

Insulina e GLP-1 RAS: insieme o separati?



razionale della combinazione insulina/GLP-1 RAs

Diapositiva preparata da ANDREA GIACCARI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Gemelli

Centro
per le Malattie
Endocrine e
Metaboliche

Catania
Mercure Catania Excelsior
10 ottobre 2017

Andrea Giaccari
andrea.giaccari@unicatt.it

conflitto di interessi

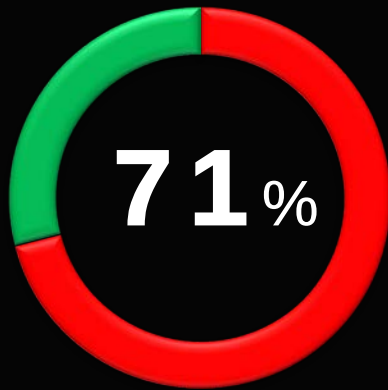
- Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Sanofi
- Takeda

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insulin intensification is delayed

Patients with $HbA_{1c} \geq 7\%$ 2 years following basal insulin initiation in US



Baseline HbA_{1c}
8.6%

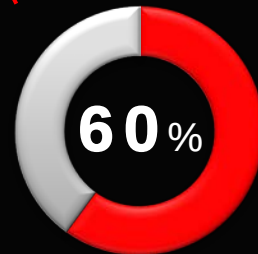
not at target

Curtis & Lage. J Med Econ 17:21, 2014

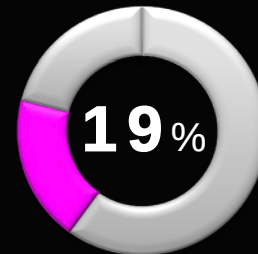
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Inertia

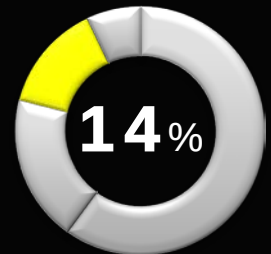
Change in insulin regimen
over 3 years in UK
Baseline HbA_{1c} 8.6%



No switch/
intensification



Intensified
(prandial/premix)



Switched
(premix)

