INSULINA E GLP-1 RAS: INSIEME O SEPARATI?

Fixed-Dose Combination: un Vantaggio o uno Svantaggio?

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Il prof. Luigi Laviola dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Boehringer Ingelheim , Astra Zeneca, Johnson&Johnson, Lilly Italia, Medtronic, MOVI, Novo Nordisk, Roche, Sanofi Aventis, Takeda (*consulenza scientifica*)

Bayer, Boehringer Ingelheim, Astra Zeneca, Guidotti, Johnson&Johnson, Lilly, Medtronic, Menarini, Movi, MSD, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Takeda (*relazioni a convegni, supporto per partecipazione a congressi*)

Dobbiamo proprio usare una combinazione precostituita?

Metformina 400 mg + glibenclamide 2,5 mg

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Metformina 400 mg + glibenclamide 2,5 mg

Perché una combinazione precostituita?

Contro?

Pro?

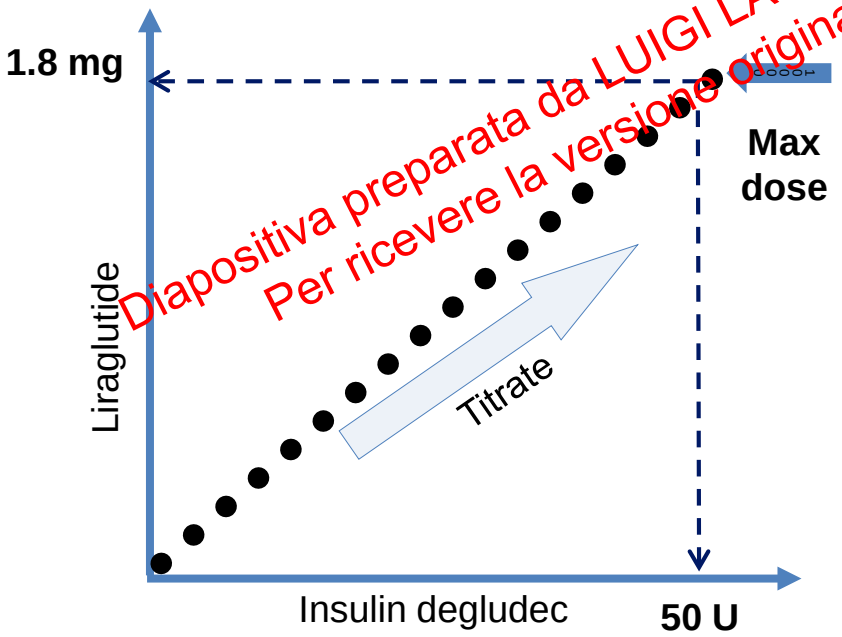
Combinazione Fissa
Insulina Basale – GLP-1 RA

Degludec/liraglutide (IDegLira)

100 unità di insulina degludec e 3,6 mg di liraglutide.

Una dose unitaria contiene 1 unità di insulina degludec e 0,036 mg di liraglutide.

→ La dose piena di liraglutide (1,8 mg) si ottiene con 50 unità di basale.



Glargine/lixisenatide (IGlarLixi)

2 formulazioni:

100 unità glargine + 50 mcg lixisenatide (rapporto 2:1)

→ La dose piena di lixisenatide (20 mcg) si ottiene con 40 unità di insulina

100 unità glargine + 33 mcg lixisenatide (rapporto 3:1)

→ La dose piena di lixisenatide (20 mcg) si ottiene con 60 unità di insulina

Quando considerare una combinazione fissa basale – GLP-1 RA?

Necessità di intensificare una terapia iniettiva:

Pazienti già in terapia con insulina basale + OAD

DUAL II: study design

Inclusion criteria

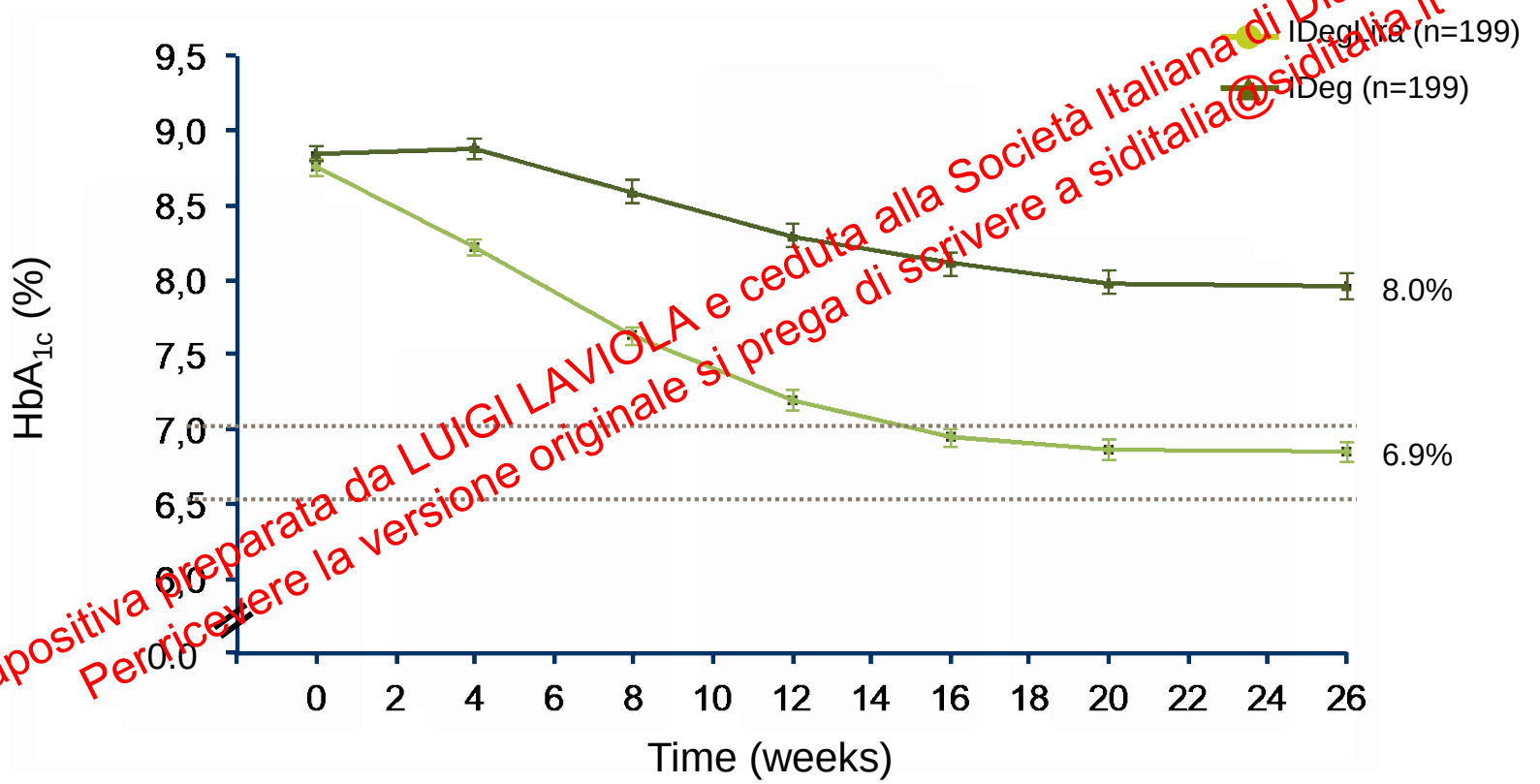
- Type 2 diabetes
- HbA_{1c} 7.5–10.0%
- BMI ≥27 kg/m^2
- Age ≥18 years
- Basal insulin (20−40 U) + metformin ± SU or glinides

