GLP-1RA and insulin: friends or foes?

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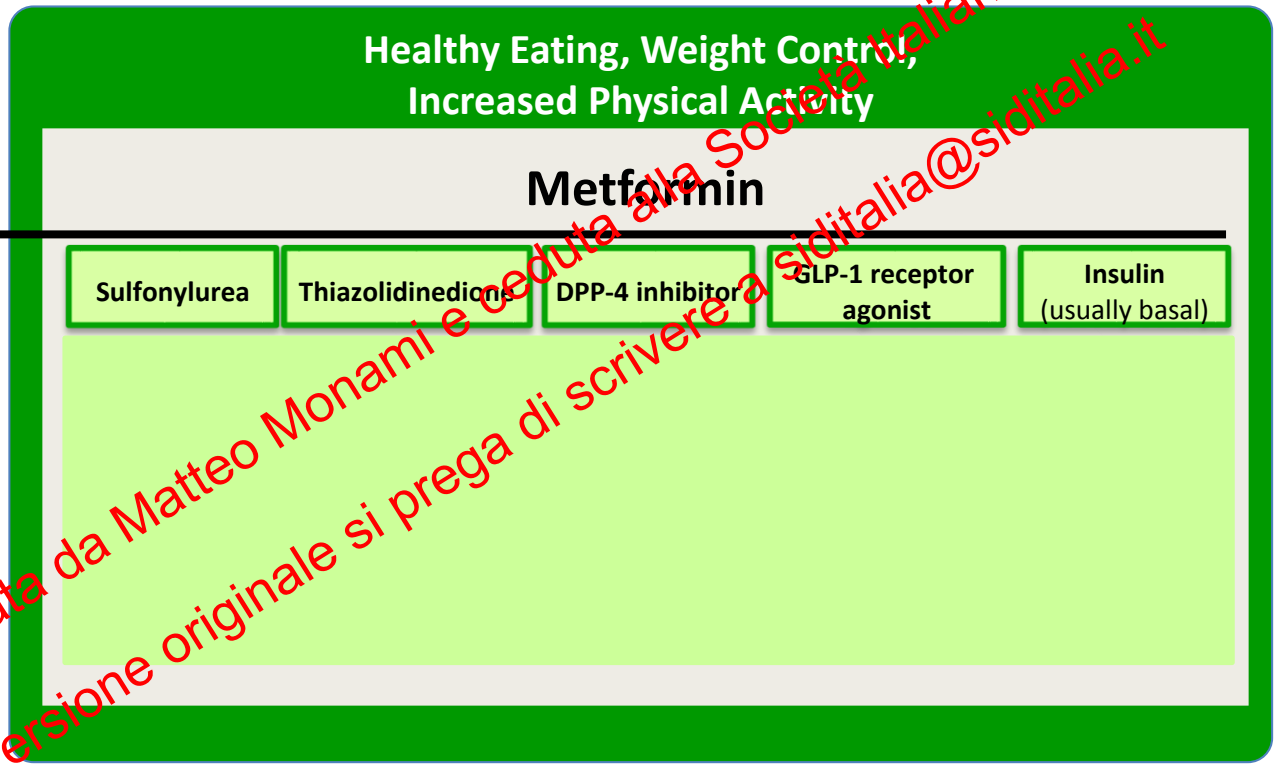
Disclosures

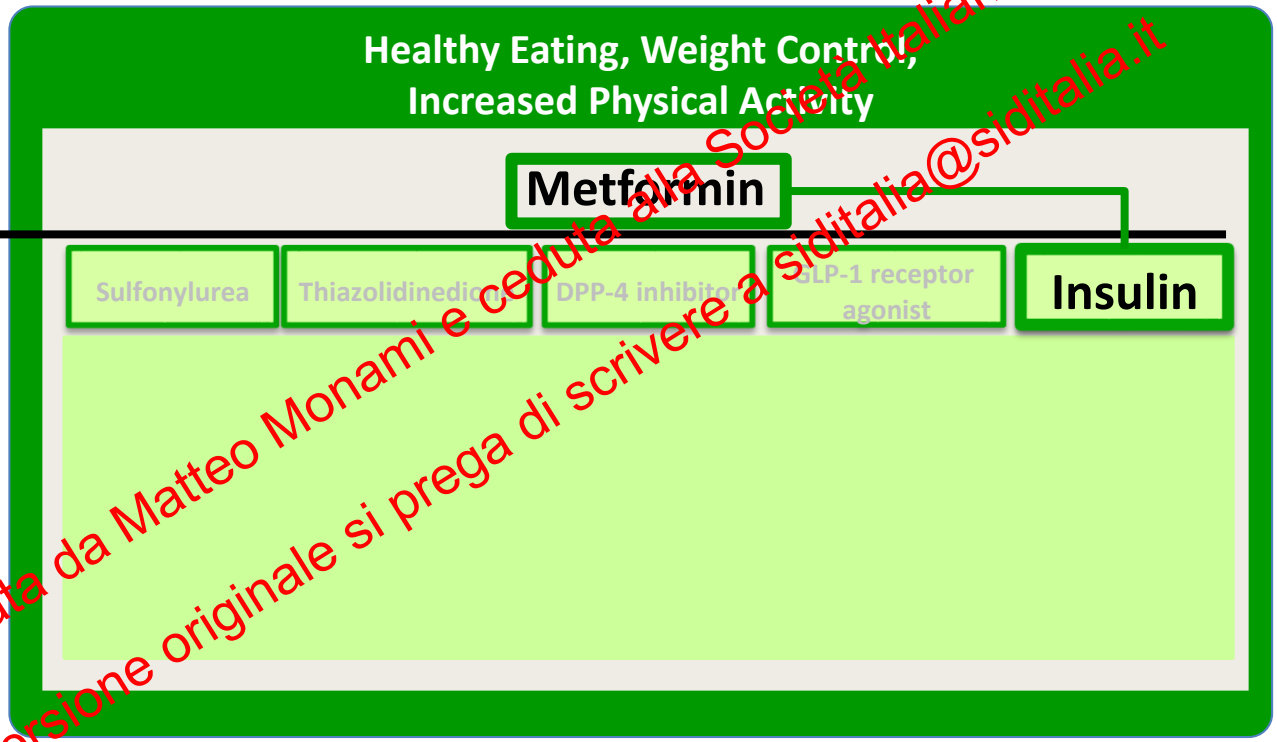
- Dr Monami has received consultancy and/or speaking fees from:
  - Merck Sharp & Dohme
  - AstraZeneca
  - Bristol-Myers Squibb
  - Eli Lilly
  - Novo Nordisk
  - Sanofi
  - Takeda
- In addition, the Diabetes Section directed by Dr Monami received research grants from AstraZeneca and BMS.

Position statement ADA/EASD 2012



Adapted from: Inzucchi *et al. Diabetes Care* 2012;35:1364-79

Position statement ADA/EASD 2012



Adapted from: Inzucchi *et al. Diabetes Care* 2012;35:1364-79

Insulin

Unsurpassed efficacy (short- and long-term)

Good cardiovascular safety

Risk of hypoglycemia

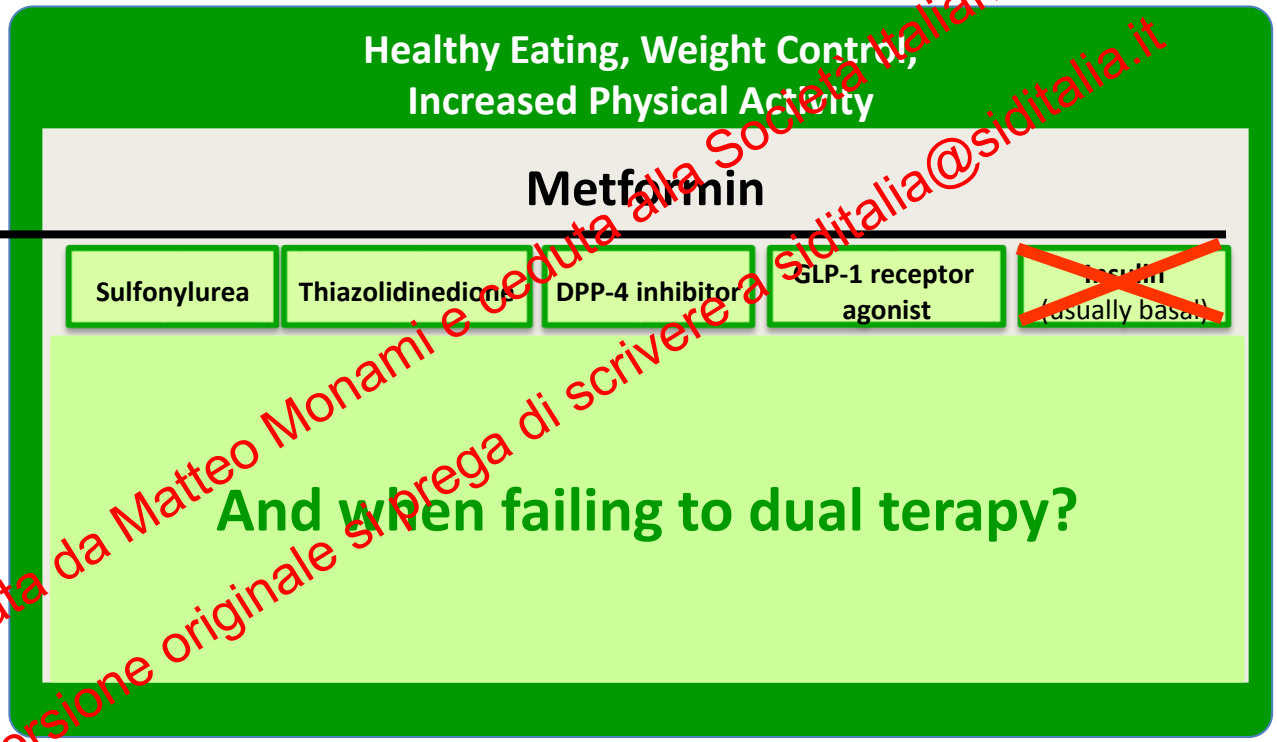
Weight gain

Insulin

Severe hyperglycemia	Moderate hyperglycemia
Ketosis/ketonuria	No ketosis/ketonuria
Lean	Obese
Weight loss	Weight gain
No other available drugs	Other available drugs