HbA_{1c} at change

N/A

9.2/9.3%

9.5%

Year 3 HbA_{1c}

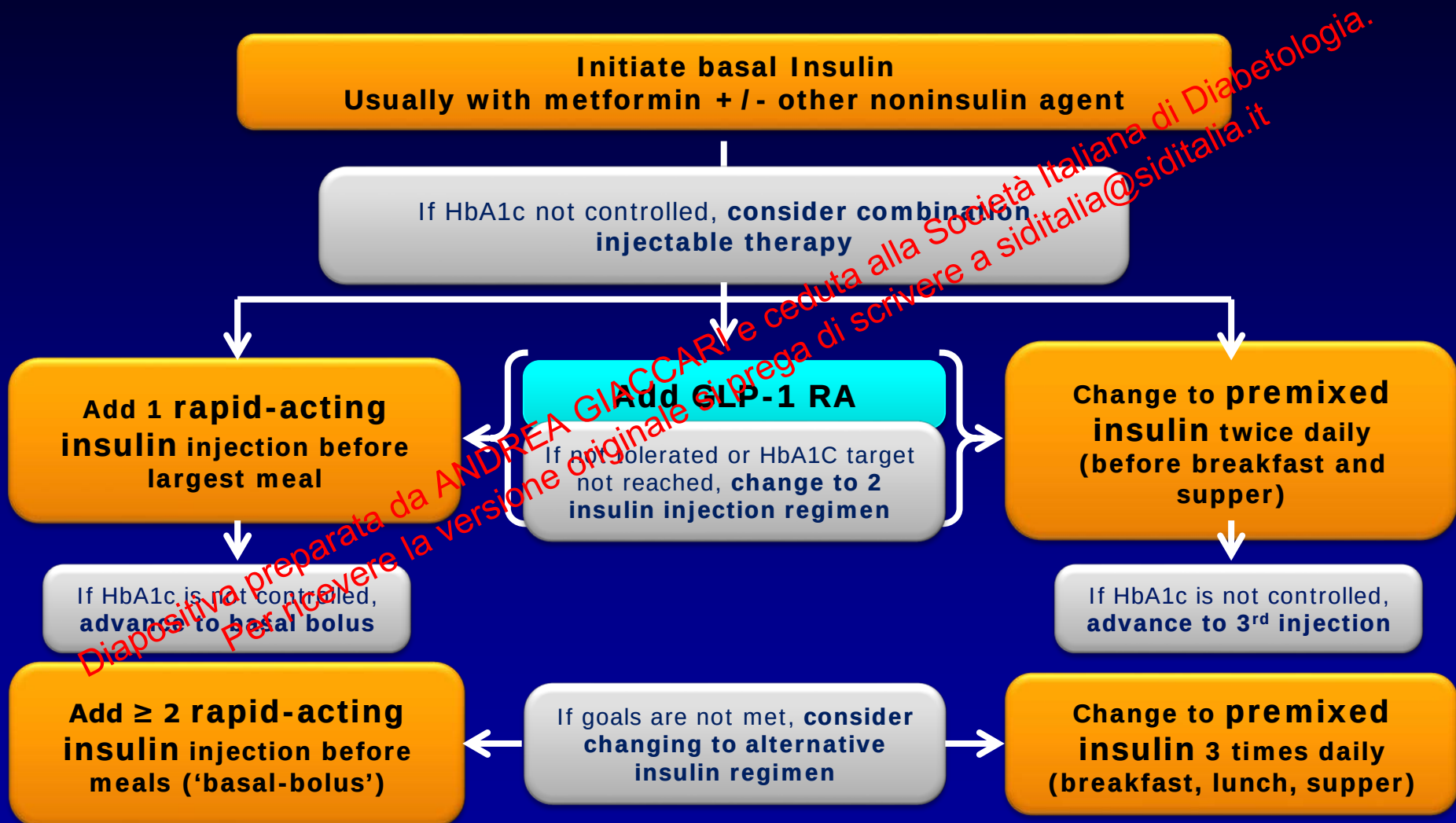
8.1%

8.6/8.7%

8.5%

Blak et al. Diabet Med 29:e13, 2012

intensification with combination injectable therapy for type 2 diabetes



GLP-1 RA, glucagon-like peptide-1 receptor agonist

Adapted from American Diabetes Association. Diabetes Care 2017;40(Suppl.1):S64–S74

medical need for alternative options to intensify basal insulin in type 2 diabetes