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

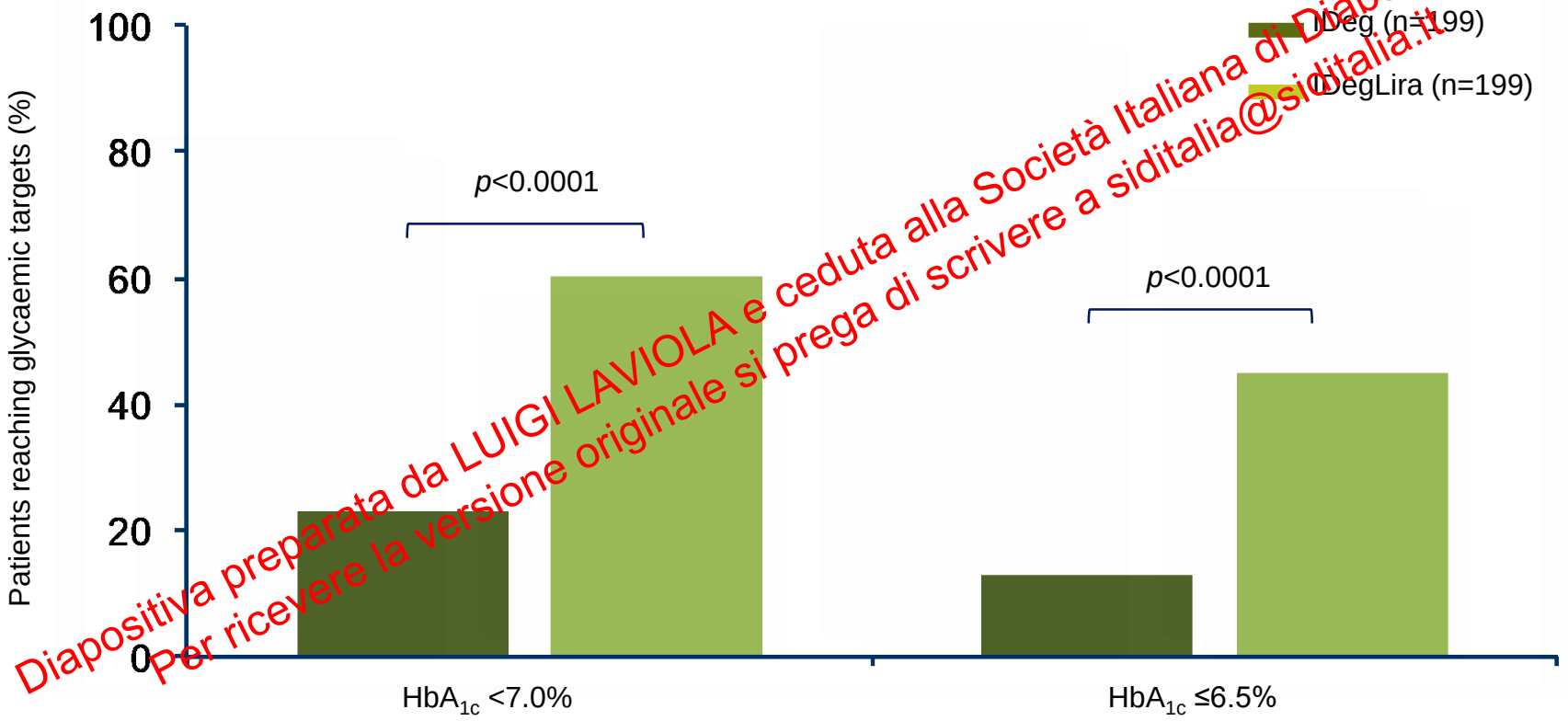
Buse et al. Diabetes Care 2014

DUAL II: HbA1c over time



Buse et al. Diabetes Care 2014

DUAL II: percentage of patients to target

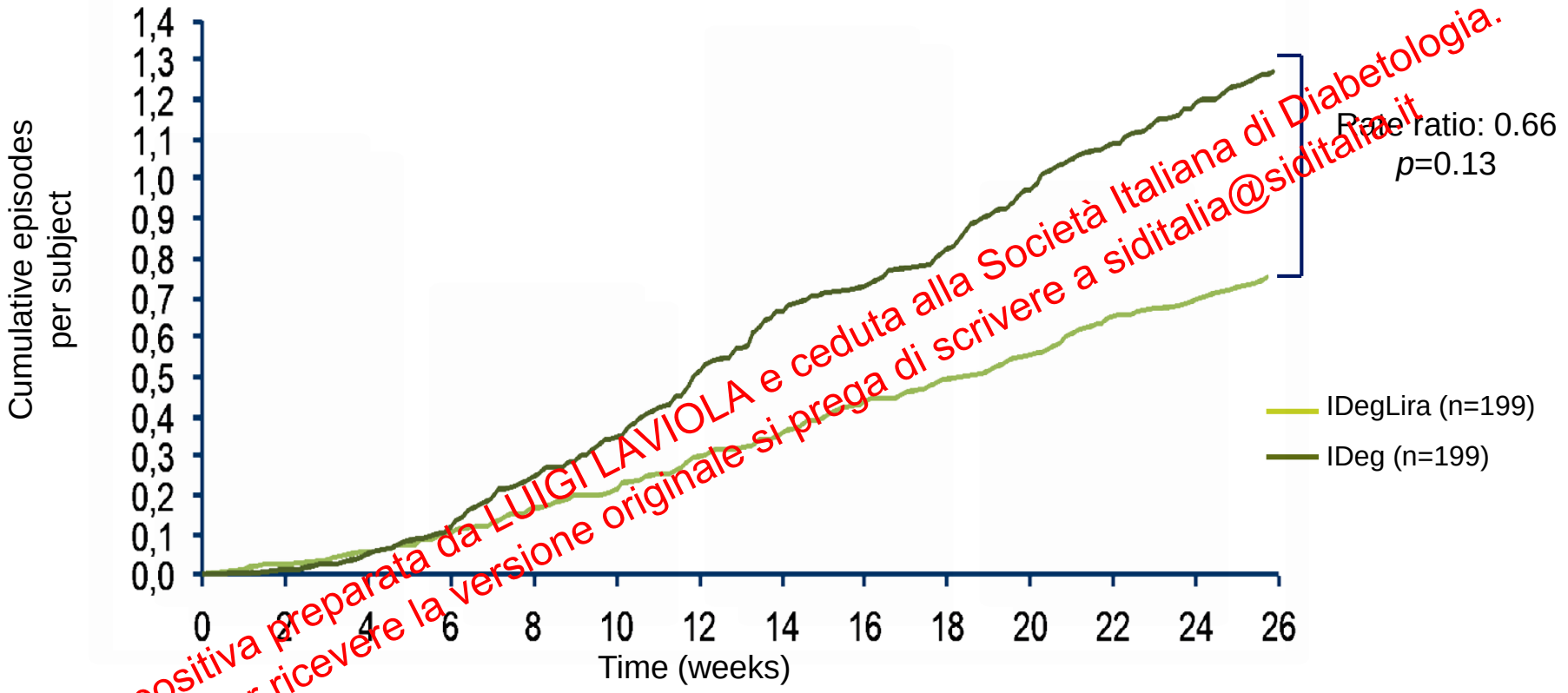


Buse et al. Diabetes Care 2014

DUAL II: 9P-SMBG - Post-prandial PG increment

Buse et al. Diabetes Care 2014

DUAL II: confirmed hypoglycaemia

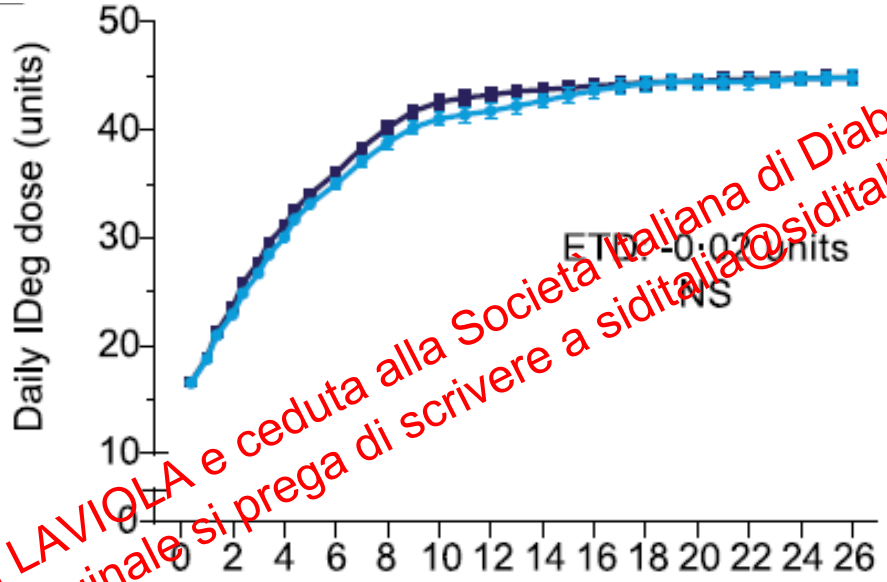


	IDegLira	IDeg
HbA_{1c} (%)	6.9	8.0

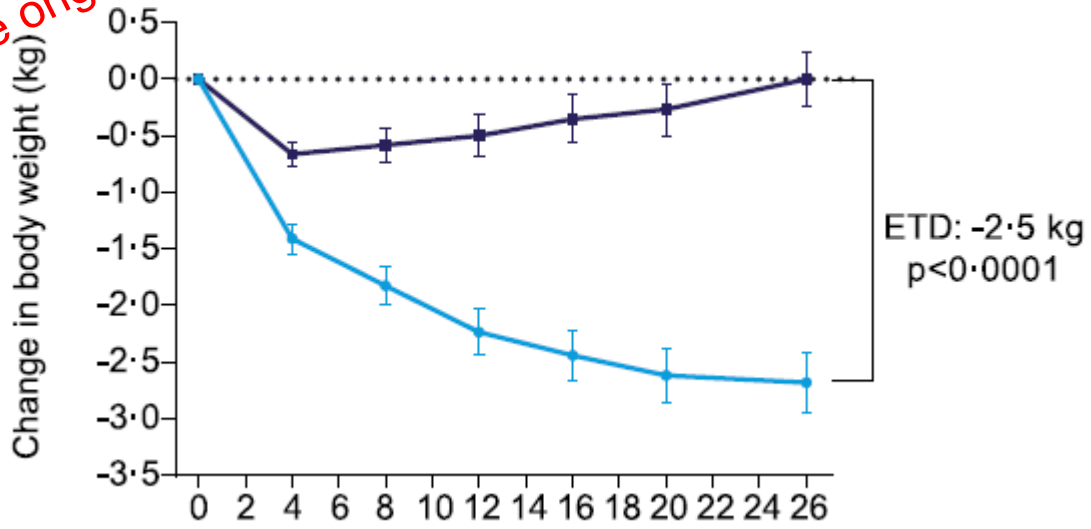
Buse et al. Diabetes Care 2014

DUAL II: Insulin Dose and Body Weight

Daily Insulin Dose