Insulin therapy can be prescribed as a transient treatment in some cases

Position statement ADA/EASD 2012



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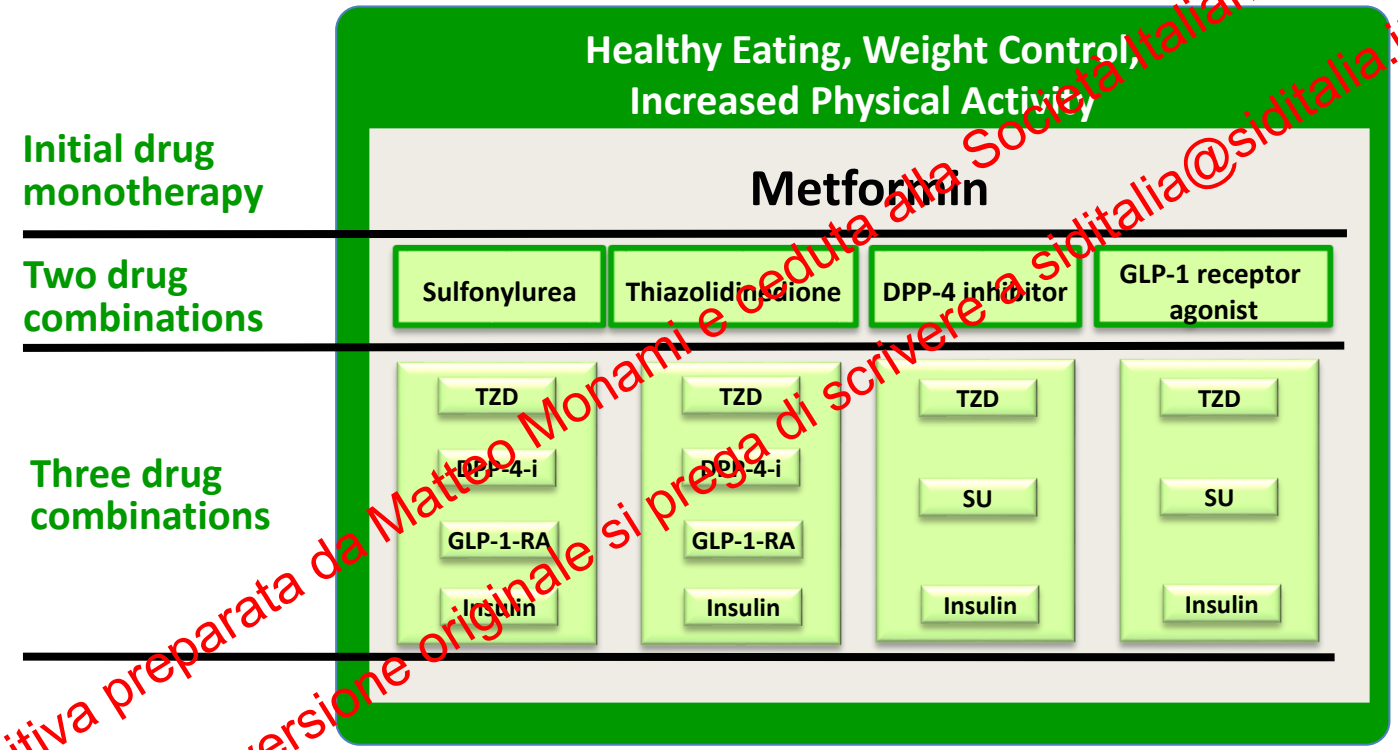

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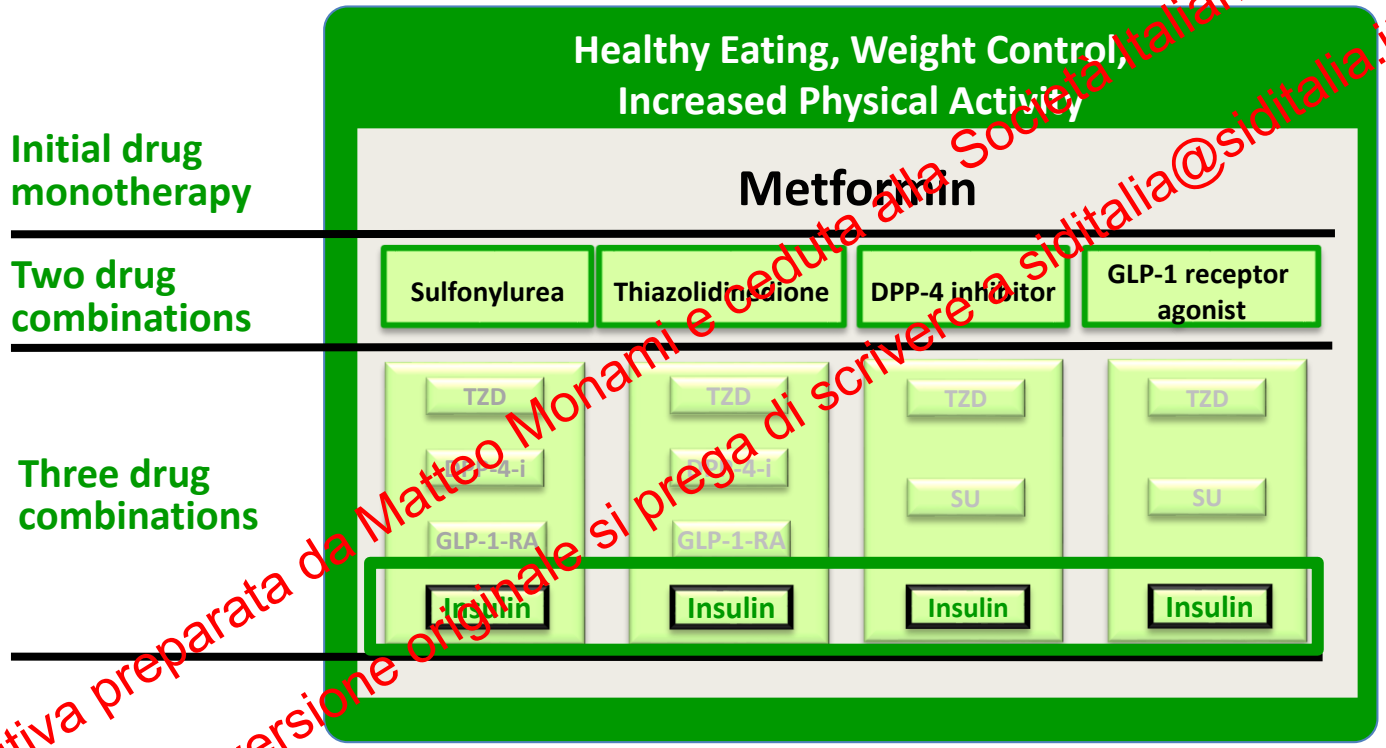

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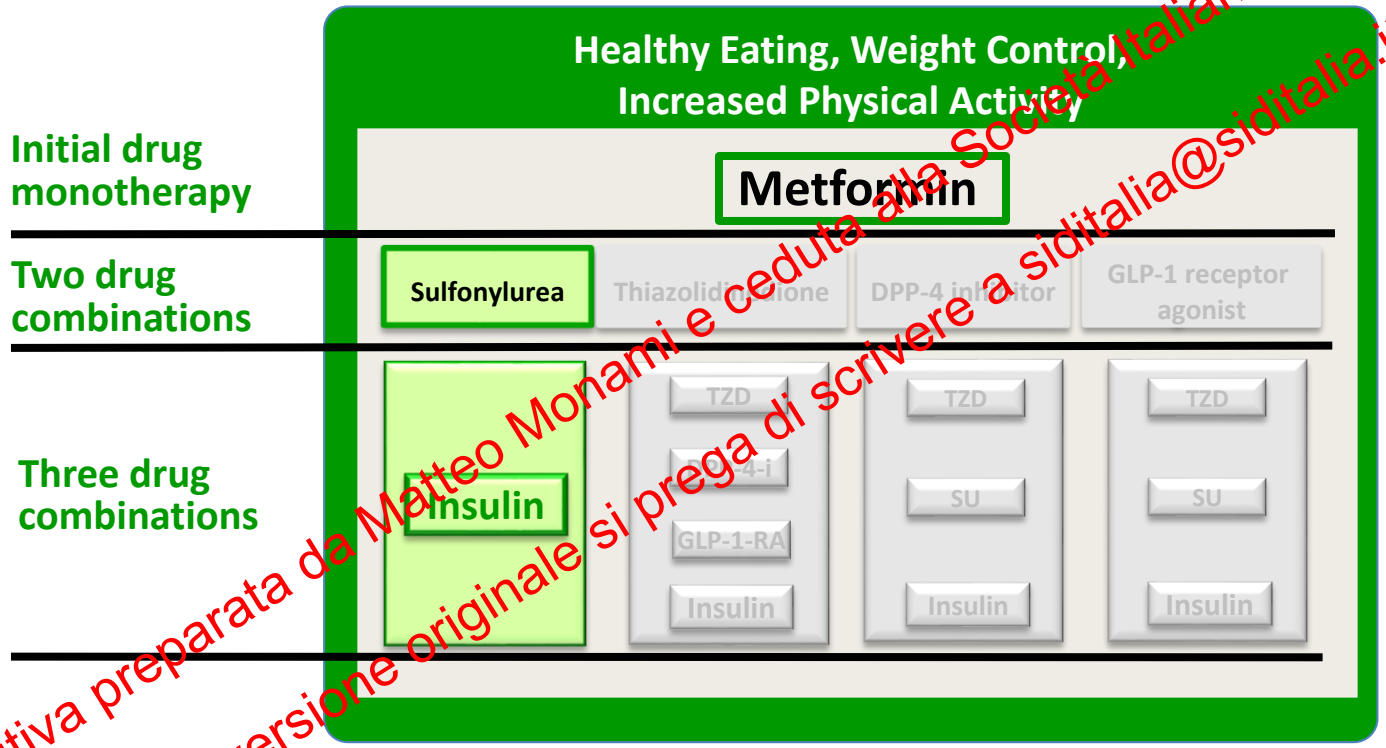

