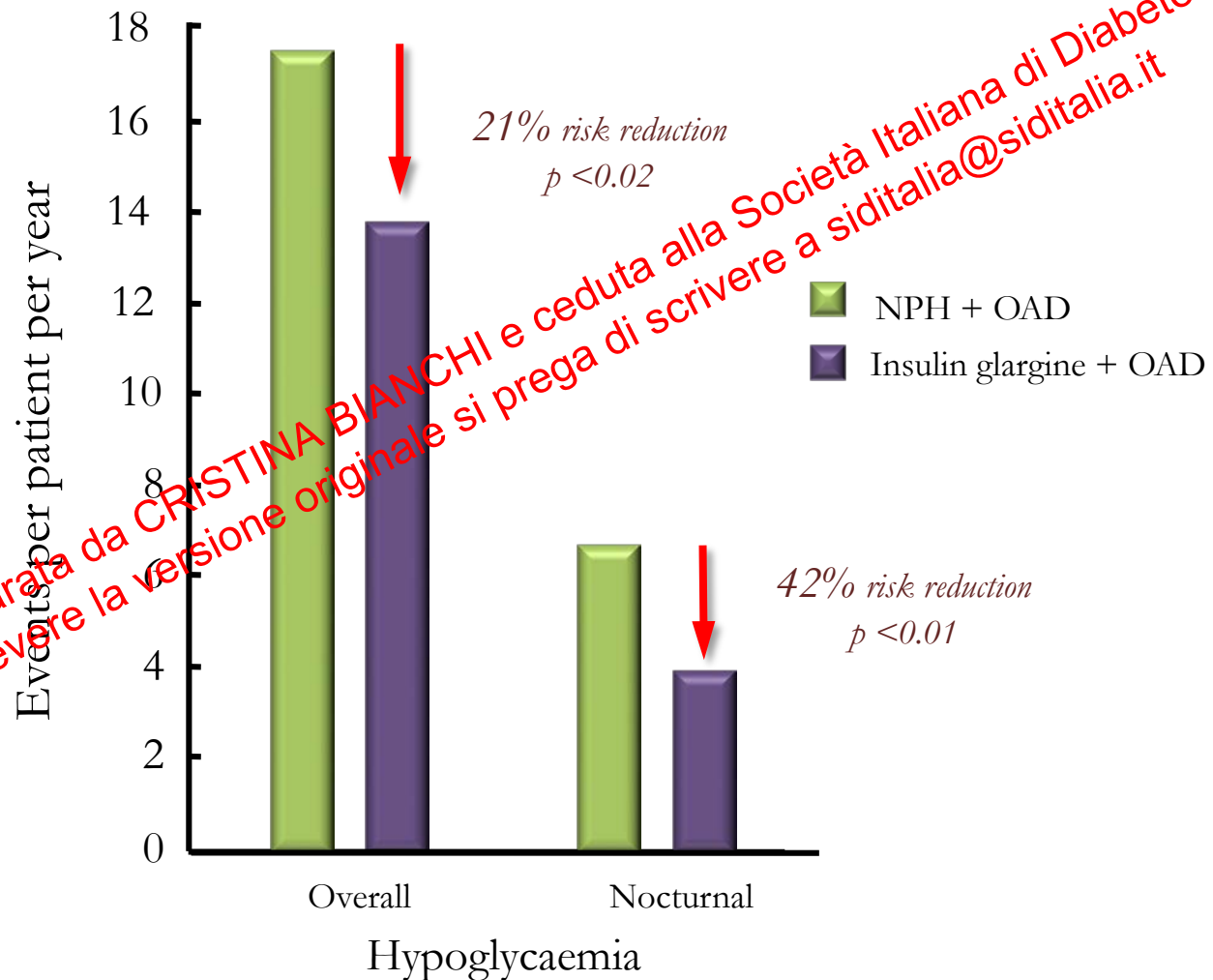
- Complexity of regimens



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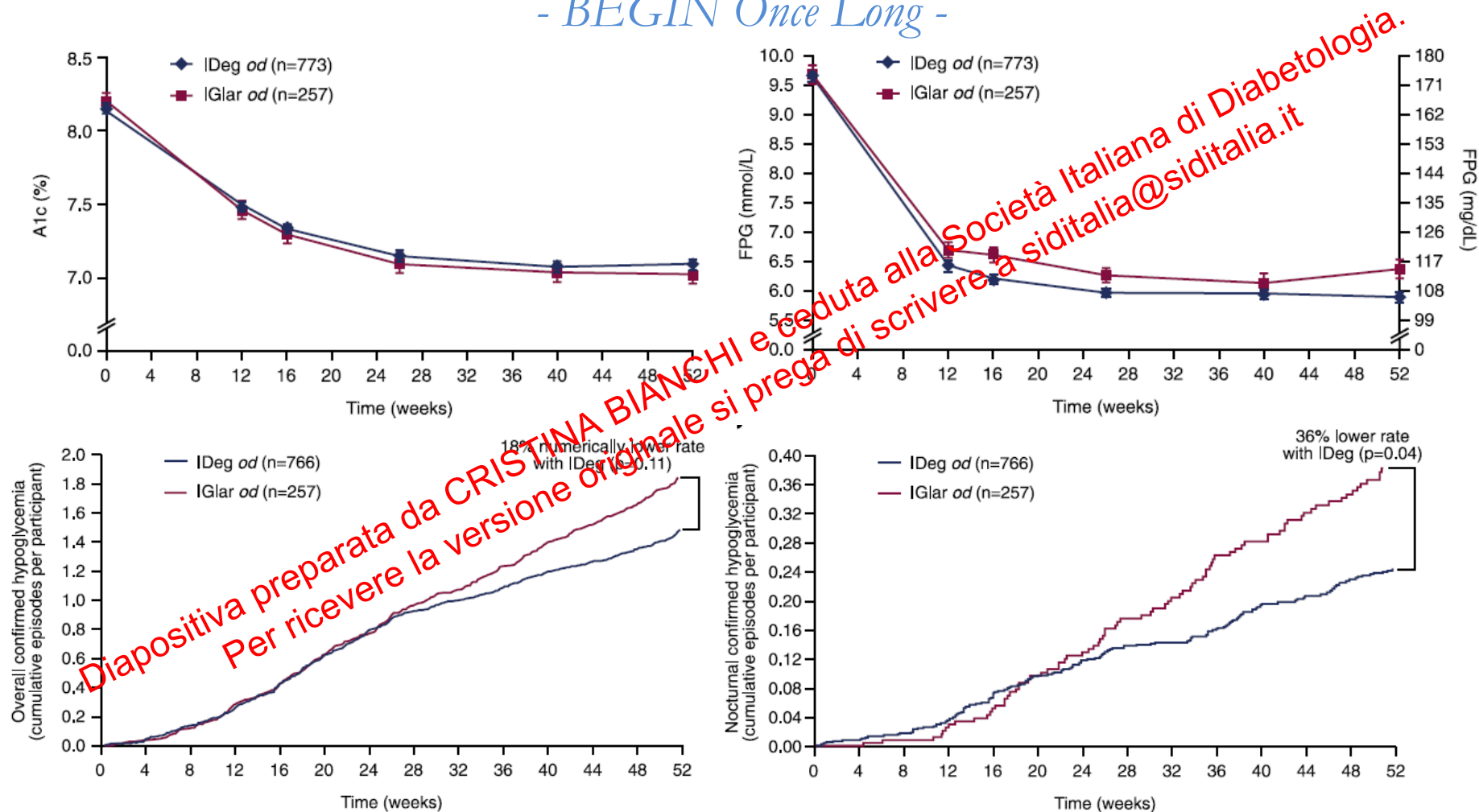
Insulin glargine or NPH combined with oral therapy in type 2 diabetes

- The Treat-to-target study -



Insulin degludec vs. insulin glargine in insulin-naïve subjects with type 2 diabetes