Body Weight

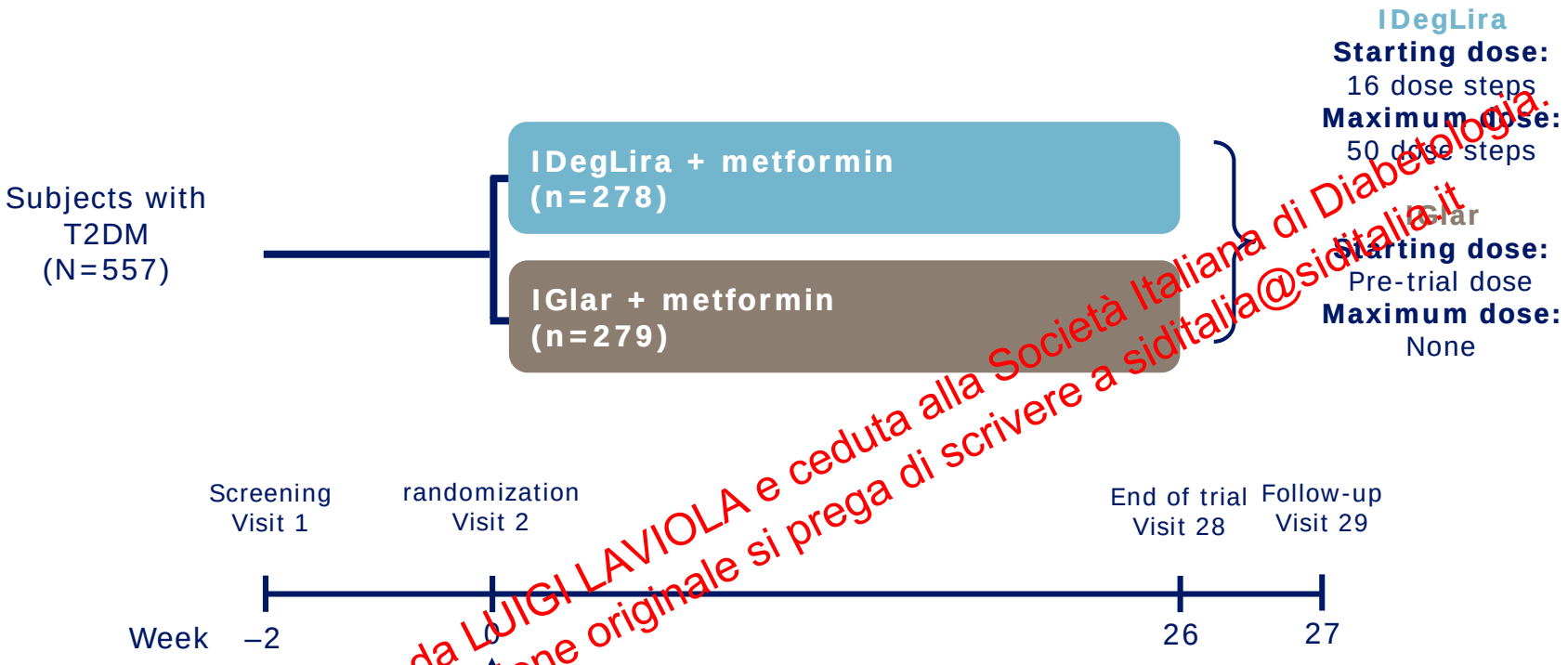


Buse et al. Diabetes Care 2014

Riassunto: IDegLira vs IDeg

- Riduzione HbA1c
- Maggior numero di pazienti a target
- Miglior profilo glicemico
- Calo ponderale
- Stessa dose di insulina (*circa 45 unità*)
- Rischio di ipoglicemia simile
- Effetti collaterali in linea con GLP-1 RA (*più lievi*)

DUAL V

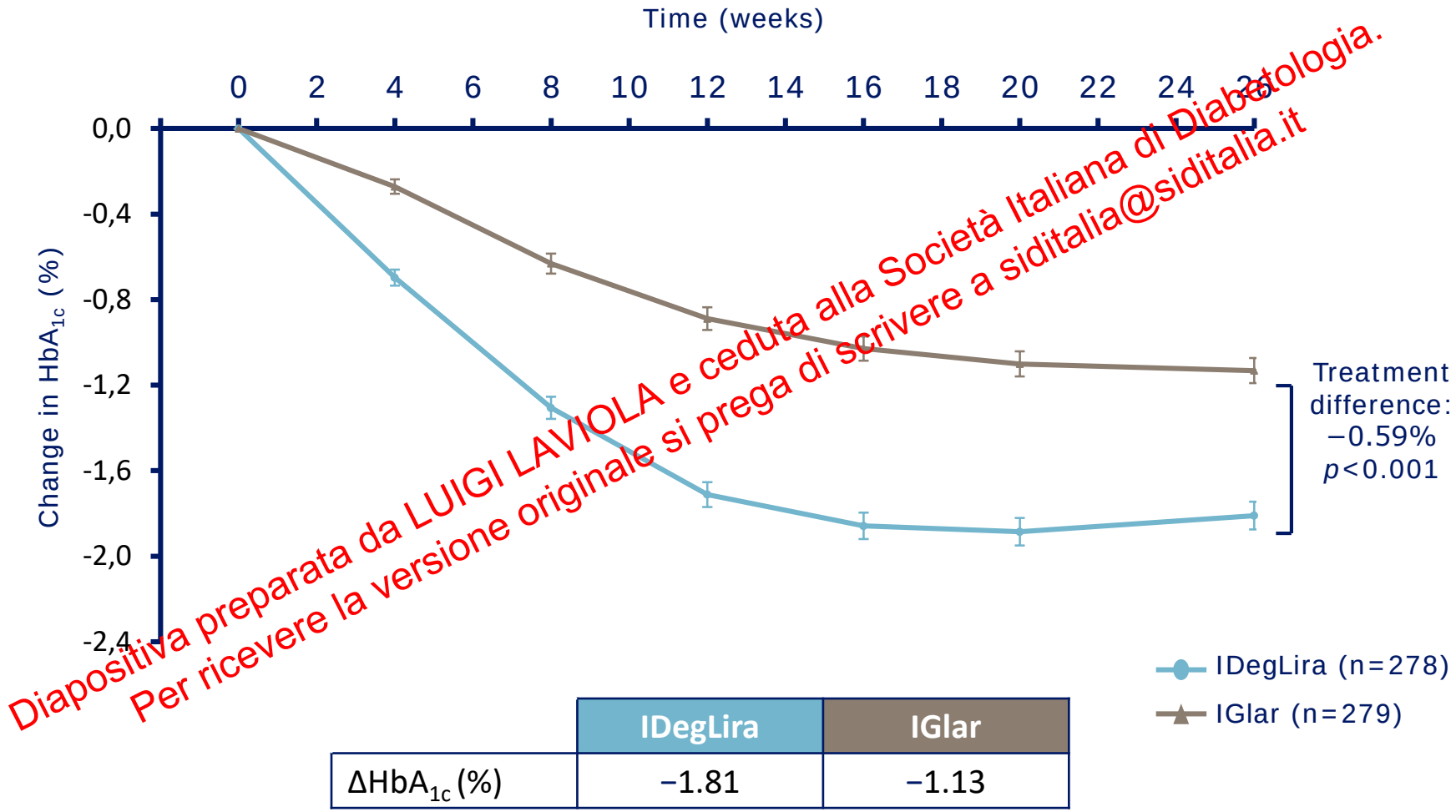


Inclusion criteria
- T2DM
- Metformin + IGlar (20–50 units)
- HbA_{1c} 7–10%
- Age ≥18 years
- BMI ≤40 kg/m^2

Mean FPG[a]		Dose change
mmol/L	mg/dL	dose steps/units
<4.0	<71	–2
4.0–5.0	71–90	0
>5.0	>90	+2