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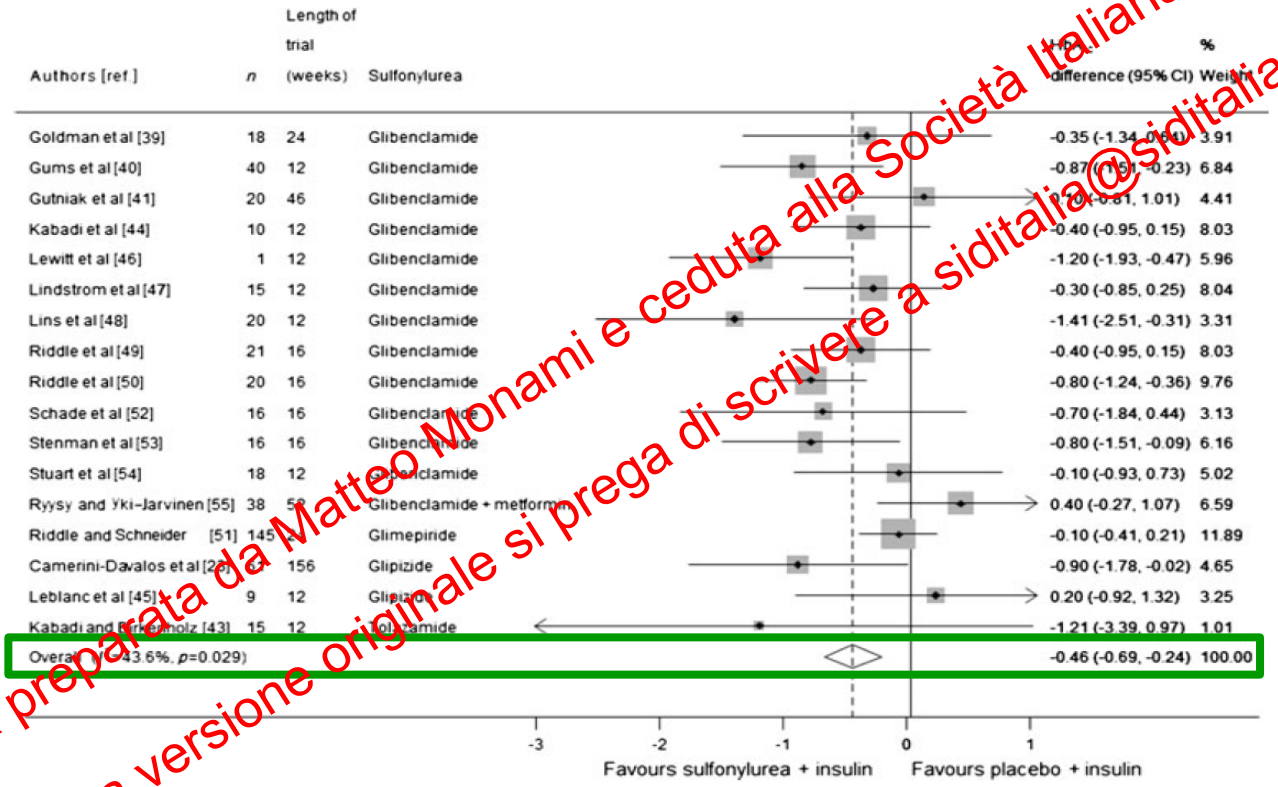
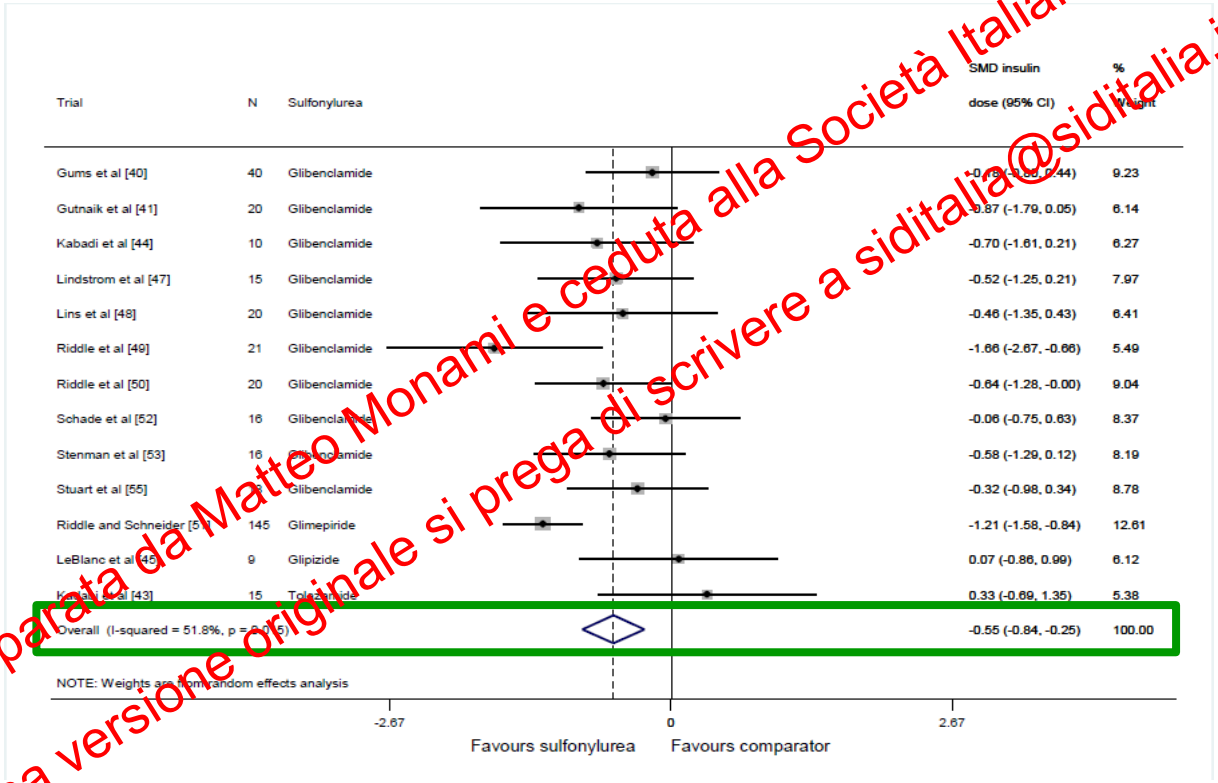
Adding insulin to SU: efficacy



Hirst JA, et al. *Diabetologia* 2013; 56:973-984

Adding insulin to SU: low doses



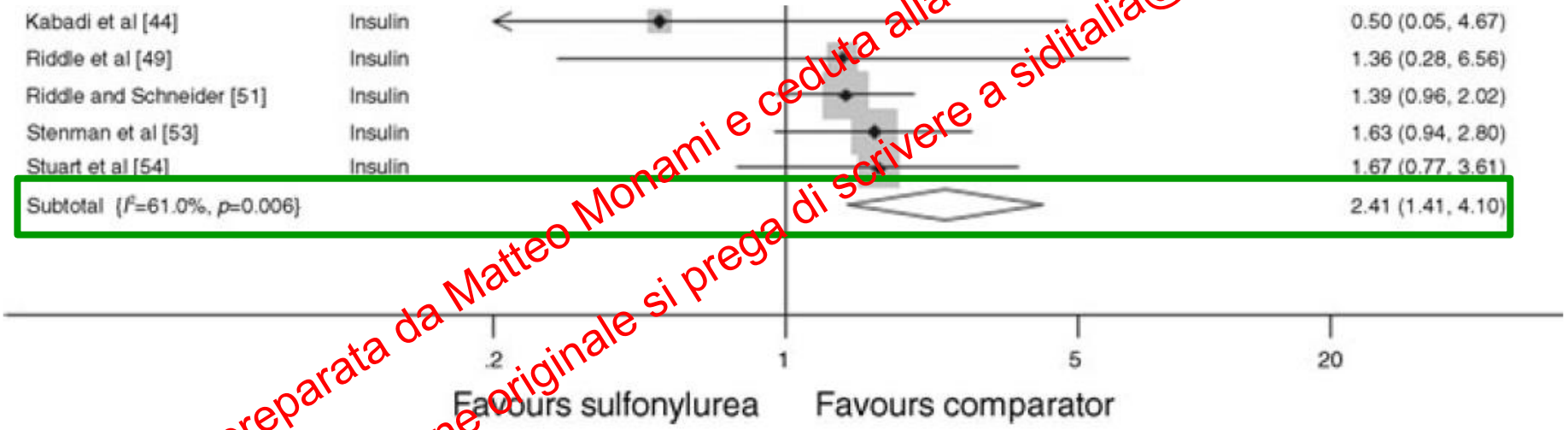
Hirst JA, et al. *Diabetologia* 2013; 56:973-984

Adding insulin to SU: weight

Change in body weight Twelve trials reported a change in body weight over the course of the trial. Pooling the results gave a mean increase in weight of 2.31 kg (95% CI 1.31, 3.32) in the sulfonylurea-treated groups compared with comparator groups (results not shown).