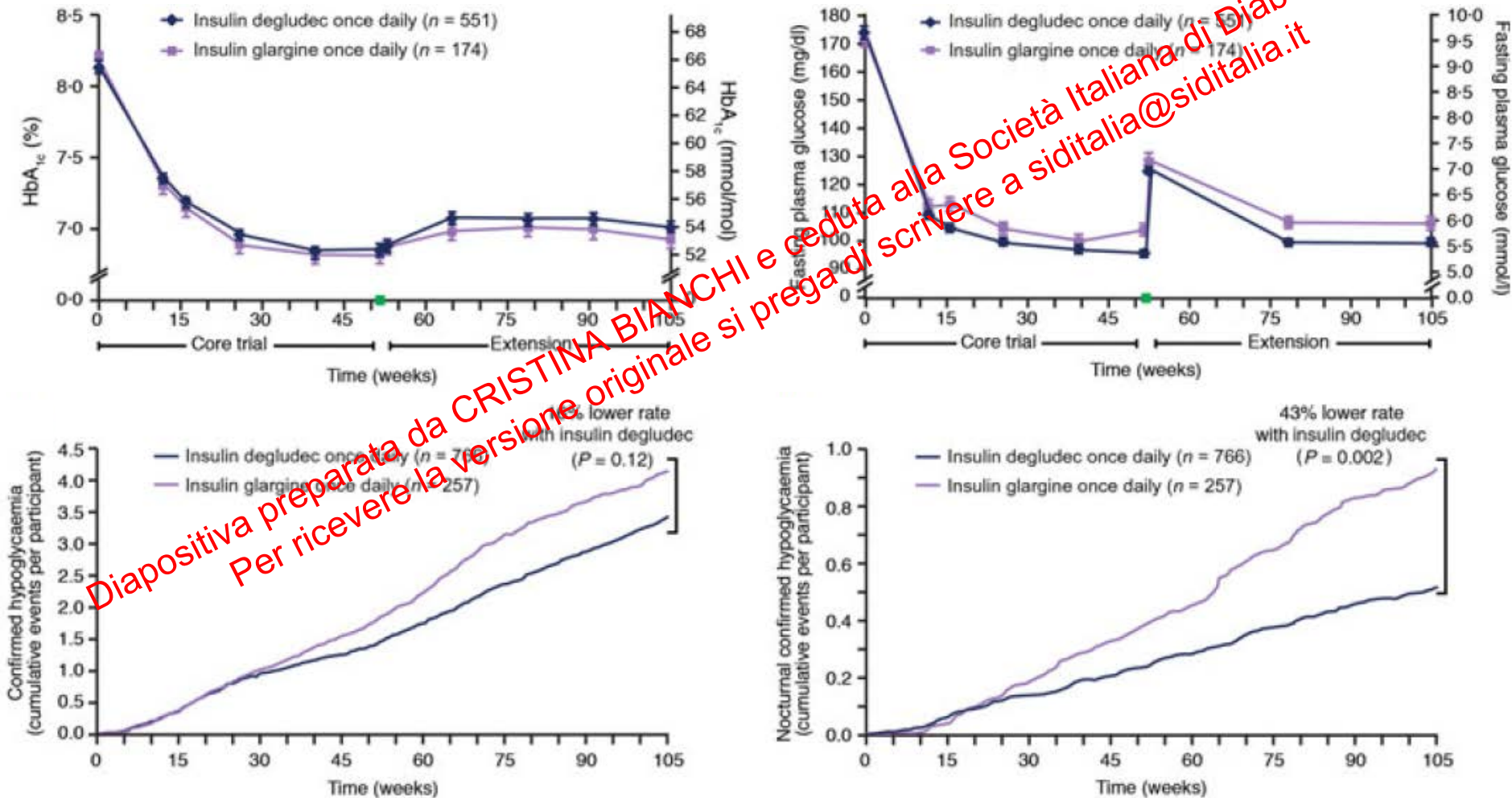
- *BEGIN Once Long* -



Similar ($p=0.28$) weight gain at the end of the trial: degludec (+2.4 kg) and glargine (+2.1 kg)

Insulin degludec vs. insulin glargine in insulin-naïve subjects with type 2 diabetes

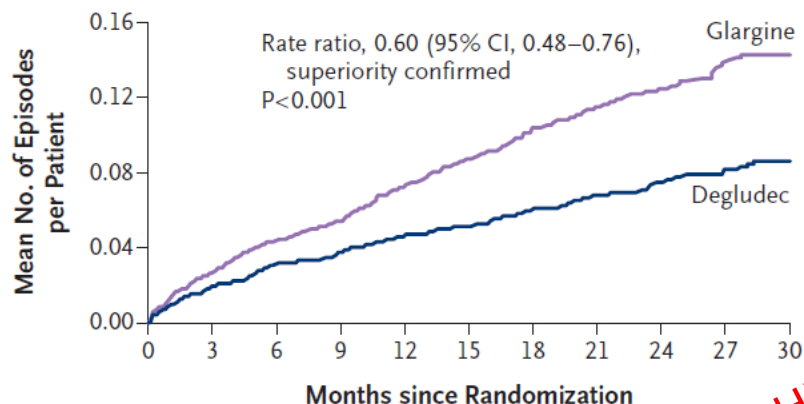
2 years extension study



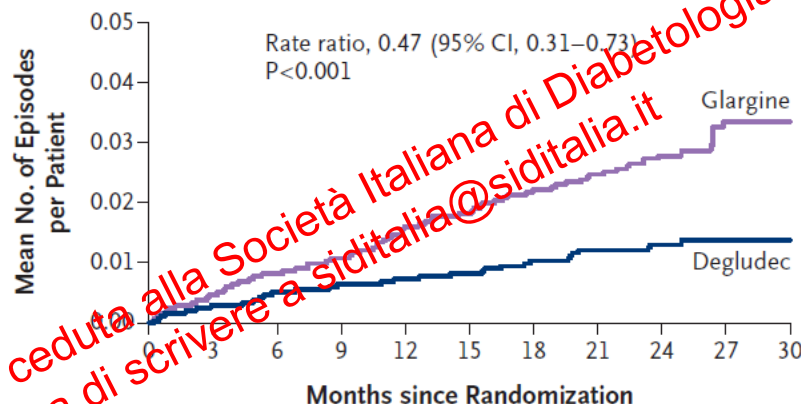
Degludec vs. Glargine in Type 2 Diabetes