Lingvay I et al. JAMA 2016

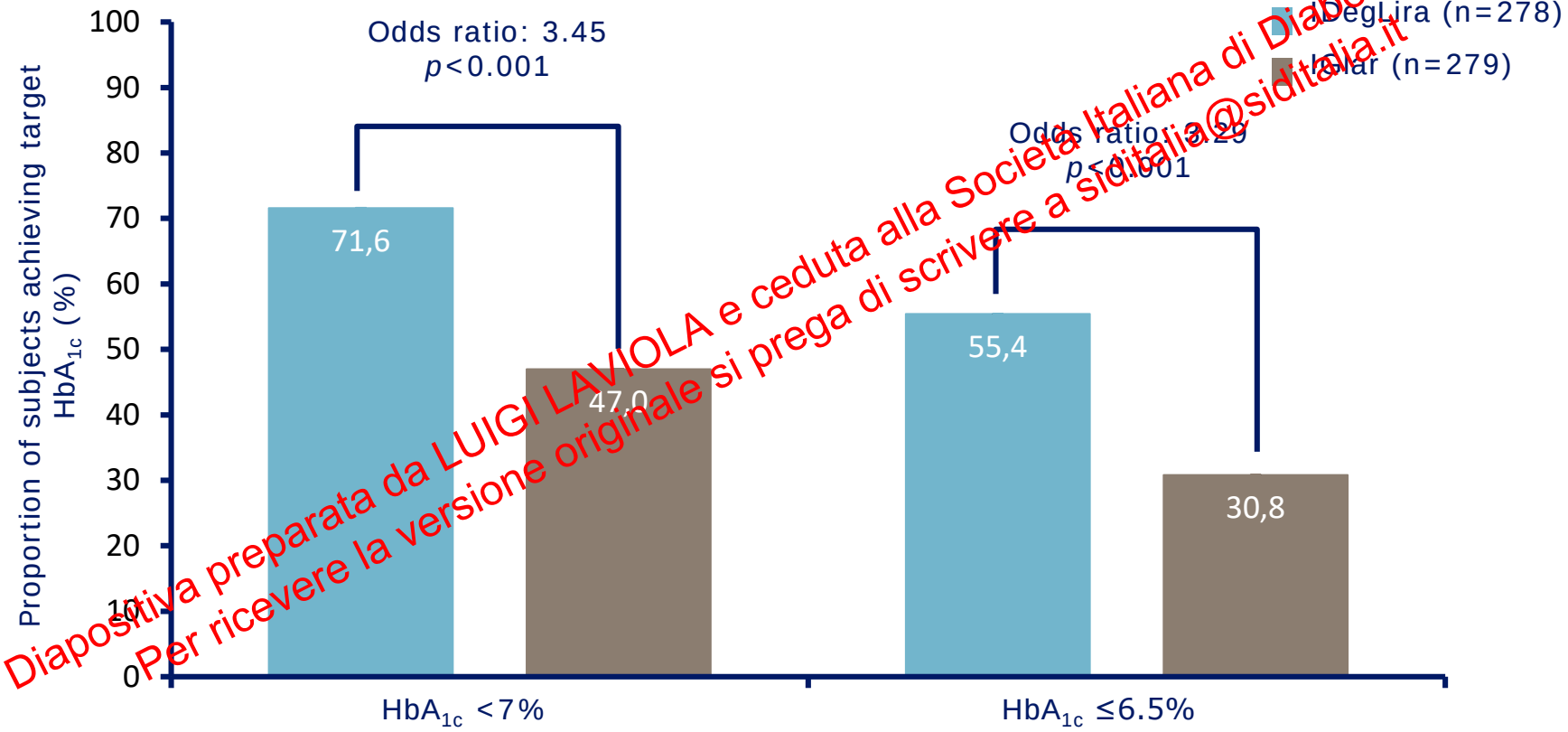
DUAL V: Change in HbA_{1c} over time



	IDegLira	IGlar
ΔHbA_{1c} (%)	−1.81	−1.13

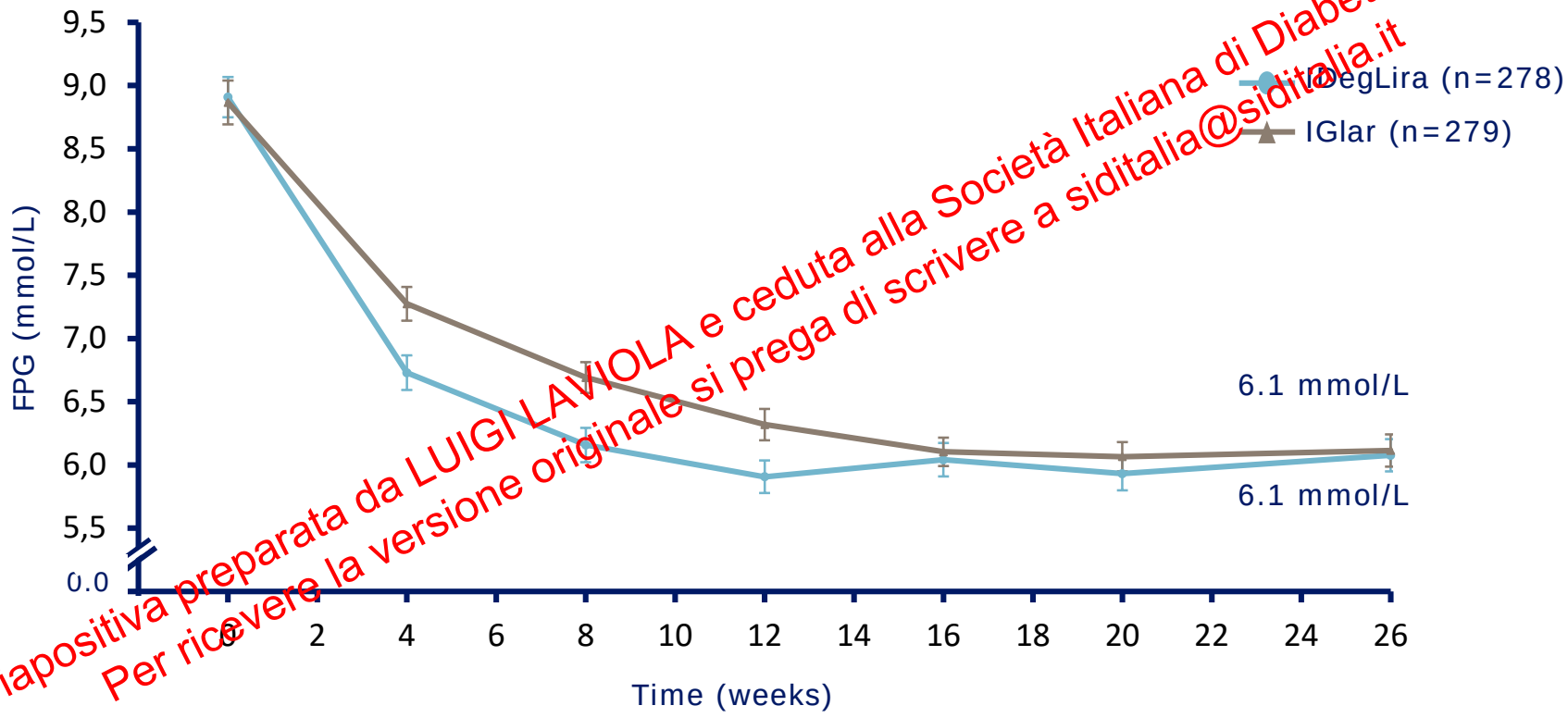
Lingvay I et al. JAMA 2016

DUAL V: Subjects achieving HbA1c targets



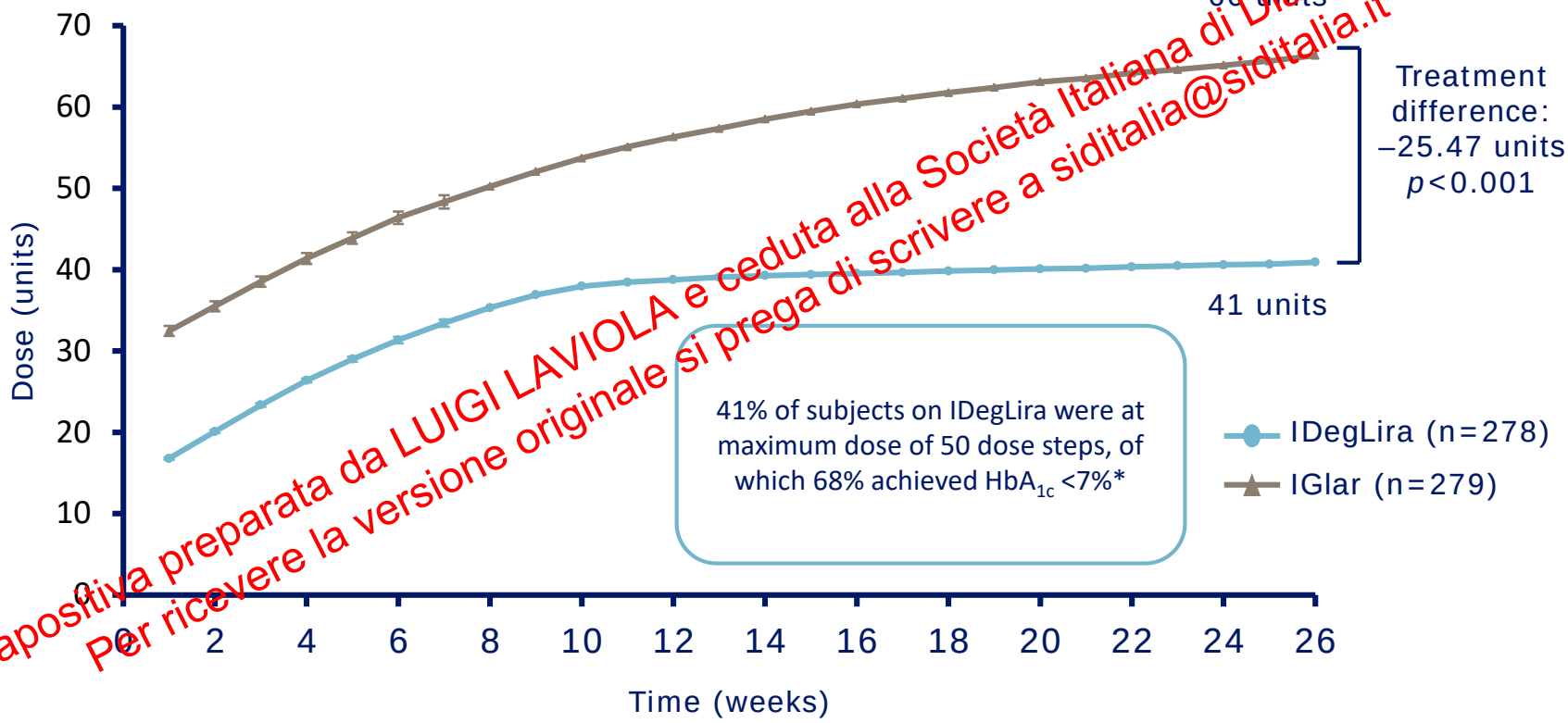
Lingvay I et al. JAMA 2016

DUAL V: FPG over time



Lingvay I et al. JAMA 2016

DUAL V: Daily insulin dose over time



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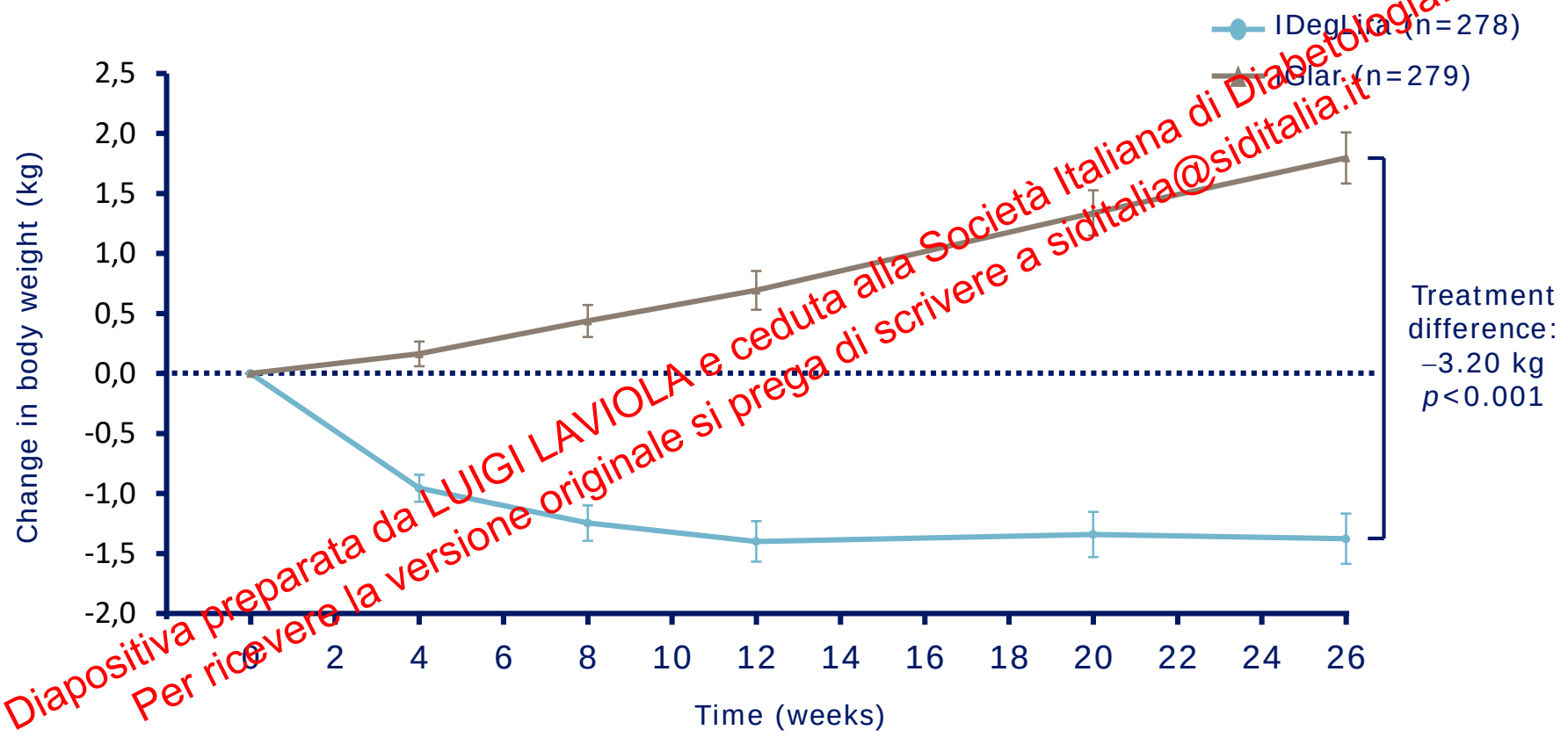
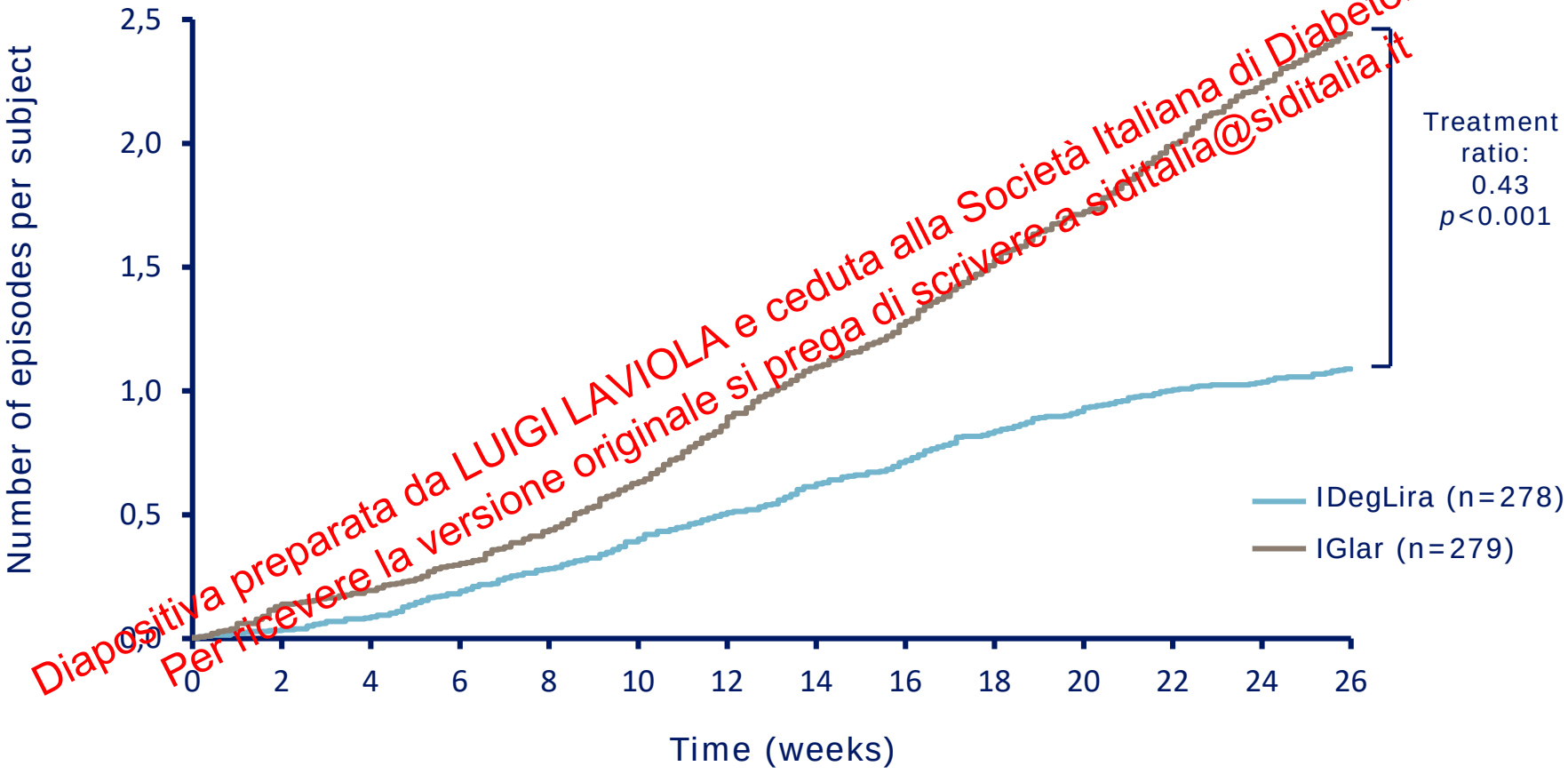
DUAL V: Change in body weight



	IDegLira	IGlar
ΔBody weight (kg)	–1.4	1.8

Lingvay I et al. JAMA 2016

DUAL V: Confirmed hypoglycaemia



Lingvay I et al. JAMA 2016

DUAL V: Composite outcomes