Hirst JA, et al. *Diabetologia* 2013; 56:973-984

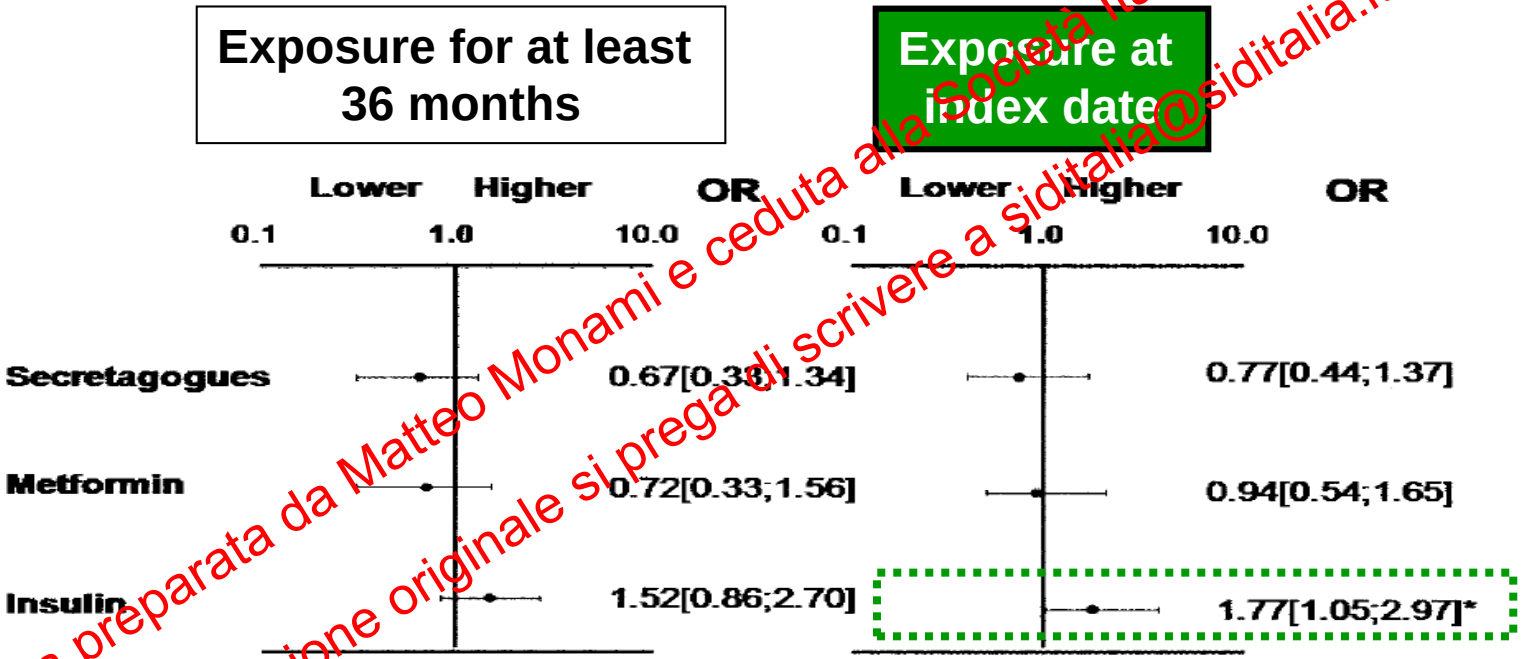
Adding insulin to SU: hypos



Hirst JA, et al. *Diabetologia* 2013; 56:973-984

Bone fracture and hypoglycemic treatments in type 2 diabetic patients

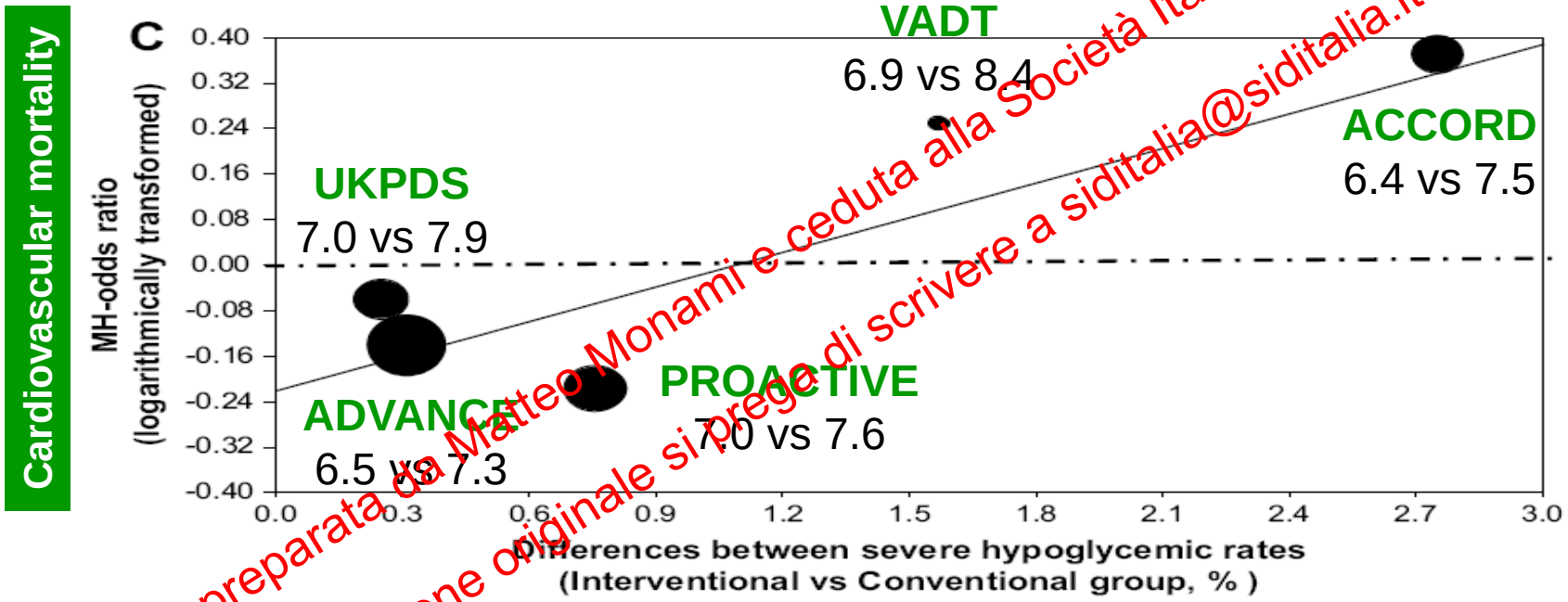
A case-control study



Monami M., et al. Diabetes Care 31:199-203, 2008

Prevention of cardiovascular disease through glycemic control in type 2 diabetes

A meta-analysis of randomized clinical trials



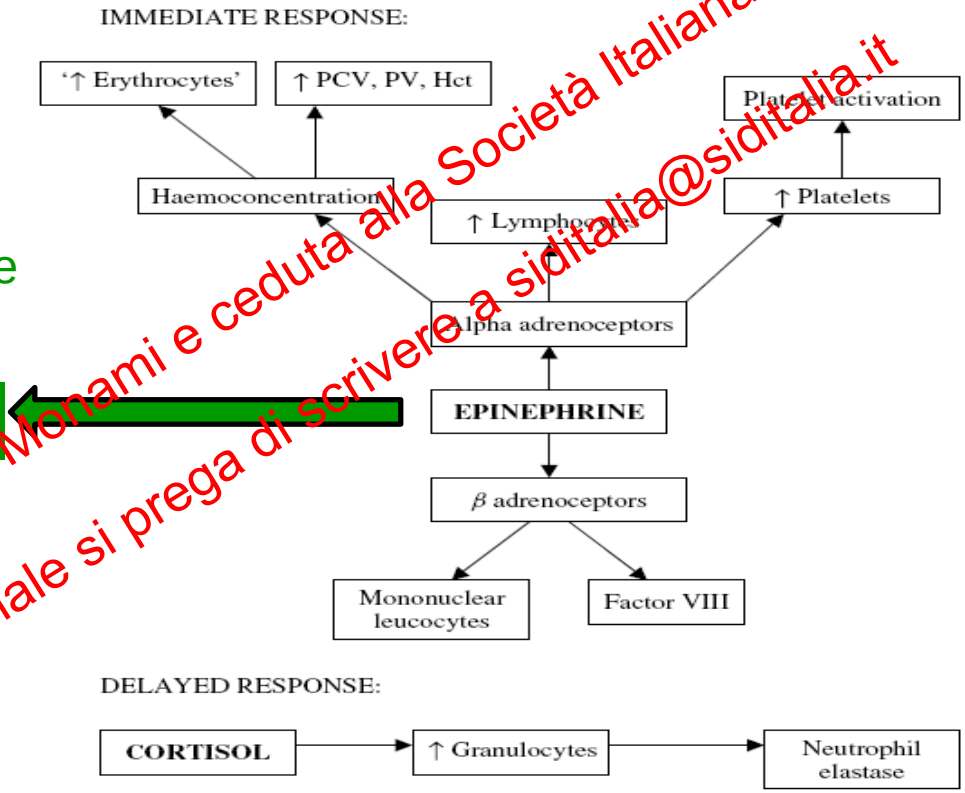
In trials in which the reduction of HbA1c was obtained with a higher incidence of hypoglycaemia, CV MORTALITY is increased

Mannucci E., Monami M., et al., NMCD 2009

Vascular disease and diabetes: is hypoglycemia an aggravator factor?

Adrenercic activation could have a negative impact on the prognosis of

MYOCARDIAL ISCHEMIA



Wright RJ, et al., DMRR 2008; 24: 353-363

Adding insulin to SU

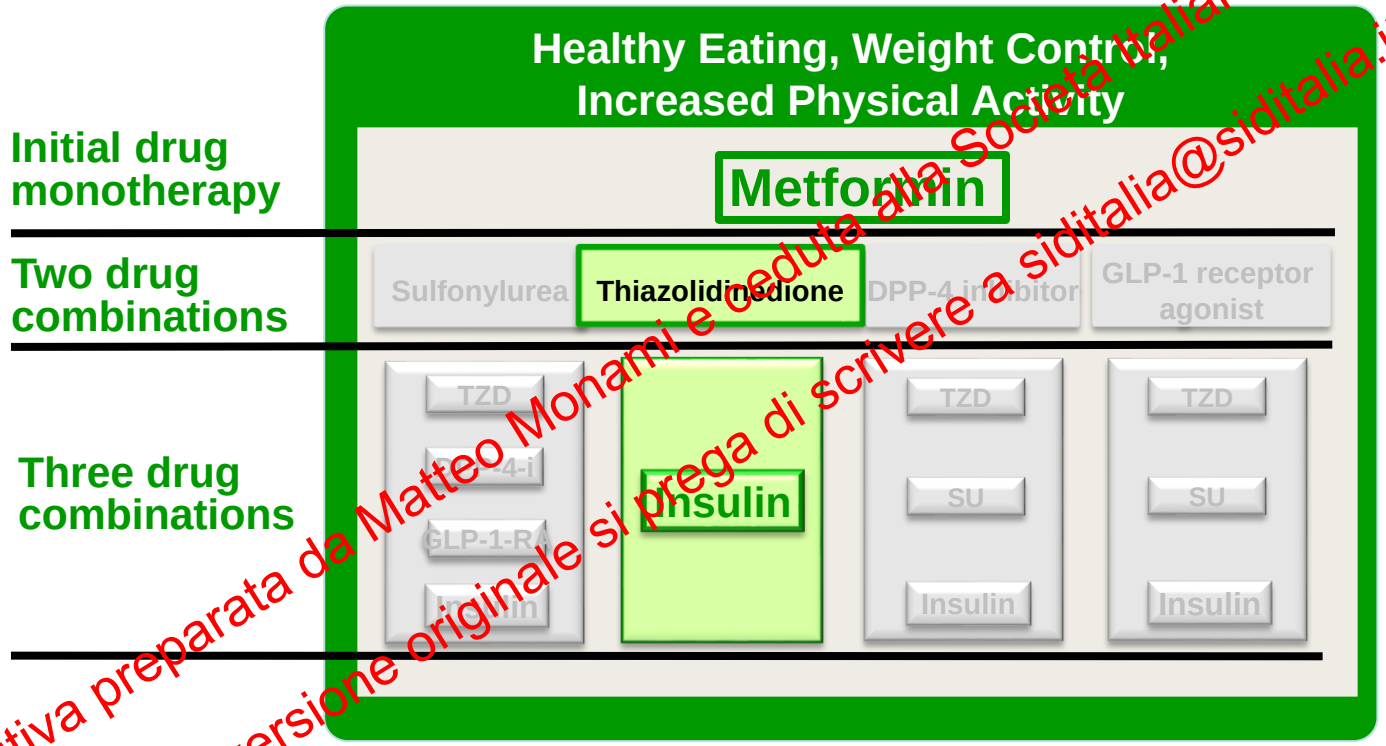
SU+Met

- Good short term efficacy
- Low cost
- Risk of hypoglycemia
- Weight gain
- Limited efficacy in the long term
- Questionable cardiovascular safety