Unmet needs



Glycemic control

Most subjects on basal insulin are not at target HbA_{1c} ^{1,2}



Hypoglycemia

Hypoglycemic events are costly³ and a barrier to achieving target HbA_{1c} ⁴



Weight gain

Weight gain is a barrier to achieving target HbA_{1c} ⁵

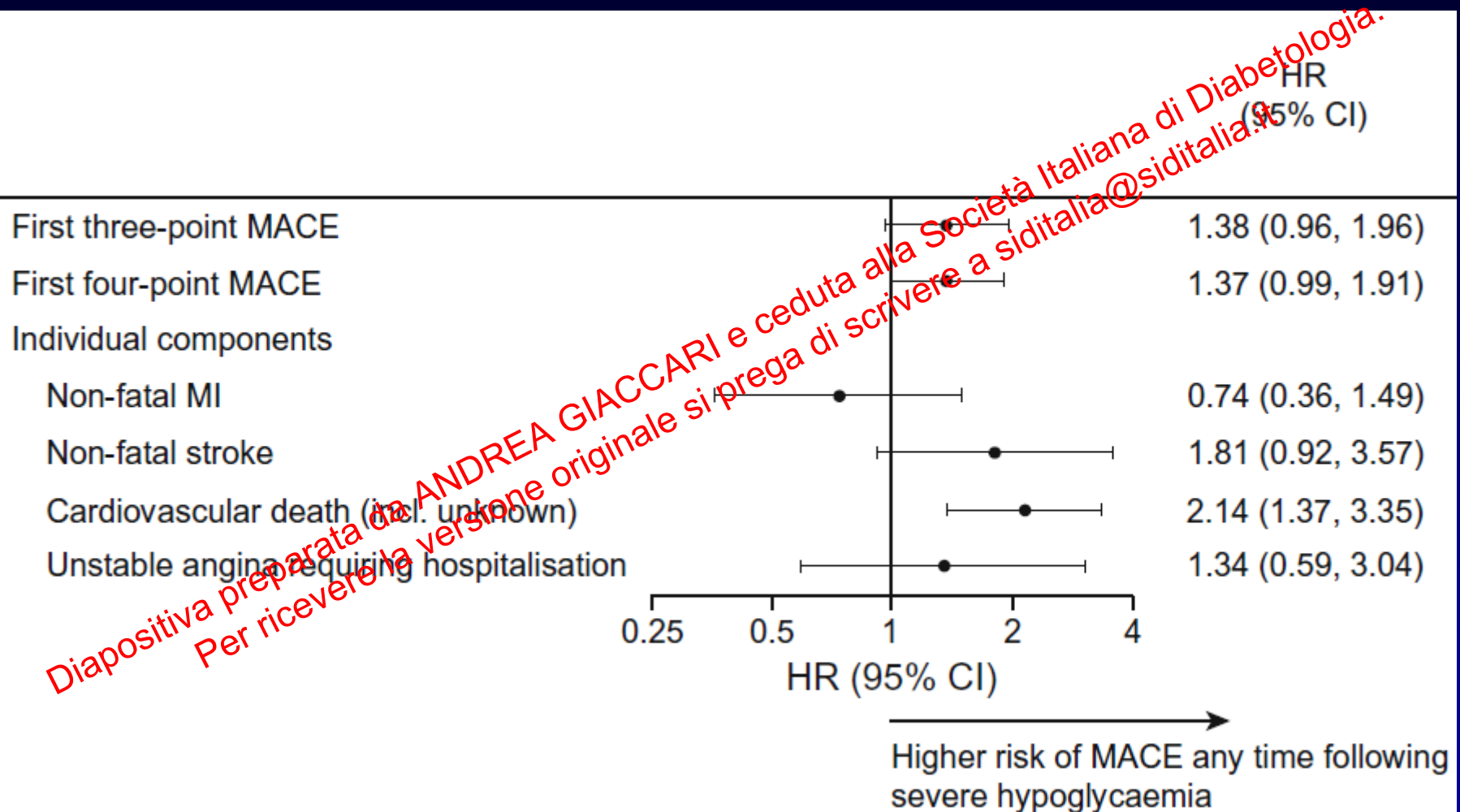


Complexity

Complex insulin regimens are a barrier to achieving target HbA_{1c} ⁴

1. Dale et al. *Prim Care Diabetes* 2010;4:85–9;
2. Giugliano et al. *Diabetes Care* 2011;34:510–17;
3. Hex et al. *Diabet Med* 2012;29:855–62;
4. Peyrot et al. *Diabet Med* 2012;29:682–9;
5. Carver. *Diabetes Educ* 2006;32:910–17

DEVOTE: MACE risk after hypo



Pieber TR et al for the DEVOTE: Diabetologia 2017 in press

Trials where GLP-1 RA started first



GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec; IDet, insulin degludec; Lira, liraglutide; Met; metformin