- The DEVOTE 3 study -

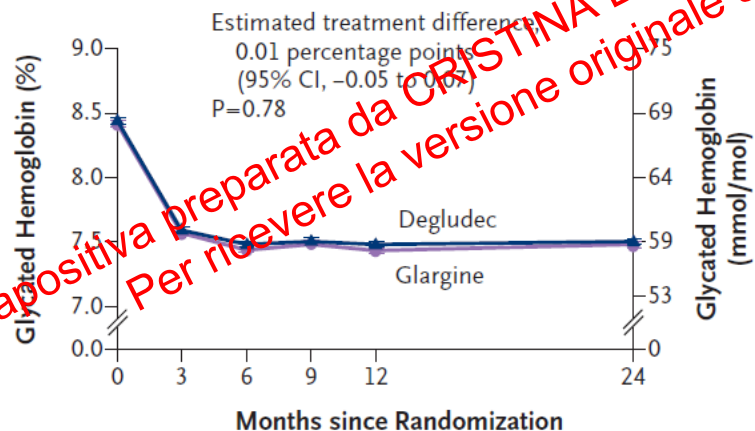
Severe Hypoglycemia



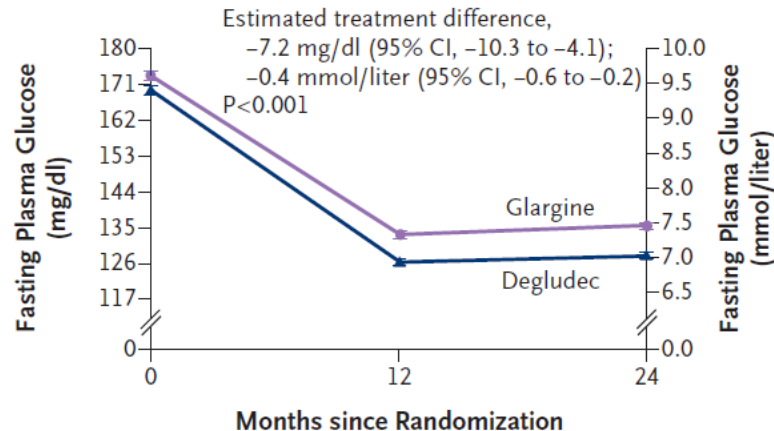
Nocturnal Severe Hypoglycemia



Glycated Hemoglobin



Fasting Plasma Glucose



No. at Risk

Degludec	3774	3656	3608	3535	3525	2458
Glargine	3776	3640	3562	3516	3500	2424

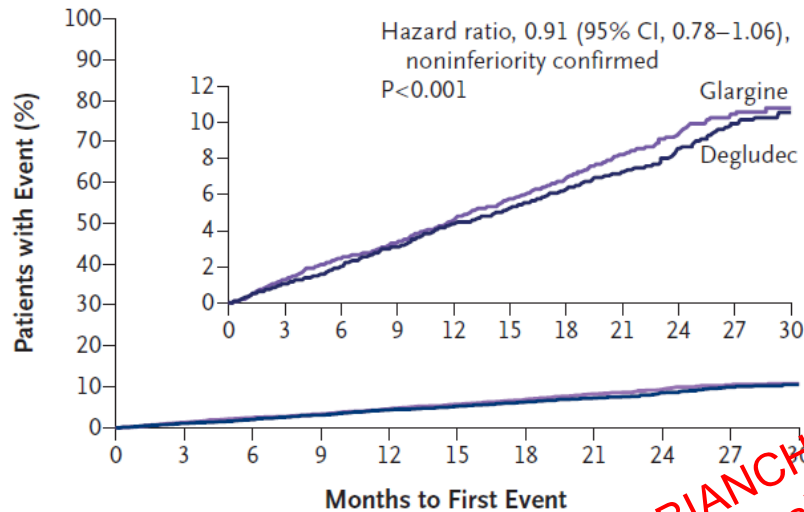
No. at Risk

Degludec	3757	3521	2457
Glargine	3760	3498	2425

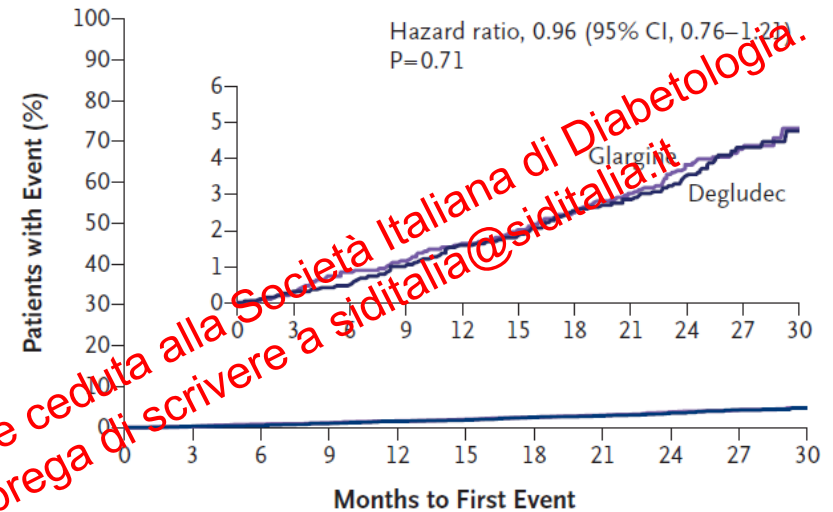
Cardiovascular safety of Degludec

- The DEVOTE 3 study -

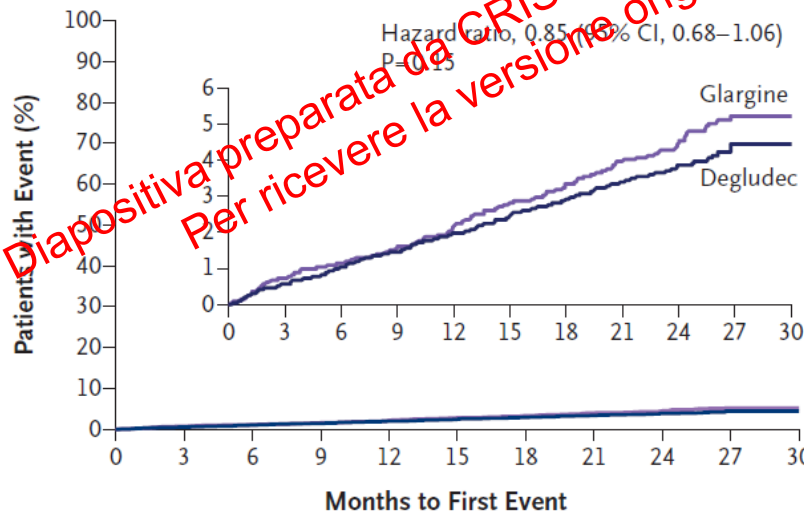
Primary Composite Outcome



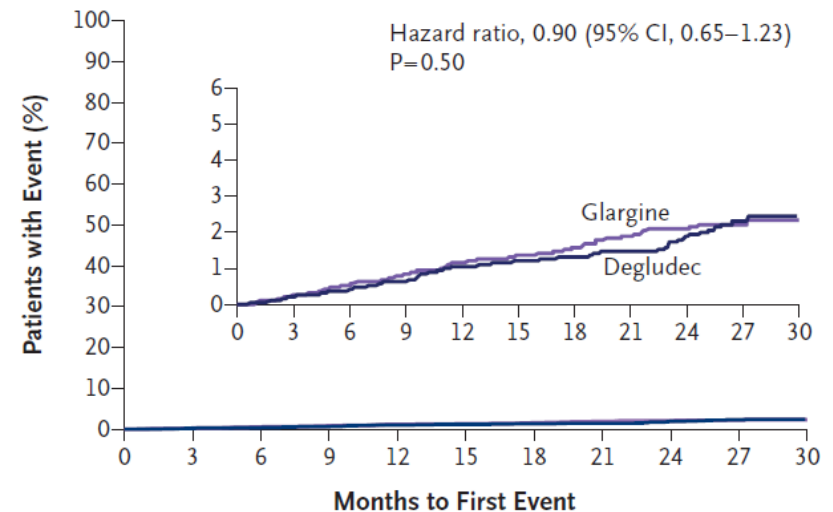
Death from Cardiovascular Causes



Nonfatal Myocardial Infarction