SU+Met+Ins

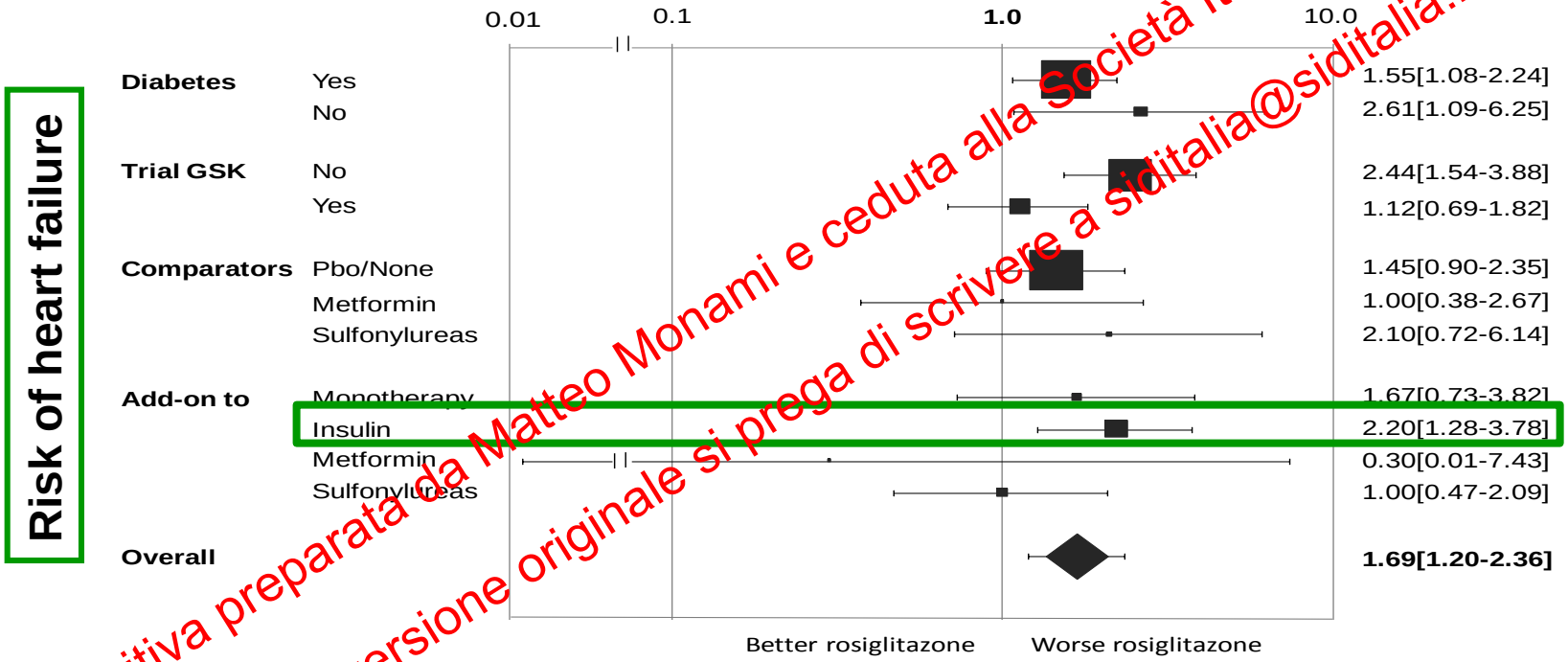
- ~~Good short term efficacy~~
- ~~Low cost~~
- Low insulin doses
- **Risk of hypoglycemia**
- **Weight gain**
- **Questionable CV safety**

Position statement ADA/EASD 2012



Adapted from: Inzucchi *et al. Diabetes Care* 2012;35:1364-79

TZD/Insulin and chronic heart failure



Mannucci E, Monami M, Di Bari M, Lamanna C, Gori F, Gensini GF, Marchionni N. *International Journal of Cardiology* 2010; 143:135-140.;

TZD and bone fractures

ADOPT study

Note added in proof: While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the prespecified analysis plan.

	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.31)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* $P<0.01$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
† $P<0.05$ for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Kahn SE et al. *N Engl J Med* 2006; 355:2427.

Insulin and bone fractures

Table 2—*Frequency of falls and proportion of fallers among older women by diabetes and insulin use*

	No diabetes	Non–insulin-treated diabetes	Insulin-treated diabetes
n	8,620	530	99
Incidence of falls (per person-year)			
70–74 years old	0.43	0.56*	1.26*†
75–79 years old	0.52	0.74*	0.82*
80–84 years old	0.61	0.89*	1.31*†
≥ 85 years old	0.98	1.32*	1.37*
All ages	0.62	0.85*	1.12*†
Fell more than once a year (%)	17.0	25.7*	35.4*†
Fell more than twice a year (%)	6.8	10.6*	15.2*
Follow-up (years)	7.2 ± 1.9	6.6 ± 2.2*	6.2 ± 2.4*

Data for follow-up are means ± SD. *$P < 0.05$ compared with women without diabetes; †$P < 0.05$ compared with women with non–insulin-treated diabetes.

Schwartz AV et al., Diabetes Care 2002; 25: 1749-1754

Adding insulin to TZDs

TZD+Met

- Good long-term efficacy
- No hypoglycemic risk
- Positive effects on the incidence of myocardial infarction
- Weight gain - Edema
- Risk of heart failure
- Risk of bone fractures and bladder cancer

TZD+Met+Ins

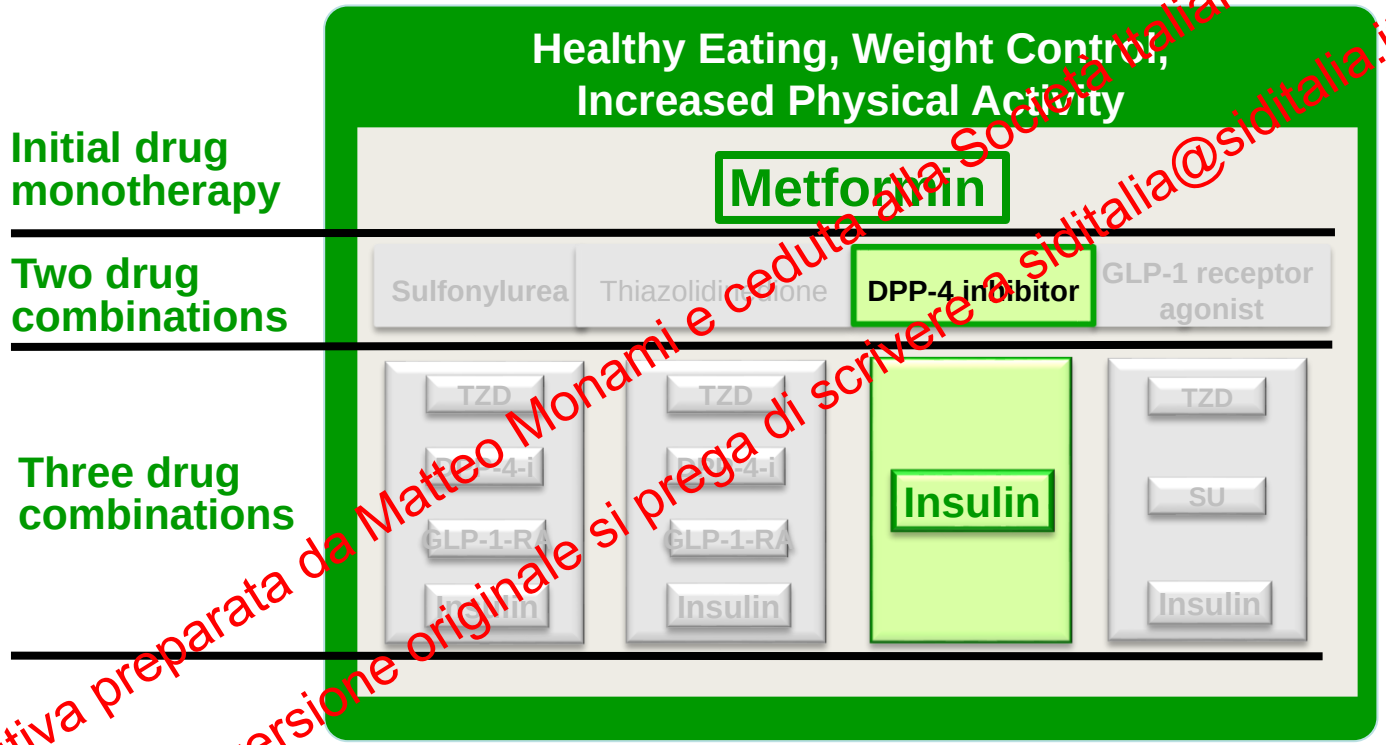
- ~~Good long-term efficacy~~
- ~~No hypoglycemic risk~~
- ~~Positive effects on the incidence of myocardial infarction~~
- Reduced insulin doses

Weight gain-Edema

Heart failure

Bone fractures

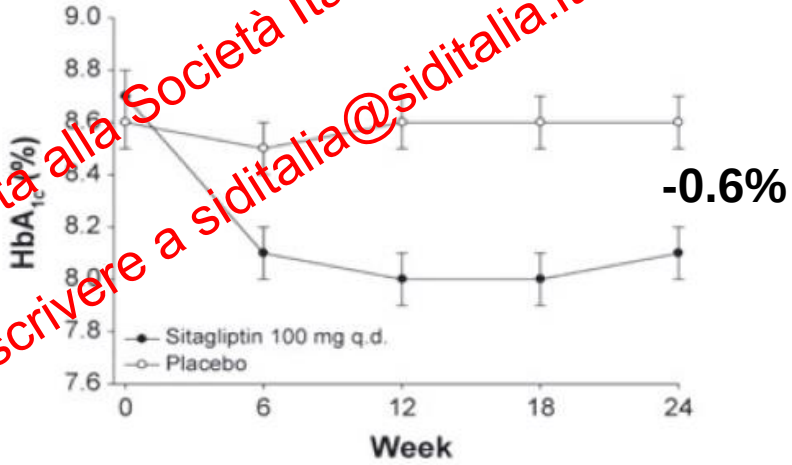
Position statement ADA/EASD 2012



Adapted from: Inzucchi *et al. Diabetes Care* 2012;35:1364-79

DPP-4i and insulin: efficacy and safety

Characteristic	Sitagliptin 100 mg q.d. + insulin (±MET) (n = 322)	Placebo + insulin (±MET) (n = 319)
Type of insulin, n (%)		
Premixed	87 (27)	82 (26)
Total daily dose, IU/day	67.4 ± 35.4	74.5 ± 36.9
Long-acting or intermediate-acting	235 (73)	237 (74)
Total daily dose, IU/day	44.2 ± 29.9	44.5 ± 25.7



Weight gain

The addition of sitagliptin to ongoing insulin therapy did not result in a significant change in body weight from baseline when compared to the addition of placebo. LS mean changes from baseline at week 24 (95% CI) were 0.1 kg (−0.2, 0.4) in the sitagliptin and 0.1 kg (−0.2, 0.4) in the placebo group.