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

2. Rosenstock et al. *J Diabetes Complications* 2013;27:492–500;

3. Aroda et al. *Diabetologia* 2014;57(Suppl.1):S68 (Abstract 145)

degludec added to liraglutide

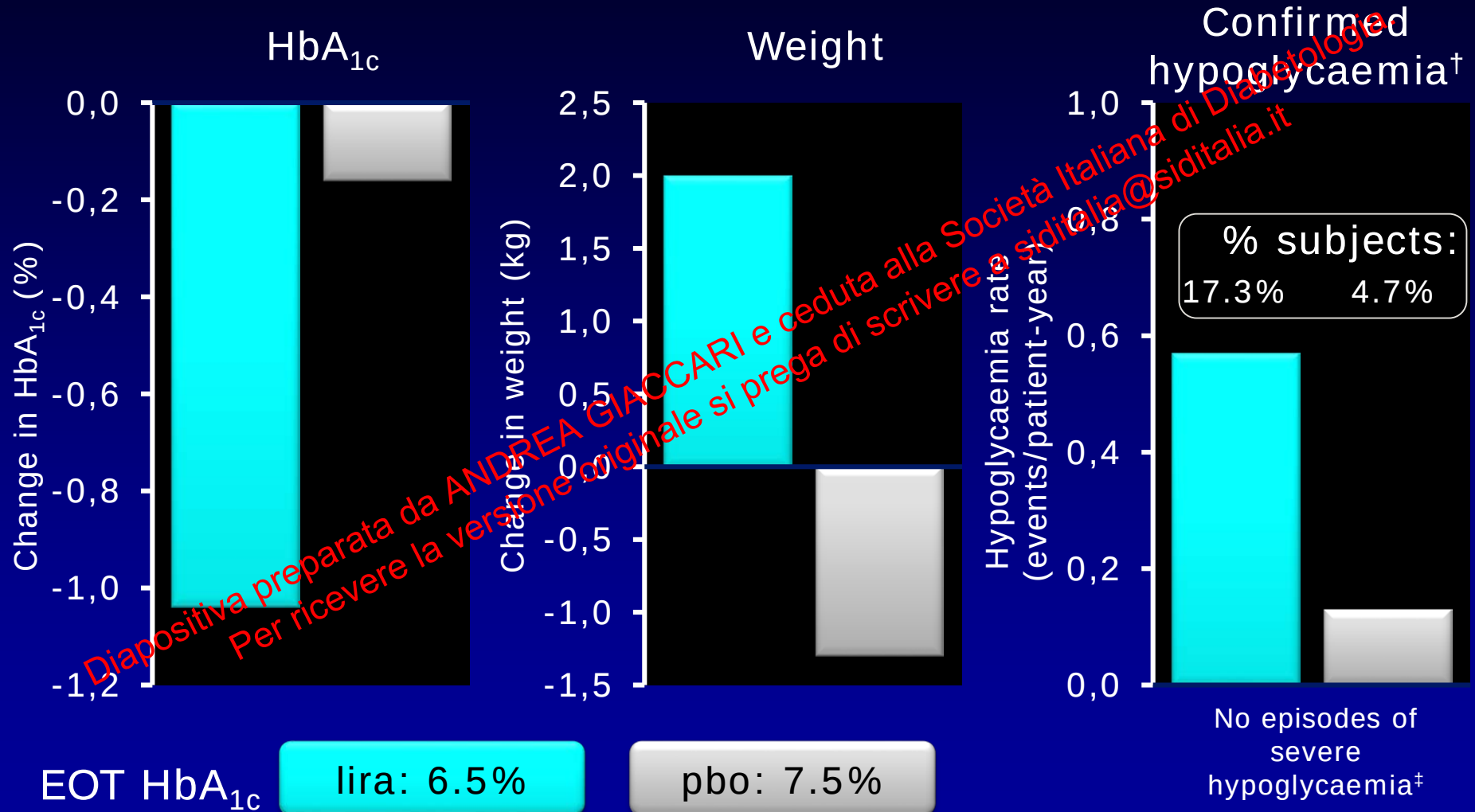


Inclusion criteria

- T2D
- Met (≥ 1500 mg) $\pm$ SU, glinides, DPP-4 or exenatide BID
- HbA_{1c} 7.5–10.0%: Met
- HbA_{1c} 7.0–9.0%: Met + SU, glinides, DPP-4 or exenatide BID

BID, twice daily; BMI, body mass index; HbA_{1c}, glycosylated haemoglobin; Lira, liraglutide; Met, metformin; OD, once daily, T2D, type 2 diabetes

degludec added to liraglutide



[†]Plasma glucose <3.1 mmol/L (56 mg/dL), with or without symptoms;

[‡]Severe: An episode requiring assistance from another person to actively administer carbohydrate, glucagon or other