	Proportion of subjects (%)				
	IDegLira	IGlar	Odds ratio IDegLira/IGlar	95% CI	*p*-value
HbA_{1c} <7%	71.6	47.0	3.45	[2.36; 5.05]	<0.001
HbA_{1c} <7%, no weight gain	50.0	19.7	5.18	[3.43; 7.83]	<0.001
HbA_{1c} <7%, no hypoglycaemic episodes	54.3	29.4	3.24	[2.24; 4.70]	<0.001
HbA_{1c} <7%, no weight gain and no hypoglycaemic episodes	38.8	12.2	5.53	[3.49; 8.77]	<0.001

Lingvay I et al. JAMA 2016

DUAL V: Subjects with nausea

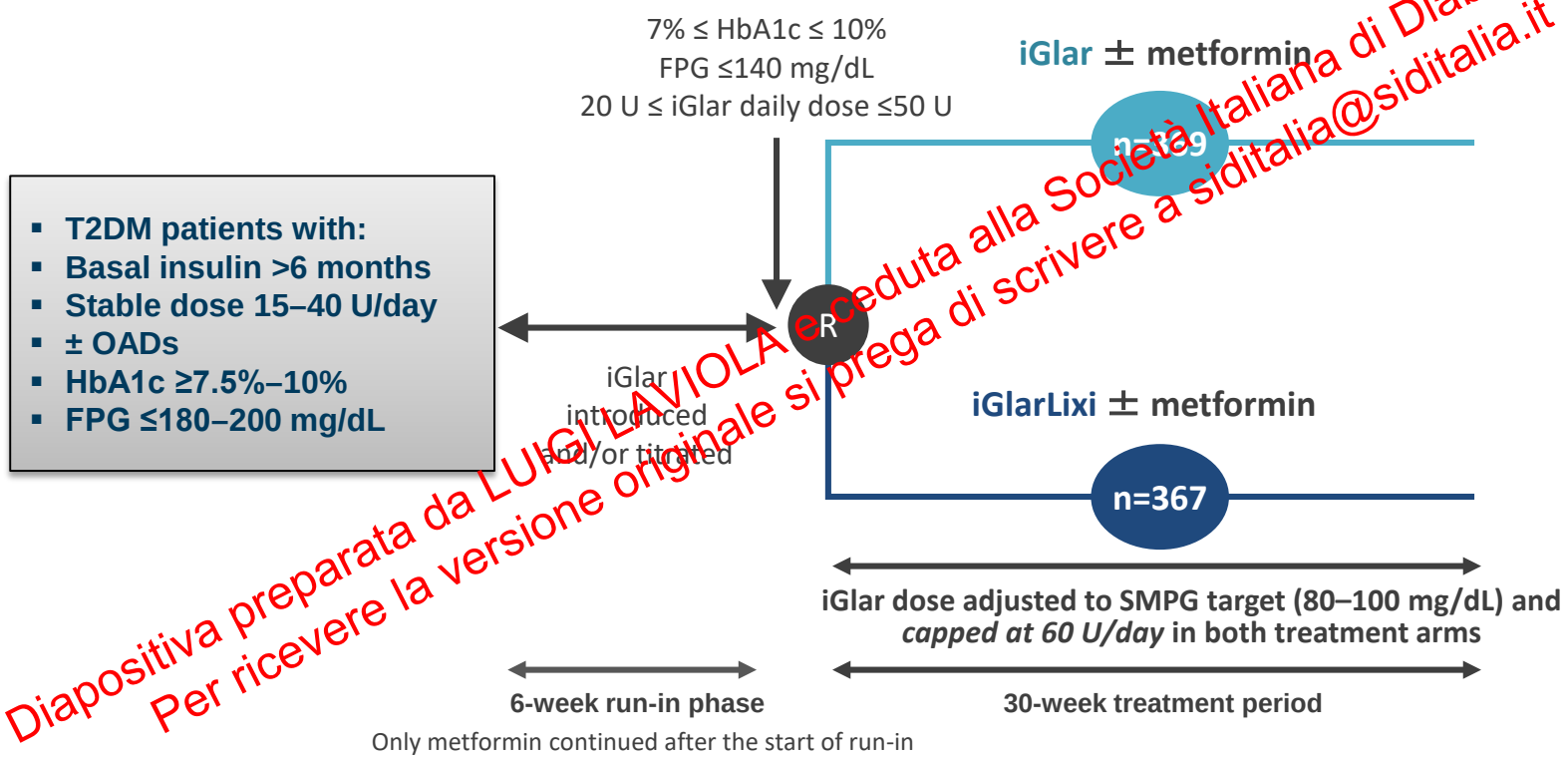
Lingvay I et al. JAMA 2016

Riassunto: IDegLira vs IGlar

- Riduzione HbA1c
- Glicemia a digiuno simile
- Maggior numero di pazienti a target
- Calo ponderale
- Riduzione dose di insulina (*66 vs 41 unità*)
- Riduzione ipoglicemie
- Miglior outcome composito
- Effetti collaterali in linea con GLP-1 RA (*più lievi*)