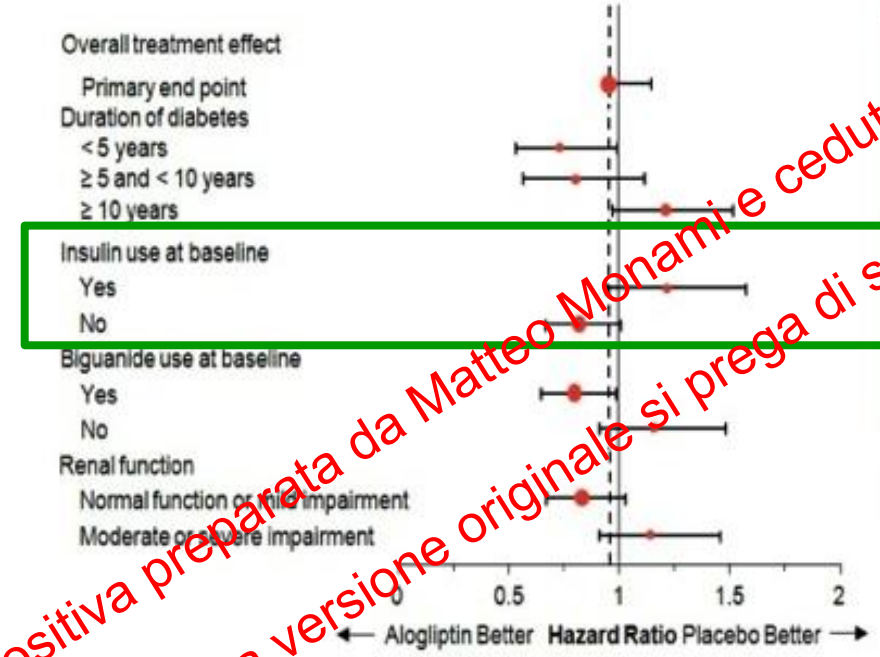
Hypoglycemic risk

When added to ongoing insulin therapy, the incidence of symptomatic hypoglycaemia was significantly (p = 0.003) increased in patients treated with sitagliptin [% (n/N) 16% (50/322)] compared with those treated with placebo [8% (25/319)]. The total number of hypoglycaemic episodes was 155

Diabetes, Obesity and Metabolism 12: 167–177, 2010.

DPP-4i and insulin: heart failure

The EXAMINE trial



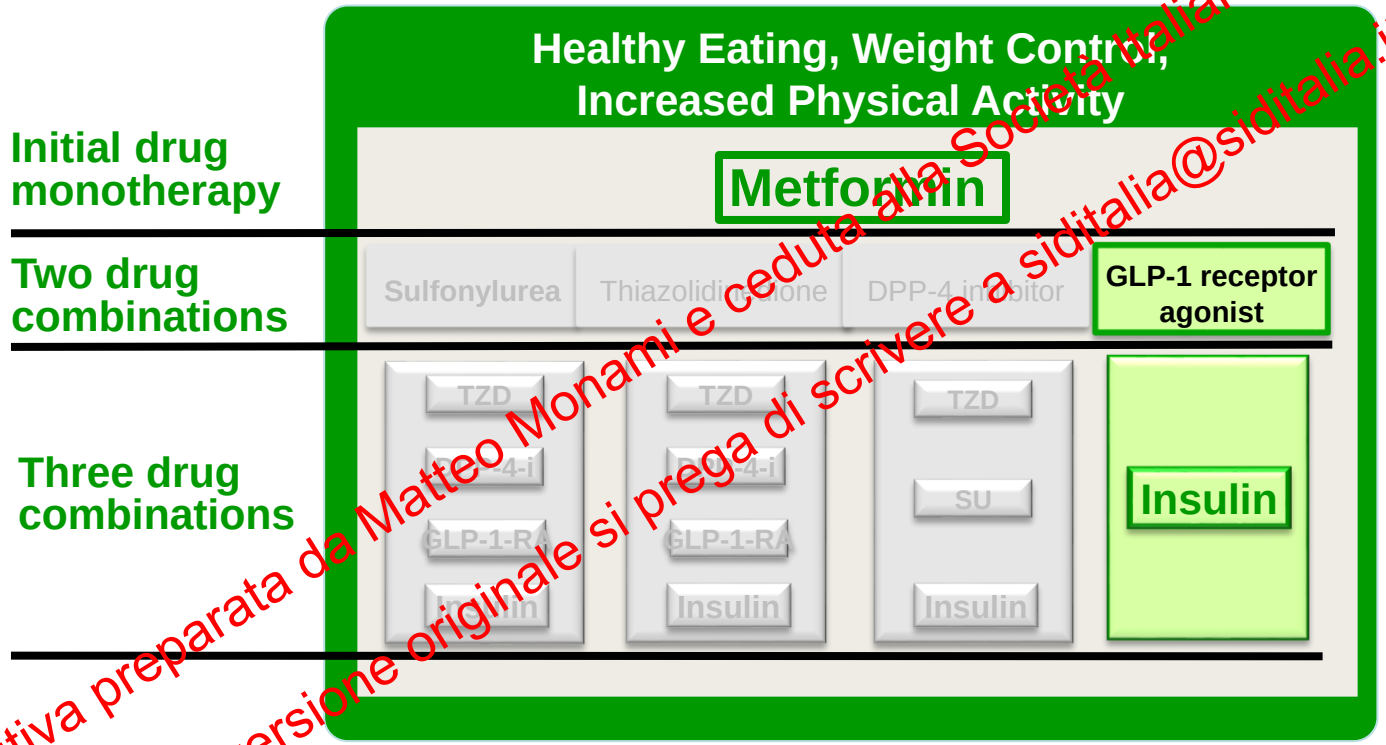
	Placebo		Alogliptin		Hazard		Interaction With Treatment
	n	%	n	%	Ratio	95% CI	P value
Overall treatment effect							
Primary end point	2679	11.8	2701	11.3	0.96	(≤1.16)*	
Duration of diabetes							
< 5 years	973	9.7	1009	7.0	0.74	(0.54, 1.01)	
≥ 5 and < 10 years	665	11.9	645	9.6	0.81	(0.58, 1.13)	
≥ 10 years	1032	13.8	1035	16.5	1.22	(0.98, 1.53)	0.014
Insulin use at baseline							
Yes	812	13.3	793	16.1	1.23	(0.95, 1.59)	
No	1867	11.1	1908	9.3	0.83	(0.68, 1.02)	0.018
Biguanide use at baseline							
Yes	1808	10.9	1760	8.8	0.81	(0.66, 1.00)	
No	871	13.7	941	16.0	1.17	(0.92, 1.50)	0.029
Renal function							
Normal function or mild impairment	1886	9.8	1929	8.3	0.84	(0.68, 1.04)	
Moderate or severe impairment	793	16.6	772	18.8	1.15	(0.91, 1.46)	0.046

N Engl J Med 2013; 369:1327-1335

Adding insulin to DPP4i

DPP-4i+Met	DPP4i+Met+Ins
No hypoglycemic risk – good tolerability	Modest increased in hypoglycemic risk
Very good cardiovascular safety	Questionable CV safety
No weight gain	Modest/No weight gain
Limited efficacy on HbA1c	Low insulin doses
Risk of hospitalization for heart failure (?)	Some advantages on HbA1c
	Risk of hospitalization for heart failure (?)

Position statement ADA/EASD 2012



Adapted from: Inzucchi *et al. Diabetes Care* 2012;35:1364-79

Noninsulin antidiabetic drugs added to metformin therapy

A meta-analysis of randomized clinical trials

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

	% Change in HbA_{1c}		HbA_{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
Group vs Placebo	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)
All drugs	20	−0.79 (−0.90 to −0.68)[a]	10	2.56 (1.99 to 3.[illegible])	12	0.14 (−1.37 to 1.65)[a]	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	−0.79 (−1.15 to −0.43)	1	3.38 (2.02 to 5.83)	2	1.99 (0.86 to 3.12)	3	2.63 (0.76 to 9.13)[a]
Glinides	2	−0.71 (−1.24 to −0.[illegible])	1	3.20 (1.[illegible]7 to 7.58)	2	0.91 (0.35 to 1.46)	2	7.92 (1.45 to 43.21)
Thiazolidinediones	3	−1.00 (−1.62 to −0.38)[b]	1	[illegible] (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	−0.65 (−[illegible] to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.[illegible] −0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.99 (−1.19 to −0.7[illegible]	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.

[a] $I^2 \geq 75\%$.

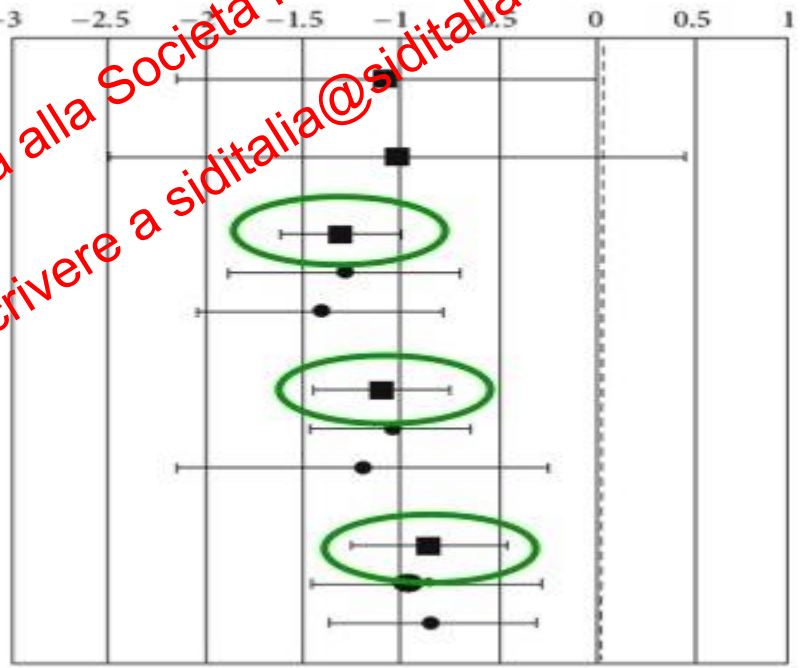
[b] $I^2 = 50\%$-75%.