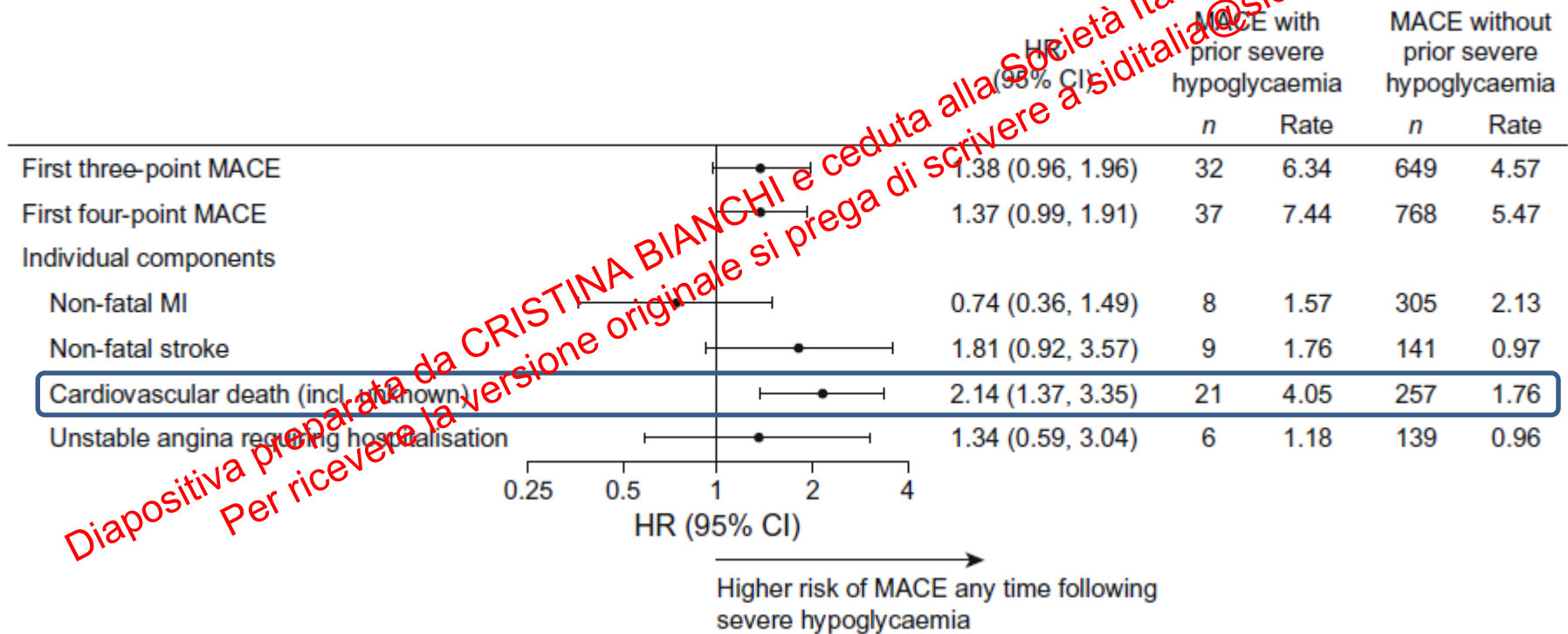


Nonfatal Stroke



Relationships between severe hypoglycaemia, cardiovascular outcomes and mortality

- The DEVOTE 3 study -





Take-home messages (II)

- ✓ The addition of insulin therapy in people with type 2 diabetes and inadequate glycaemic control who are on oral glucose-lowering agents has positive effects on glycaemic control.
- ✓ Patients who added a basal or prandial insulin-based regimen to oral therapy had better glucose control than patients who added a biphasic insulin-based regimen.
- ✓ Fewer hypoglycemic episodes and less weight gain occurred in patients adding basal insulin, especially basal insulin analogue (degludec > glargine/detemir).
- ✓ In patients starting insulin therapy, the concomitant use of metformin and/or SGLT-2 inhibitor may positively impact on body weight and insulin doses, while continuing a secretagogues may result in more hypoglycaemia and weight gain.

Insulin in combination with oral drugs: some concerns

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- Hypoglycemia
- Complexity of regimens



Combination injectable therapy for type 2 diabetes

Initiate Basal Insulin

Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day

Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target

For hypo: Determine & address cause; if no clear reason for hypo,
↓ dose by 4 units or 10–20%