LixiLan-L: Patients with T2DM not controlled on basal insulin

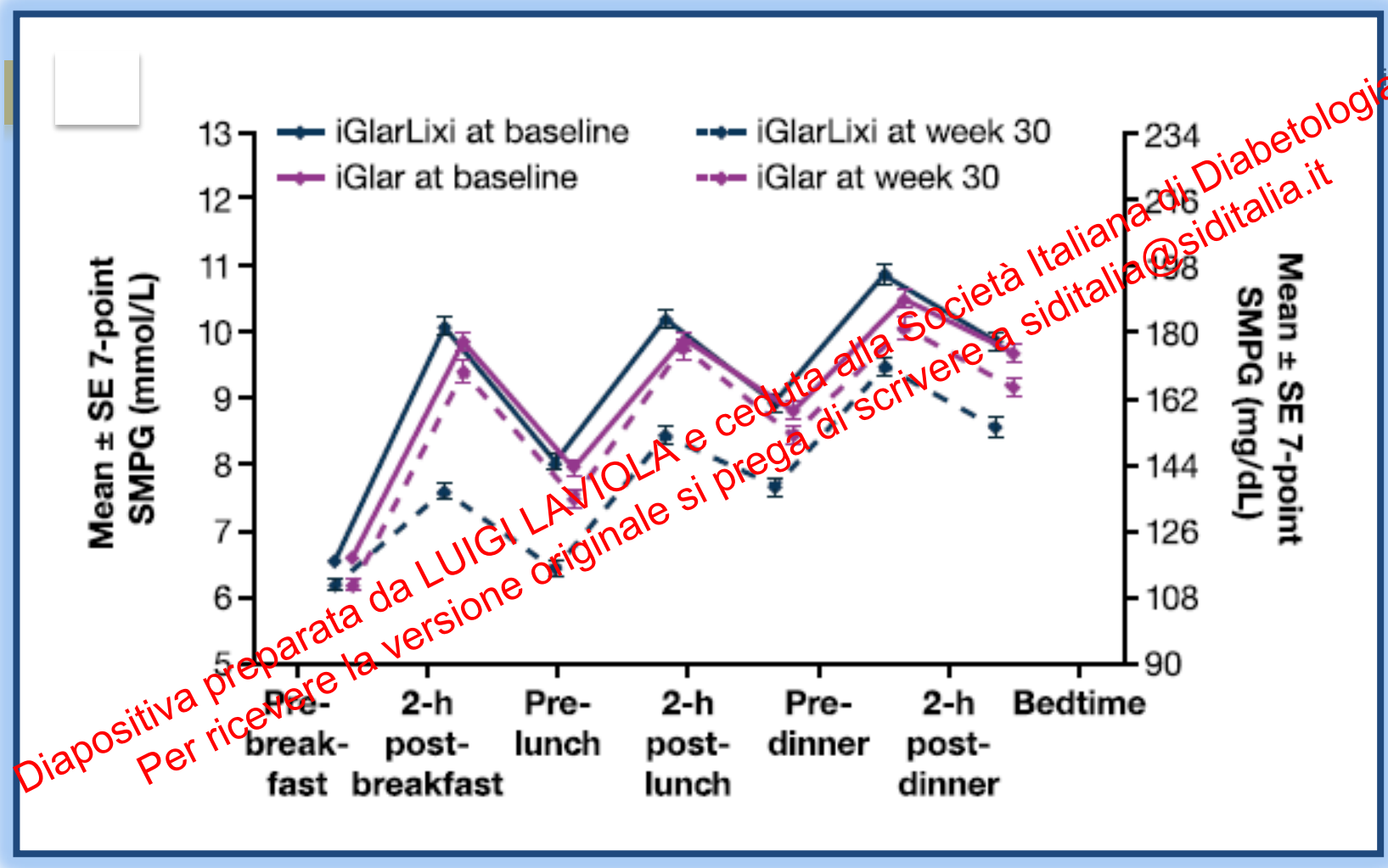
DESIGN: Randomized, open label, parallel-group, 30-week treatment study



Primary objective: Superiority of iGlarLixi over iGlar in HbA1c change at Week 30

Aroda VR, et al. Diabetes Care 2016

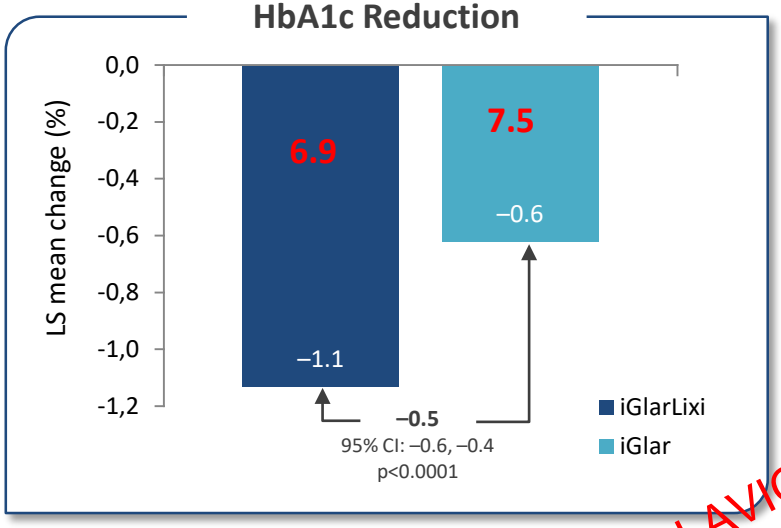
LixiLan-L: Mean change in HbA1c

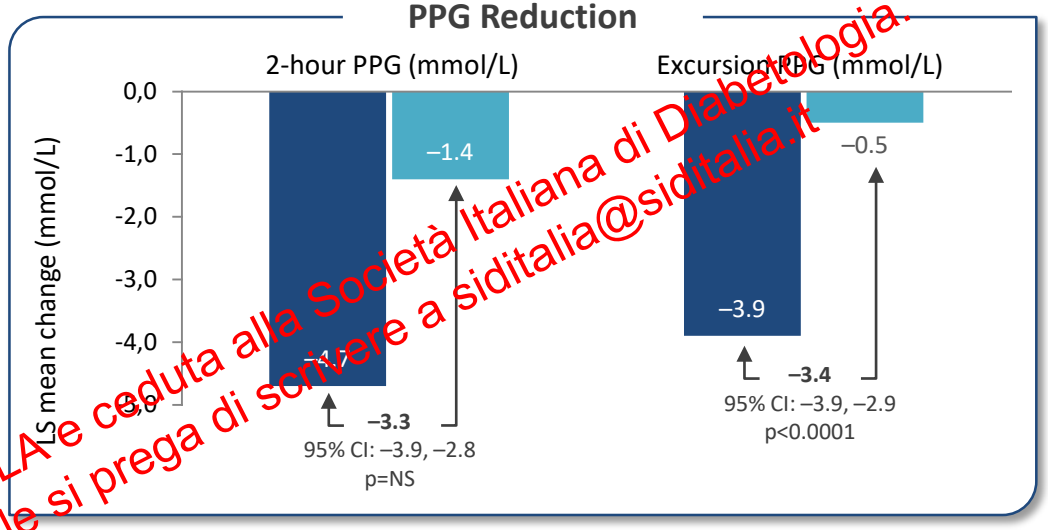


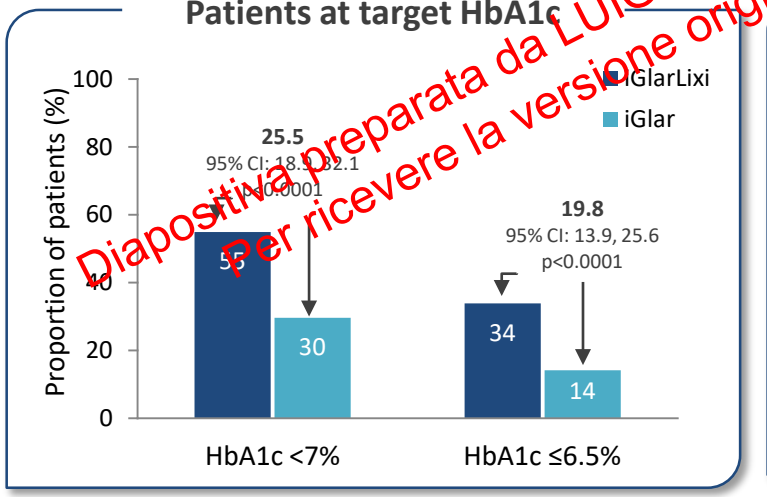
Aroda VR, et al. Diabetes Care 2016

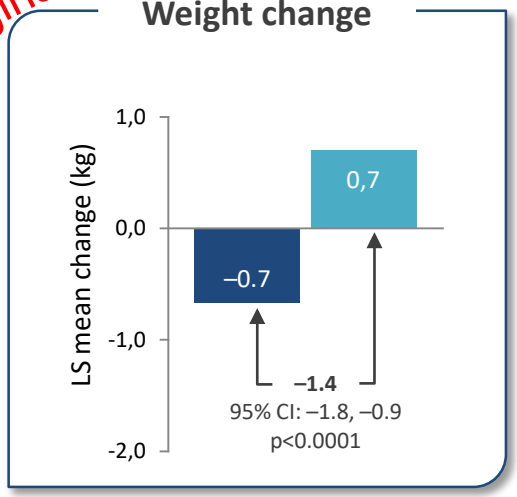
LixiLan-L: Key results

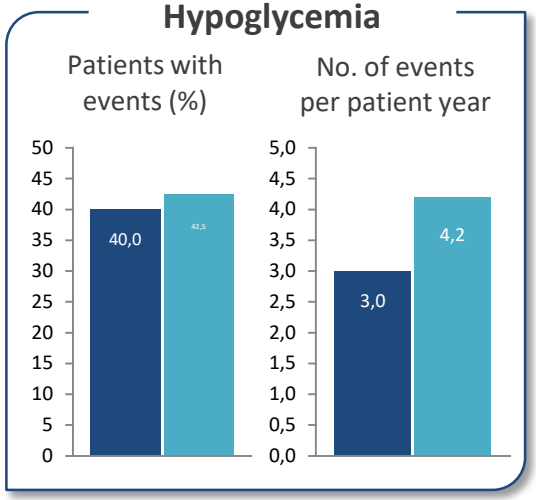
Mean (SD) HbA1c*, %	8.1 (0.6)	8.1 (0.7)