Phung OJ, JAMA 2010 – vol. 303, No 14

GLP-1 RA and body weight

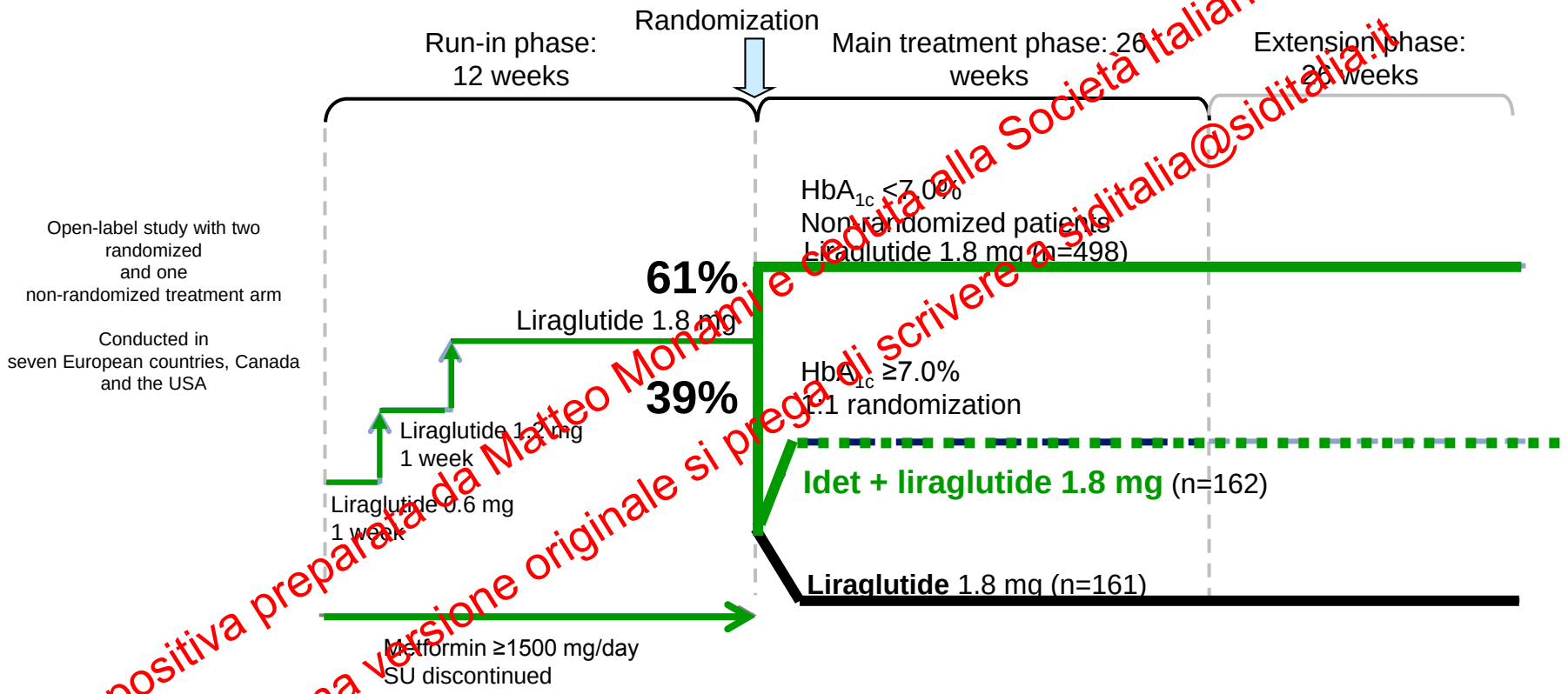
A meta-analysis of available RCTs

	MD	LL,95% CI	UL,95% CI	*P*	Number of trials
DPP-4 inhibitors	−1.08	−2.15	0.001	0.05	2
Thiazolidinediones	−1.02	−2.49	0.45	0.17	2
Sulfonylureas	−1.31	−1.62	−1	<0.001	4
Exenatide	−1.29	−1.88	−0.7	<0.001	2
Liraglutide	−1.41	−2.03	−0.79	<0.001	2
Insulin	−1.1	−1.45	−0.75	<0.001	4
Exenatide	−1.05	−1.47	−0.64	<0.001	4
Liragl./Exen. LAR	−1.2	−2.1	−0.25	0.001	2
Placebo	−0.96	−1.322	−0.591	<0.001	9
Exenatide	−1.058	−1.563	−0.554	<0.001	5
Liraglutide	−0.85	−1.37	−0.315	0.002	4



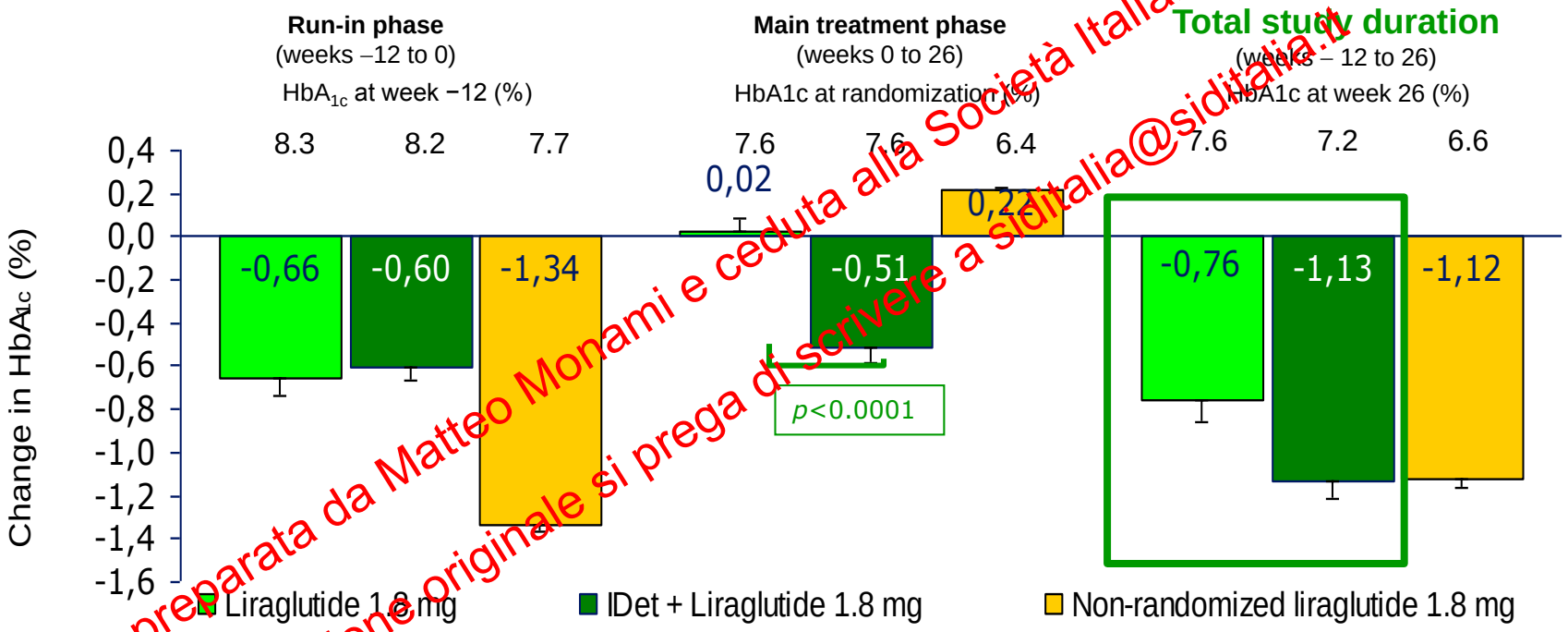
Monami M, Dicembrini I, Marchionni N, Rotella CM, Mannucci E.
Exp Diabetes Res ID 672658, 2012

Combining liraglutide with detemir



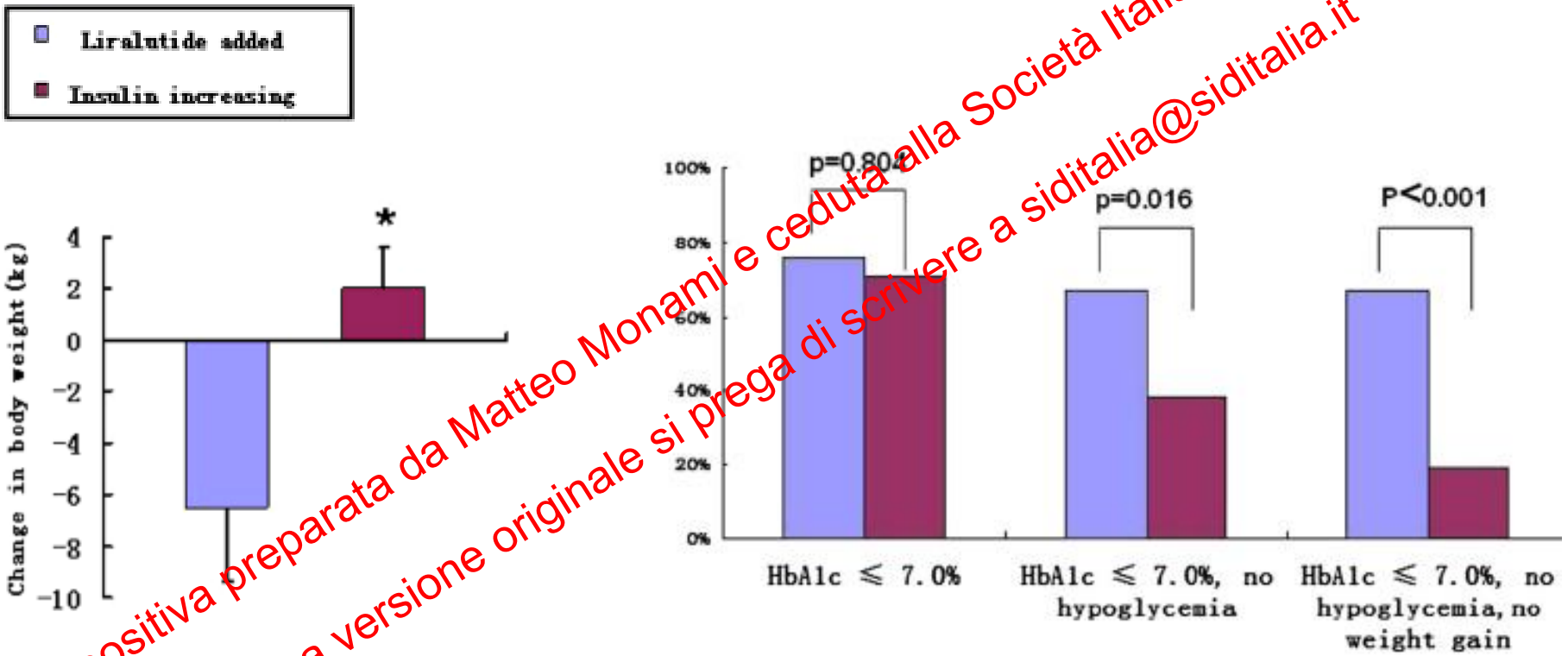
DeVries *et al. Diabetes Care* 2012;35:1446–54