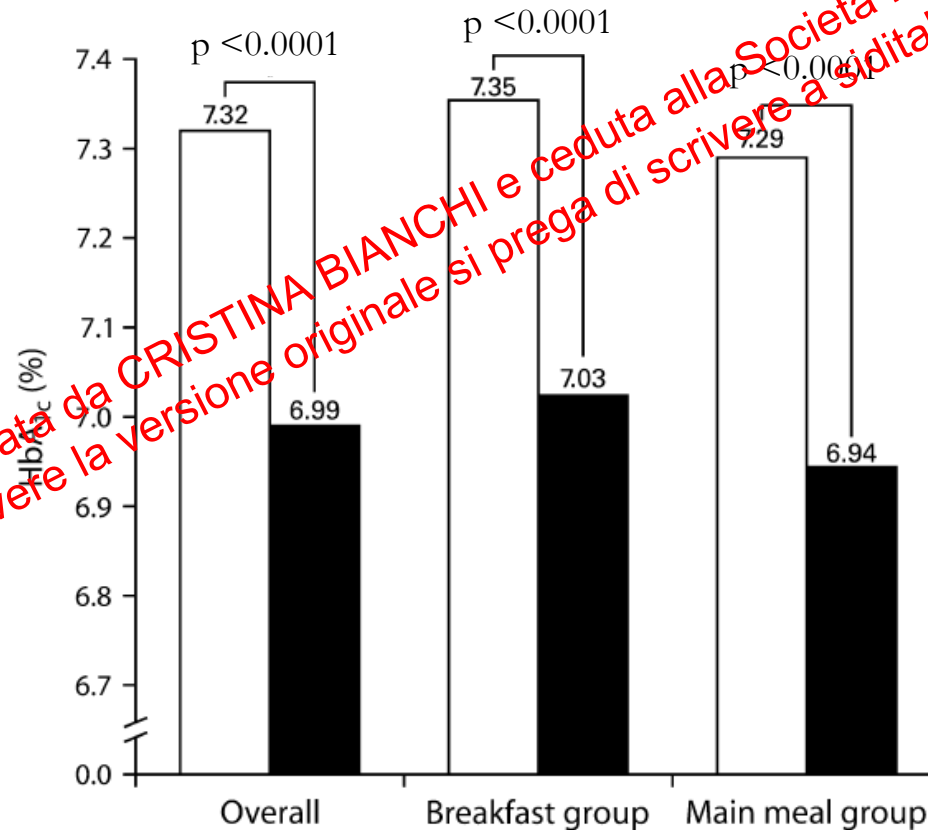
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Two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs

- OPAL Study -

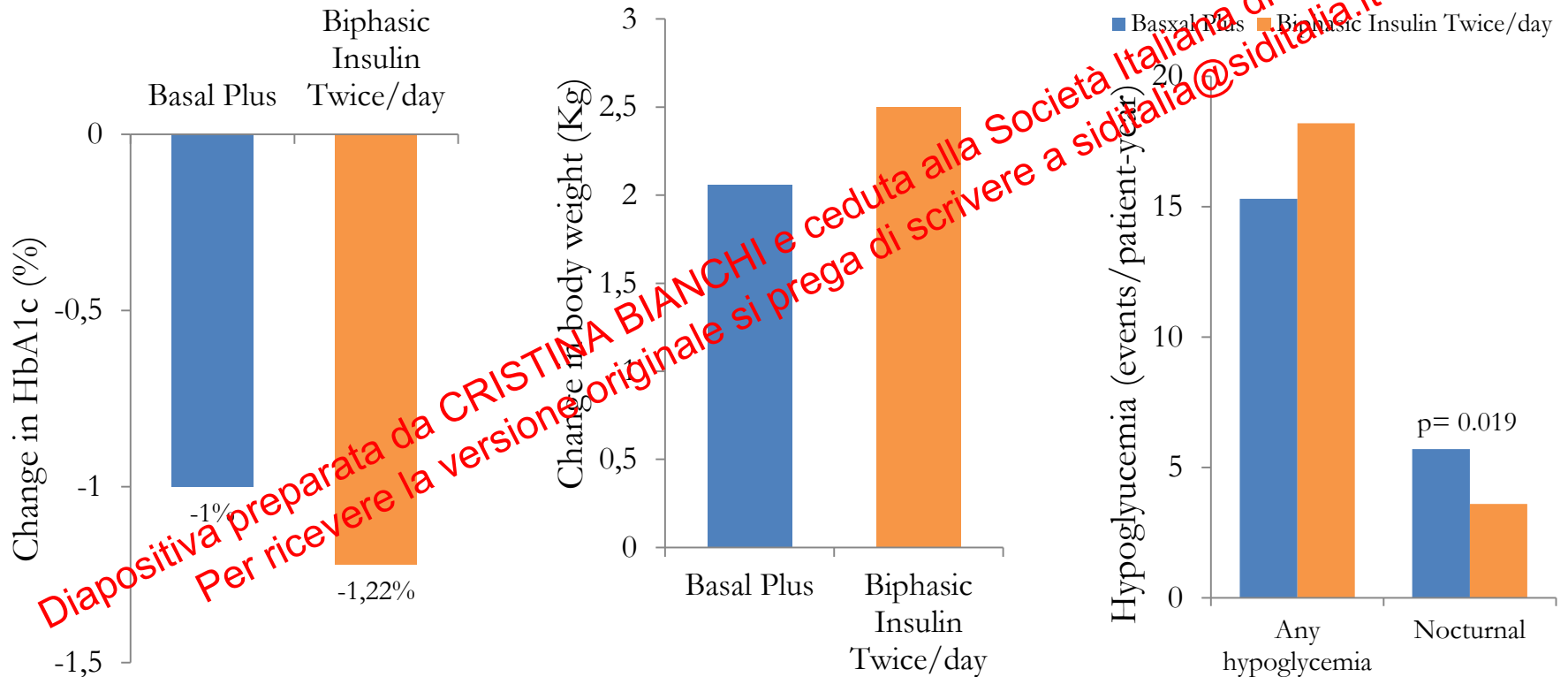
393 patients with type 2 diabetes

HbA1c at baseline □ and end-point ■

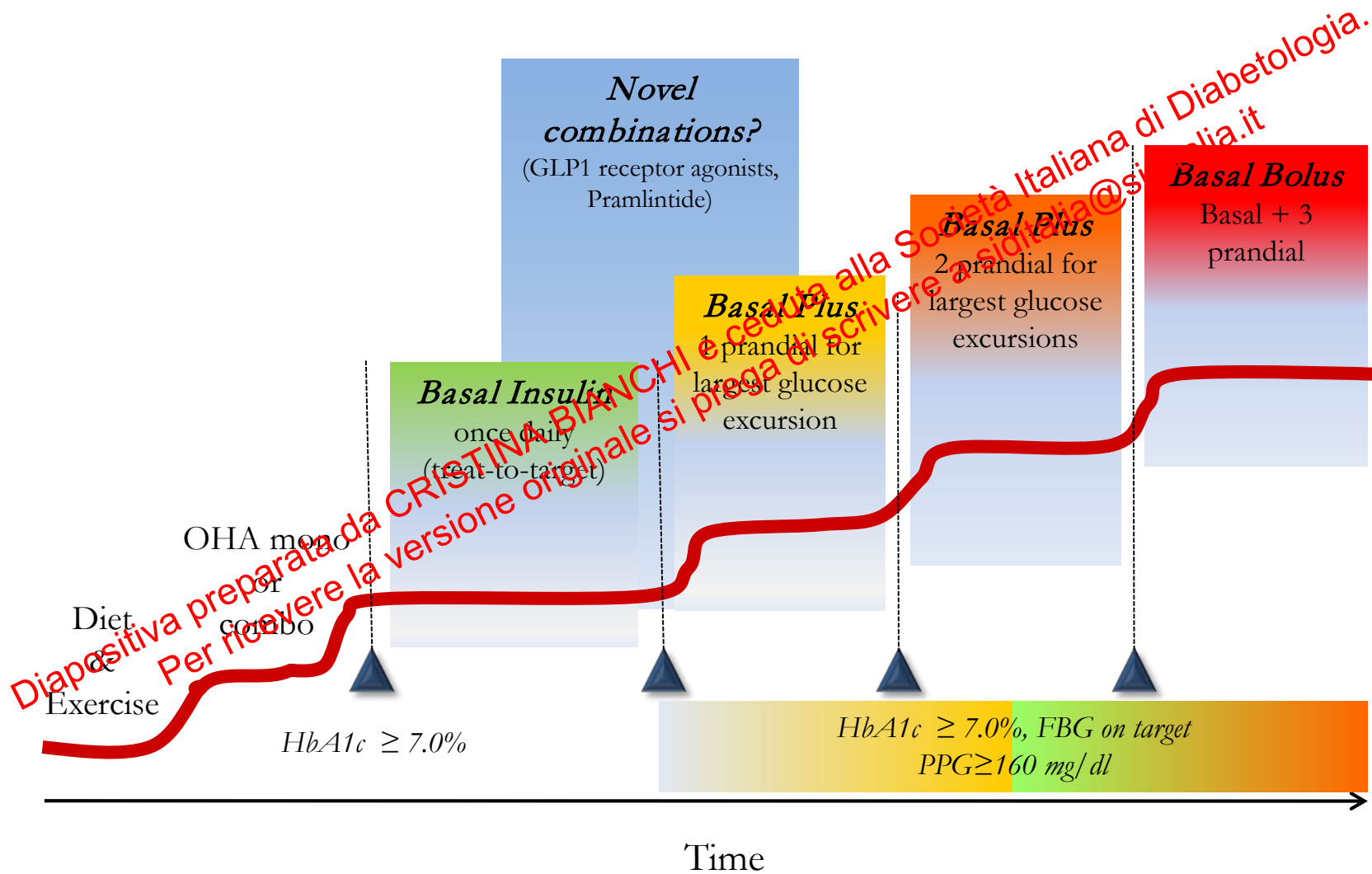


Basal Plus *vs.* Biphasic Insulin in Type 2 Diabetes

- *LanScape Study* -



A stepwise approach for treatment intensification in Type 2 diabetes





unite for diabetes

Grazie per
l'attenzione!



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