Aroda et al. *Diabetologia* 2014;57(Suppl. 1):Abstract 147

Trials where insulin started first



GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec; IDet, insulin degludec; Lira, liraglutide; Met; metformin

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

2. Rosenstock et al. *J Diabetes Complications* 2013;27:492–500;

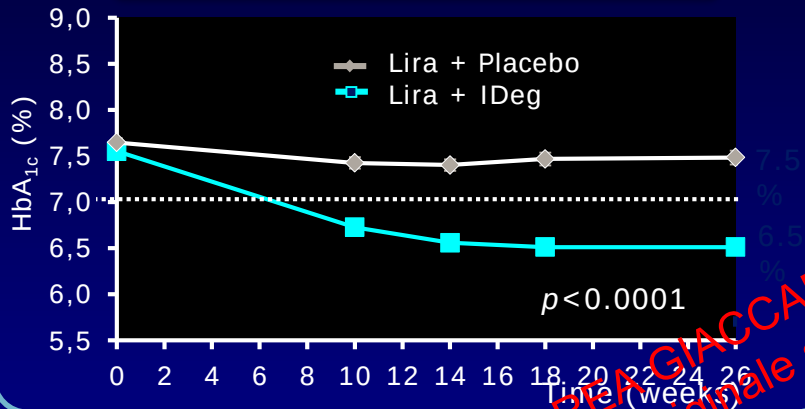
3. Aroda et al. *Diabetologia* 2014;57(Suppl.1):S68 (Abstract 145)