Combining liraglutide with detemir



DeVries *et al. Diabetes Care* 2012;35:1446–54

Insulin and GLP-RA: efficacy and safety



Li *et al. Cardiovascular Diabetology* 2012, **11**:142

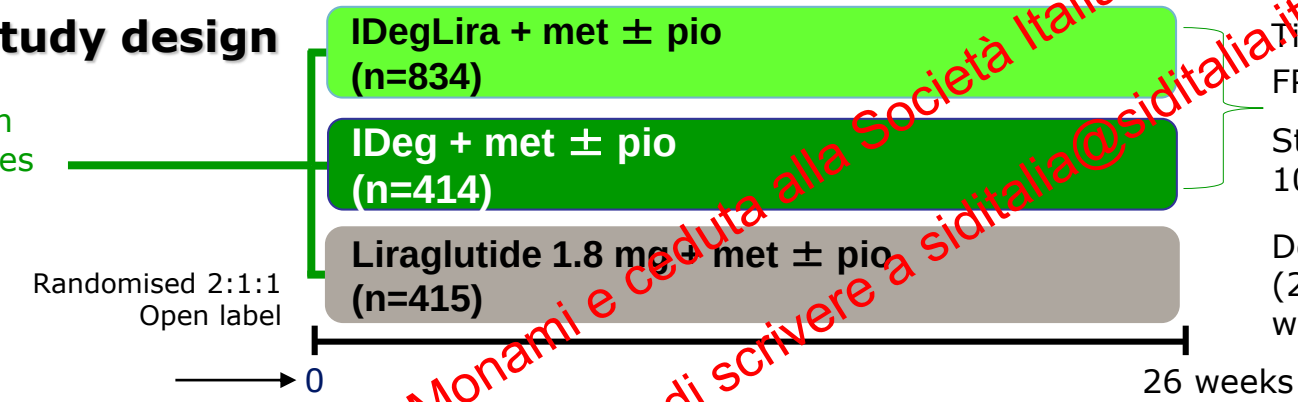
Adding insulin to GLP-1RA

GLP-1RA+Met → **GLP-1RA+Met+Ins**

GLP-1RA+Met	GLP-1RA+Met+Ins
Very good effect on HbA1c	**Very good effect on HbA1c**
Nice reduction of body weight	**Neutral on body weight**
No hypoglycemic risk	**Reduction of insulin doses**
Very good CV safety	**Relatively low hypoglycemic risk**
Some cases of pancreatitis	unknown CV safety
Transient Nausea/vomiting	Some cases of pancreatitis
	Transient nausea/vomiting

IdegLira: the future

DUAL™ I: Study design



Titration algorithm: IDegLira and IDeg

Mean fasting PG	Dose change
mmol/L	dose steps or U
<4.0	-2
4.0–5.0	0
>5.0	+2

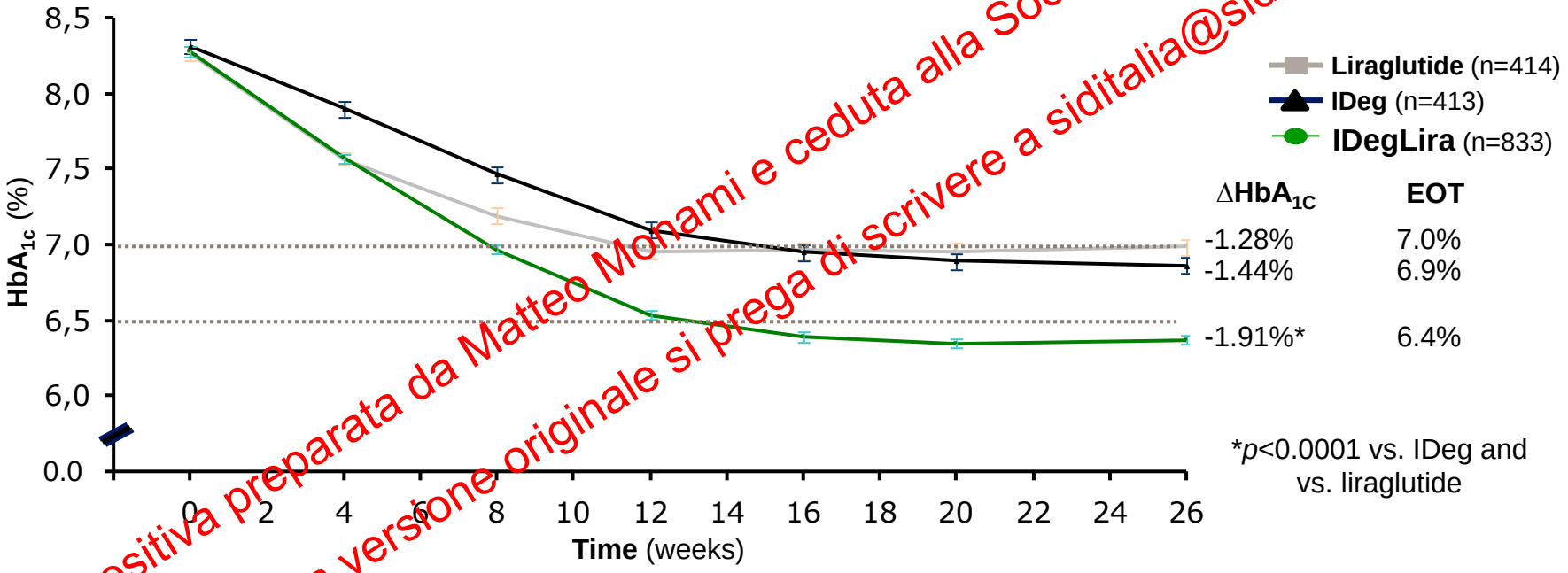
Inclusion criteria

- Type 2 diabetes
- Insulin naïve treated with metformin ± pioglitazone
- HbA_{1c} 7.0–10.0%
- BMI ≤40 kg/m^2
- Age ≥18 years*

Buse et al. ADA 2013: 65-OR; Gough et al. EASD 2013: 219-OR

IdegLira: the future

DUAL™ I: HbA1c over time

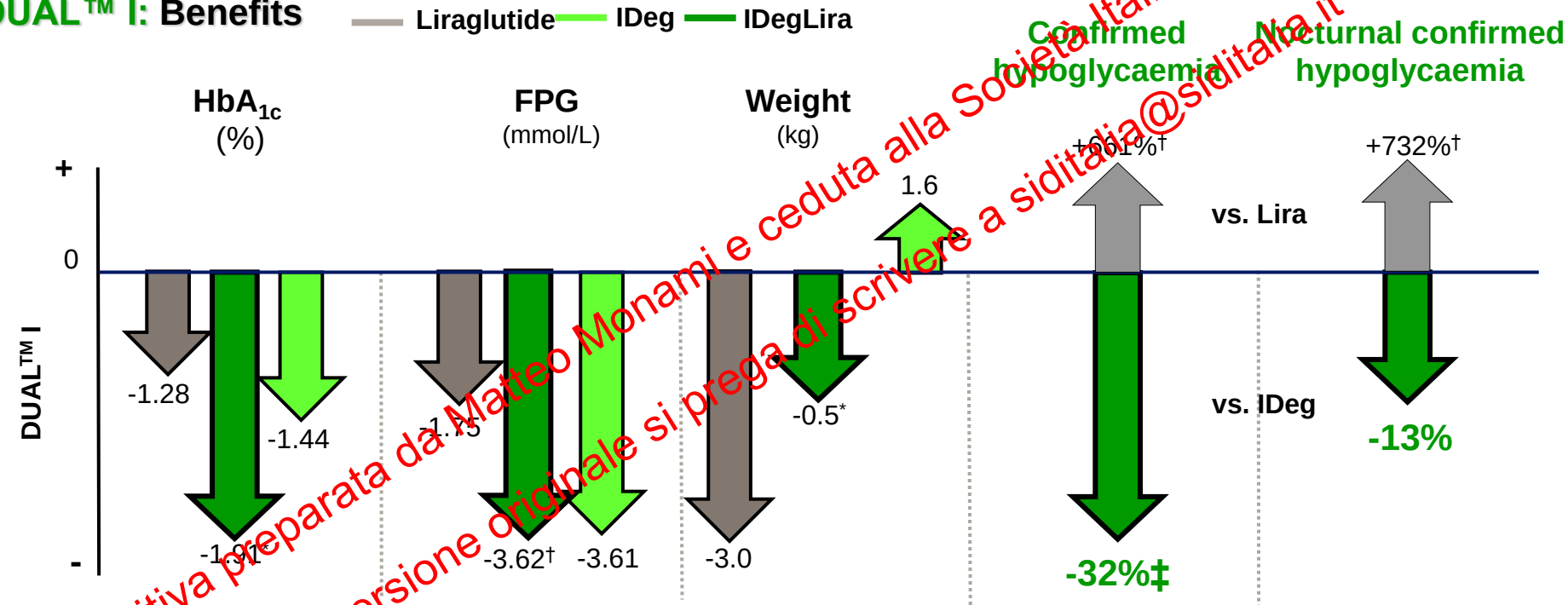


**p*<0.0001 vs. IDeg and vs. liraglutide

Buse et al. ADA 2013: 65-OR; Gough et al. EASD 2013: 219-OR

IdegLira: the future

DUAL™ I: Benefits



Buse et al. ADA 2013: 65-OR; Gough et al. EASD 2013: 219-OR

Conclusions

1. The addition of insulin to GLP-1RA+Met is an effective choice in terms of A1c reduction and seems to be superior to other possible combinations with OAD and insulin.
2. The reduction of A1c is obtained with no weight gain and a relatively low hypoglycemic risk.
3. The future of this strategy seems to be “IdegLira” which appears to be superior in reducing A1c with a lower hypoglycemic risk and weight gain.

Conclusions (2)

If it was possible….(GLP1 RA add-on to pre-existing insulin therapy)

- Significant A1C lowering
- Alternative to intensification with prandial / premixed insulin
- Weight gain expected with insulin may be reversed with GLP1RA
- It should be considered an insulin dose reduction to prevent hypoglycemia