Aroda VR, et al. Diabetes Care 2016

Lixi Lan L: Composite outcomes

	Proportion of subjects (%)		
	IGlarLixi	IGlar	*p*-value
HbA_{1c} <7%	54.9	29.6	<0.001
HbA_{1c} <7%, no weight gain	34.2	13.4	<0.001
HbA_{1c} <7%, no hypoglycaemic episodes	31.7	18.6	<0.001
HbA_{1c} <7%, no weight gain and no hypoglycaemic episodes	19.9	9.0	<0.001

Aroda VR, et al. Diabetes Care 2016

Riassunto: IGlarLixi vs IGlar

- Riduzione HbA1c
- Glicemia a digiuno simile, miglior profilo glicemico
- Maggior numero di pazienti a target
- Calo ponderale
- Stessa dose di insulina (*47 unità*)
- Rischio di ipoglicemie simile
- Migliore outcome composito
- Effetti collaterali in linea con GLP-1 RA (*più lievi*)

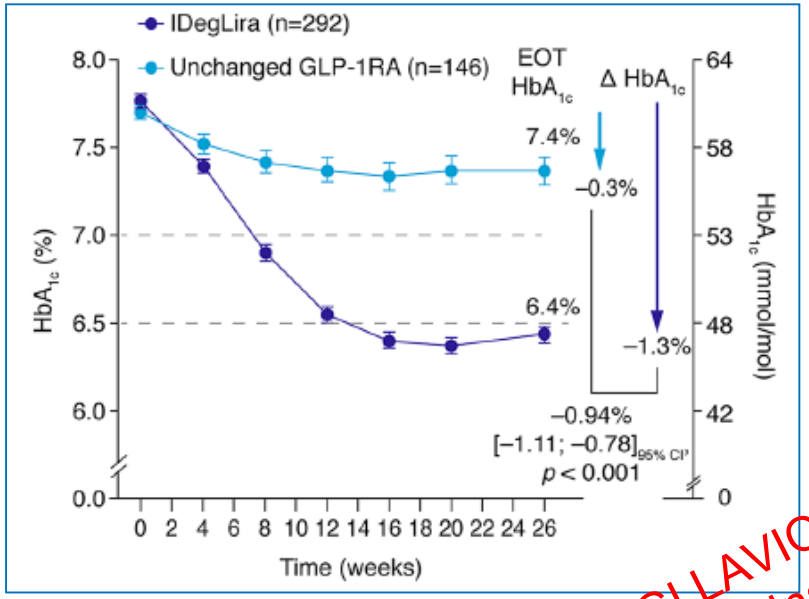
Quando considerare una combinazione fissa basale – GLP-1 RA?

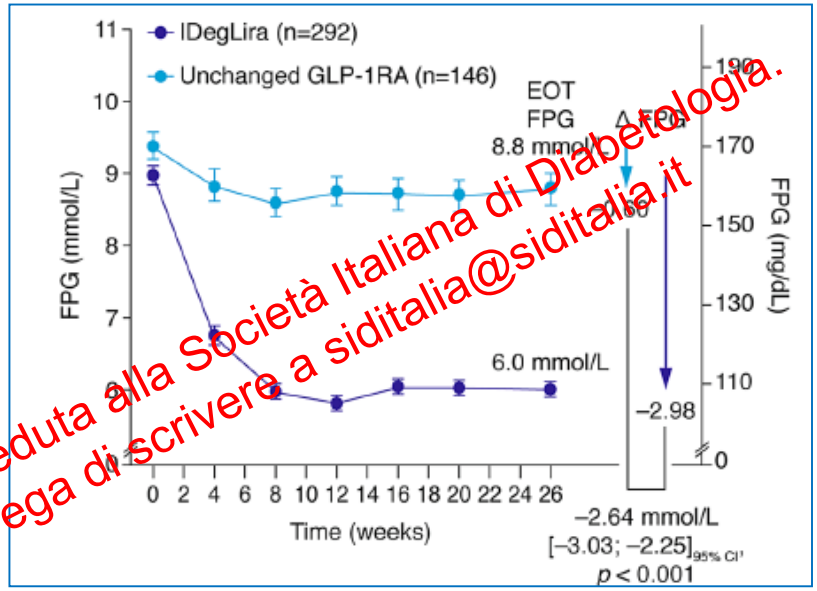
Necessità di intensificare una terapia iniettiva:

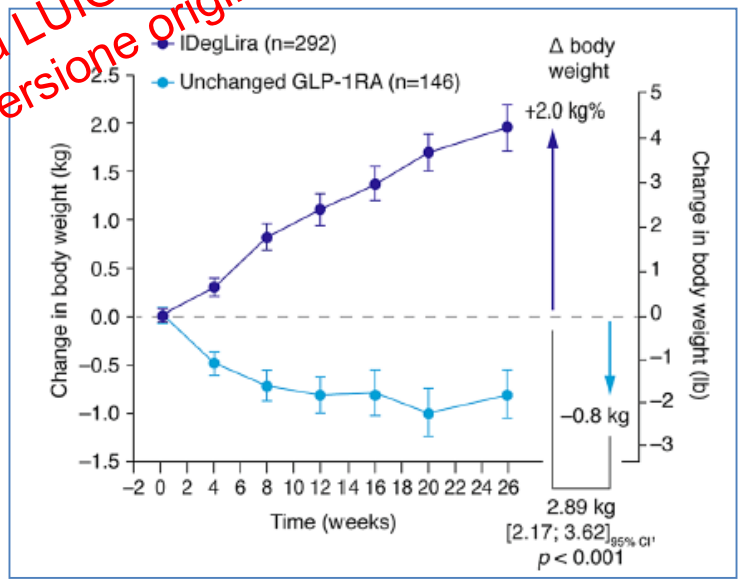
Pazienti già in terapia con insulina basale + OAD

Pazienti già in terapia con GLP-1 RA + OAD

DUAL III: IDegLira vs GLP-1 RA







Linjawi et al. Diabetes Ther 2017

Perché una combinazione precostituita?

- Miglior compenso glicemico (*HbA1c, profilo*)
- Controllo del peso (*vs basale*)
- Eventi ipoglicemici correlati alla dose di insulina (*pari/ridotta*)
- Migliore outcome composito

- Limitata flessibilità nella titolazione
- Dose di GLP-1 RA non massimale *(→ migliore tollerabilità)*

Farmaco anti-inerzia!

Meta-analysis of clinical trials comparing basal insulin/GLP-1 RA and basal/bolus insulins

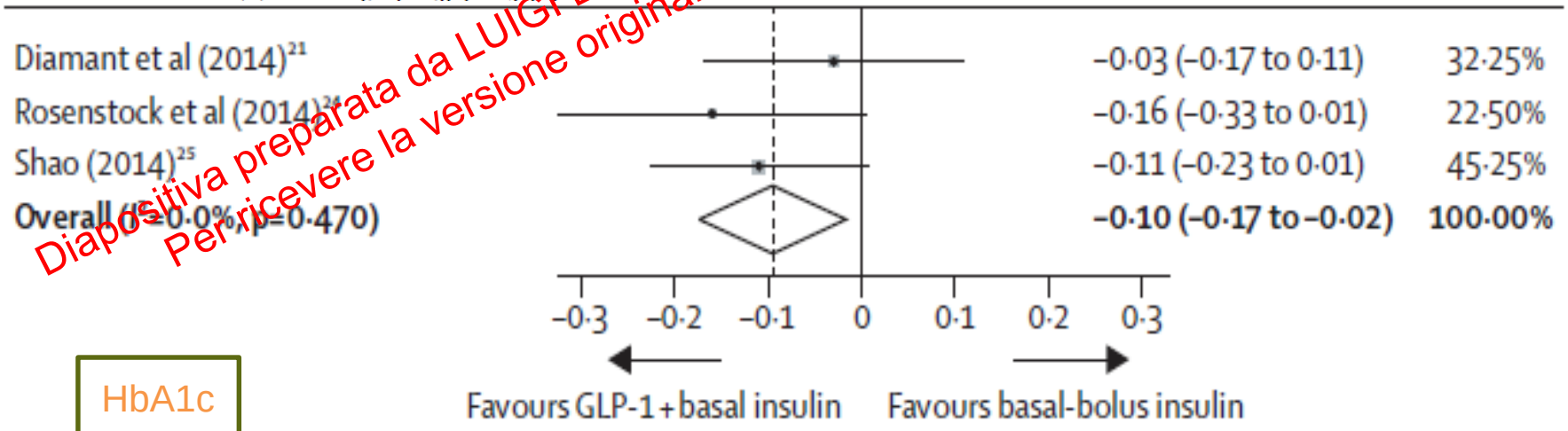
Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng*, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran

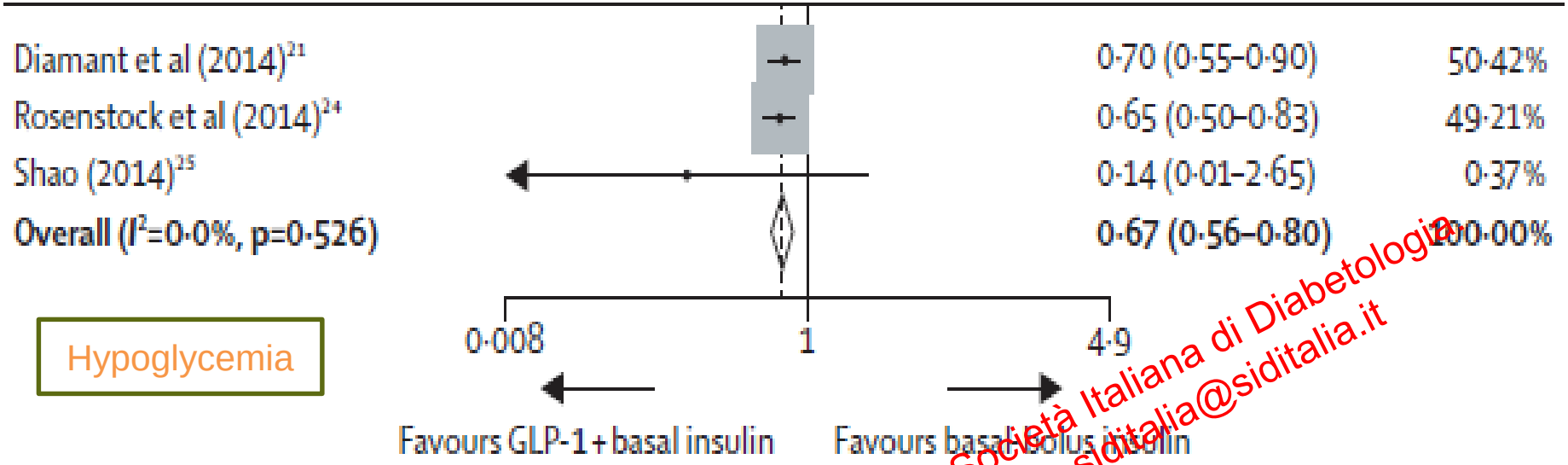
Lancet 2014; 384: 2228–34
Published Online September 12, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61335-0

Summary

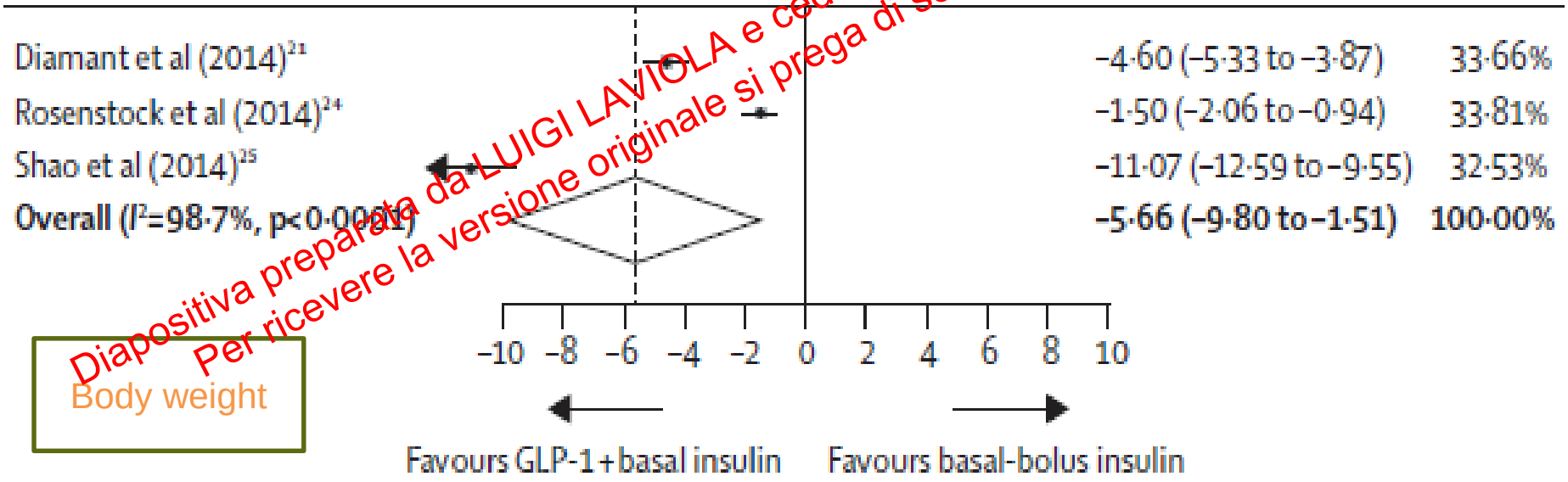
Background Combination treatment with a glucagon-like peptide-1 (GLP-1) agonist and basal insulin has been proposed as a treatment strategy for type 2 diabetes that could provide robust glucose-lowering capability with low risk of hypoglycaemia or weight gain. We thus did a systematic review and meta-analysis of randomised controlled trials to assess the effect of this combination treatment on glycaemic control, hypoglycaemia, and weight gain in



HbA1c



Hypoglycemia



Body weight

Basal i therap recept the tre guide t

Gerhard H. Sc

Comorbid conditions which may affect the use of GLP-1RA

Obesity (BMI ≥ 30 kg/m²) Preferred, if of android origin with visceral/liver fat accumulation Reduction in liver fat correlated with improvement in HbA1c	
Enhanced risk of hypoglycemia (older age, renal failure, medication) or need to avoid hypoglycemia (e.g. professional reasons)	
Age No use below 18 years, in older patients preferred use in 'young old' (65-79 years), no data in 'old old' (80-89 years) and older	
Previous macro- and microvascular diseases Until now, no additional risks observed, protective effects possible, Caution: preexisting maculopathy, higher grade retinopathy, longer diabetes duration	
Renal failure Use with care (lixisenatide: CrCl < 50 ≥ 30 ml/min), dose reduction (exenatide: CrCl < 60 ≥ 30 ml/min), not suggested (liraglutide: CrCl < 60 ml/min, exenatide and lixisenatide: CrCl < 30 ml/min).	
Liver disease Exenatide/lixisenatide: side effects not expected but no conclusive information, liraglutide: not suggested in mild, severe and very severe liver failure	
Gastrointestinal and pancreatic diseases Exenatide, liraglutide and lixisenatide are not recommended in patients with severe gastrointestinal diseases and contraindicated in patients with previous pancreatitis and pancreas carcinoma	

Figure 2. Comorbid conditions which may affect the use of GLP-1 RAs. BMI, body mass index; CrCl, creatinine clearance; GLP-1 RA, glucagon-like protein 1 receptor agonist; HbA1c, hemoglobin A1c.

IDegLira: Phase 3 Clinical Development Plan

Uncontrolled on OADs

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL IV
IDegLira add-on to SU vs. placebo

Uncontrolled on GLP-1RA

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

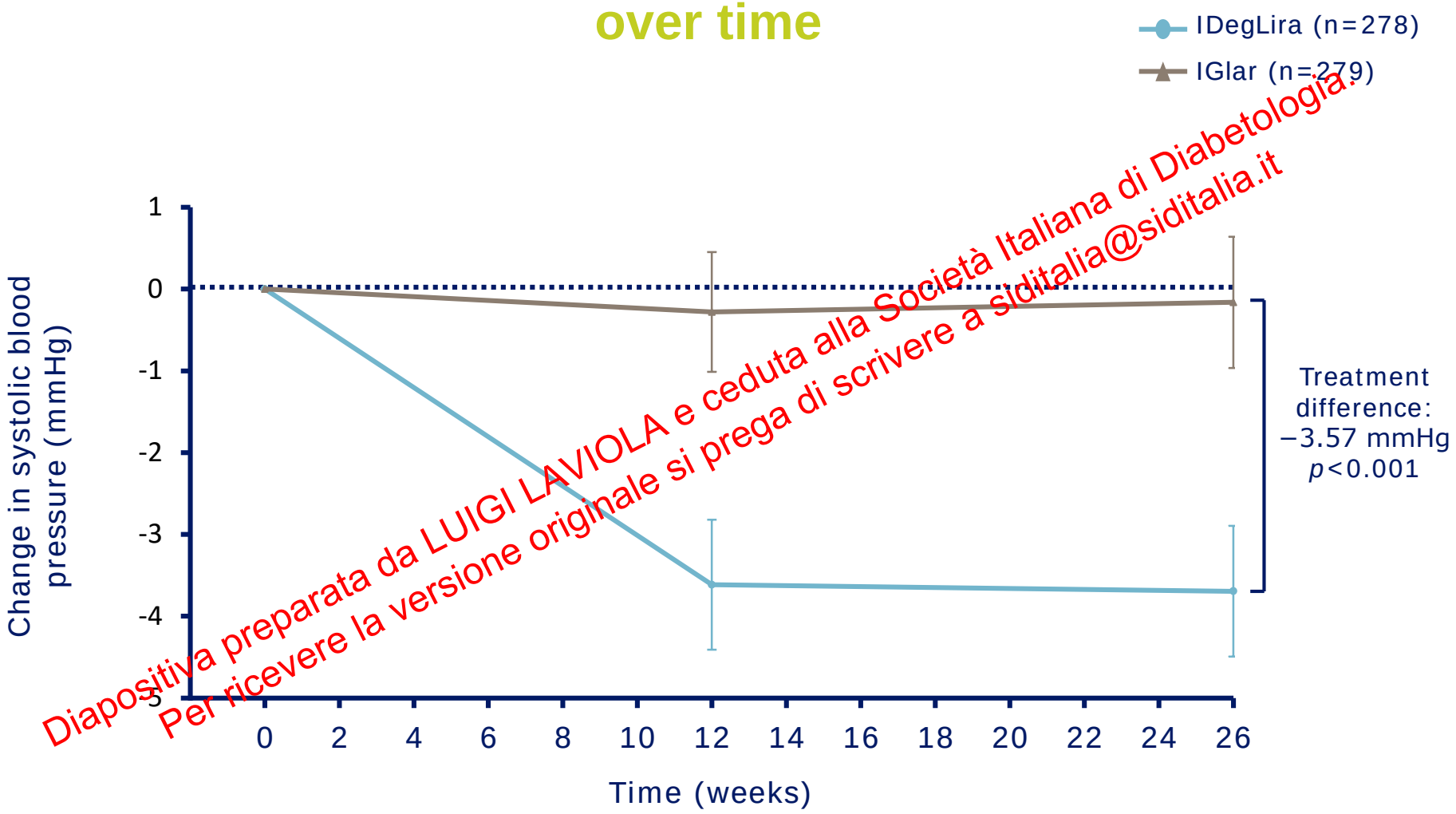
Uncontrolled on basal insulin

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL V
IDegLira vs. basal insulin optimisation

www.clinicaltrials.gov

Change in systolic blood pressure over time



Mean observed values with error bars (standard error mean) based on FAS and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis
NN9068-3952; IDegLira vs. IGlar