GLP-1 RA and basal insulin combined efficacy

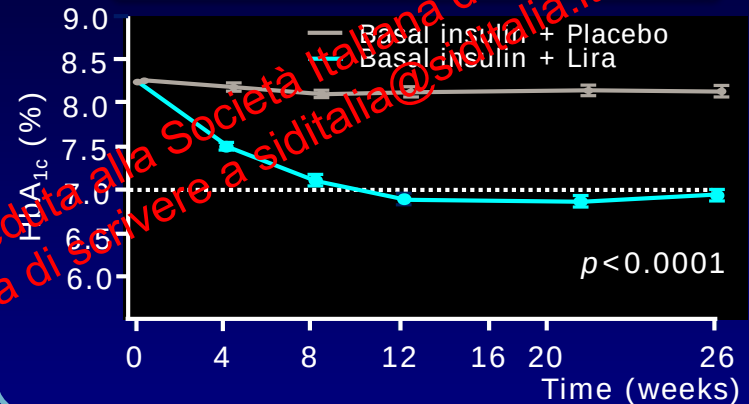
Basal insulin added to liraglutide

Liraglutide added to basal insulin

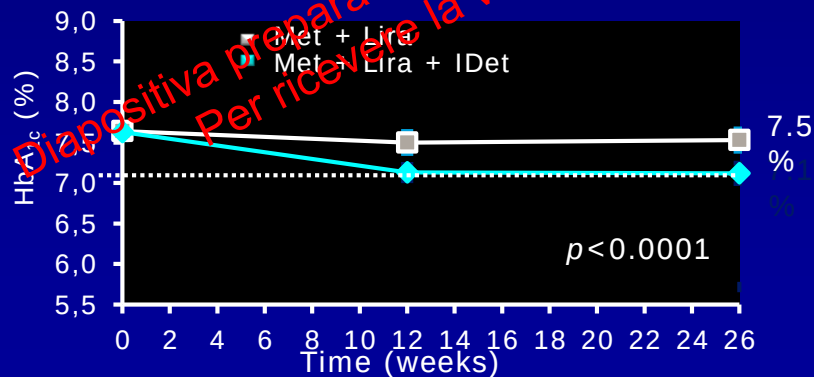
BEGIN: ADD TO GLP-1



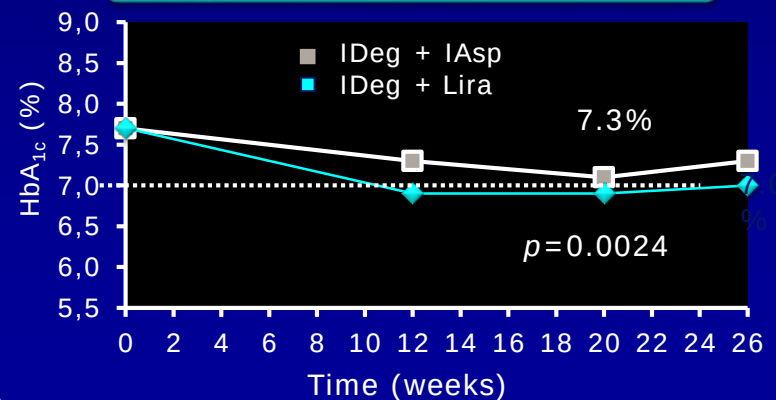
LIRA-ADD2BASAL⁴



LIRA-DETEMIR¹



BEGIN: VICTOZA ADD-ON³

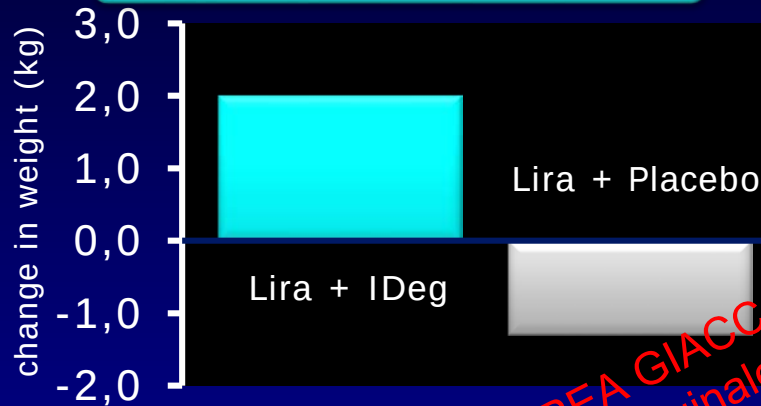


GLP-1 RA and basal insulin combined

body weight

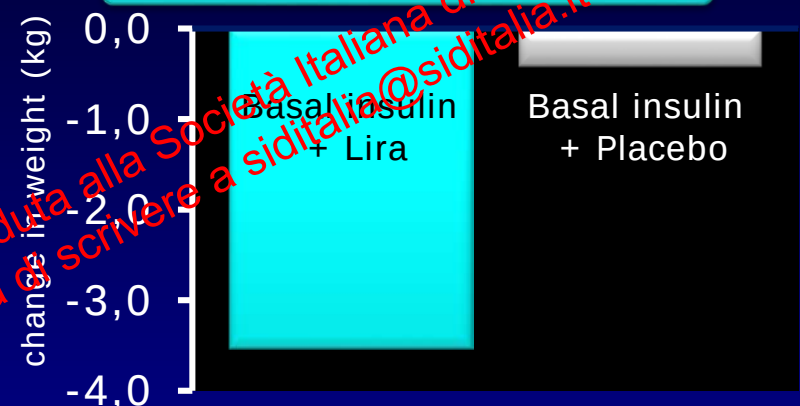
Basal insulin added to liraglutide

BEGIN: ADD TO GLP-1



Liraglutide added to basal insulin

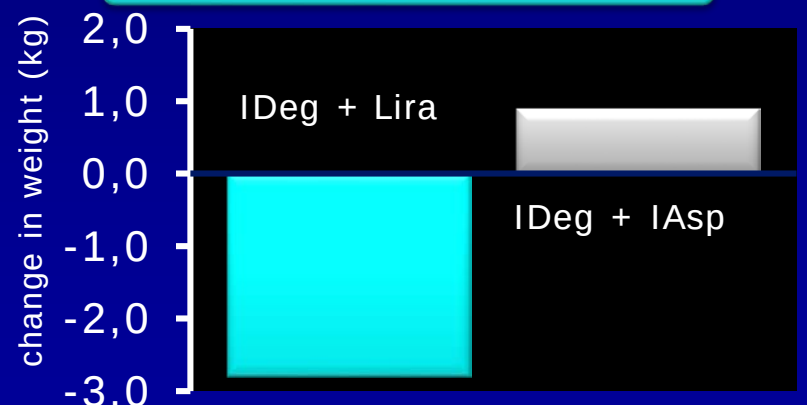
LIRA-ADD2BASAL⁴



LIRA-DETEMIR¹



BEGIN: VICTOZA ADD-ON³



GLP-1 RA and basal insulin combined hypoglycemia

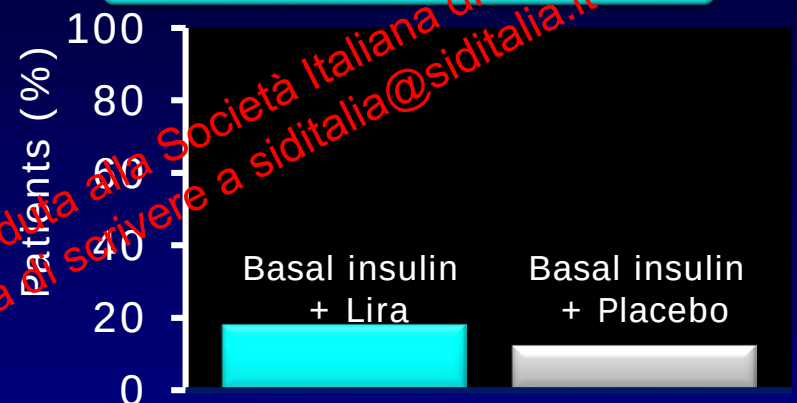
Basal insulin added
to liraglutide

BEGIN: ADD TO GLP-1



Liraglutide added to
basal insulin

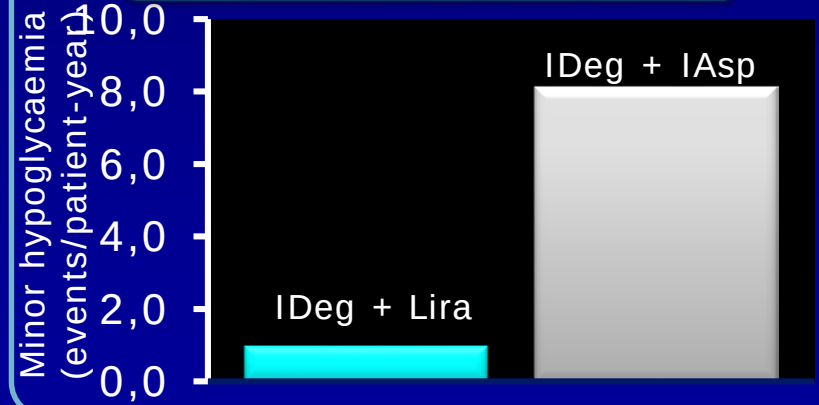
LIRA-ADD2BASAL⁴



LIRA-DETERMIR¹



BEGIN: VICTOZA ADD-ON³



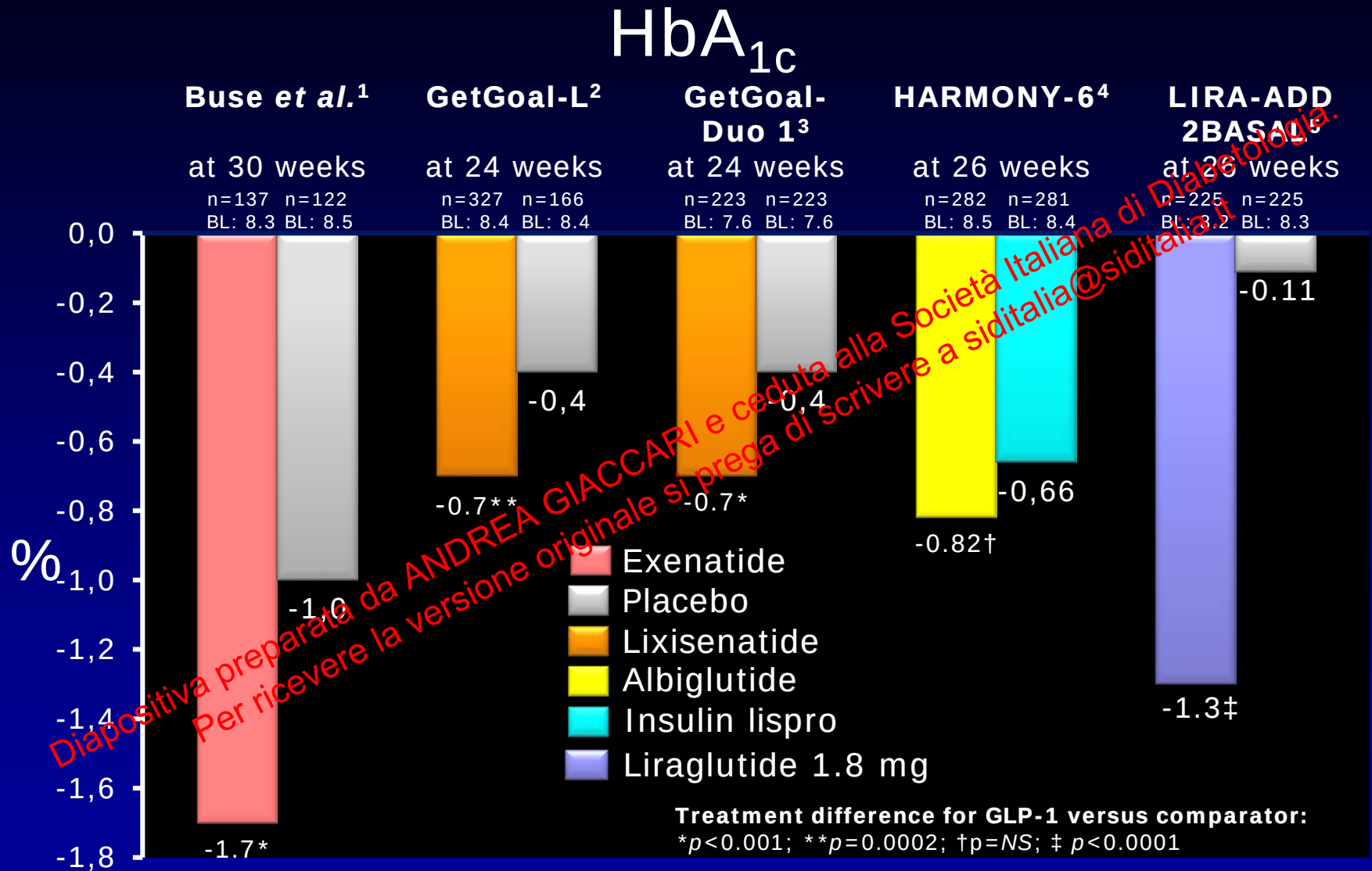
Trials where basal insulin started first

Study name	Background therapy		Added at randomisation
Buse et al. 2011	± Met ± Pio	IGlar	Exenatide BID vs pbo
GetGoal-Duo-1	± Met	IGlar	Lixisenatide vs pbo
GetGoal-L	± Met	Basal insulin	Lixisenatide vs pbo
LIRA-ADD2BASAL	± Met	Basal insulin	Lira 1.8 mg vs pbo
Harmony-16	Met ± TZD	IGlar	Albi OW vs lispro

BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IGlar, insulin glargine; Met, metformin; OD, once daily; OW, once weekly; TID, three-times daily; TZD, thiazolidinedione

1. Ahmann et al. *Diabetes Obes Metab* 2015;17:1056–64; 2. Riddle et al. *Diabetes Care* 2013;36:2497–503; 3. Riddle et al. *Diabetes Care* 2013;36:2489–96; 4. Buse et al. *Ann Intern Med* 2011;154:103–12; 5. Mathieu et al. *Diabetes Obes Metab* 2014;16:636–44; 6. Rosenstock et al. *Diabetes Care* 2014;37:2317–25

GLP-1 RAs added to basal insulin

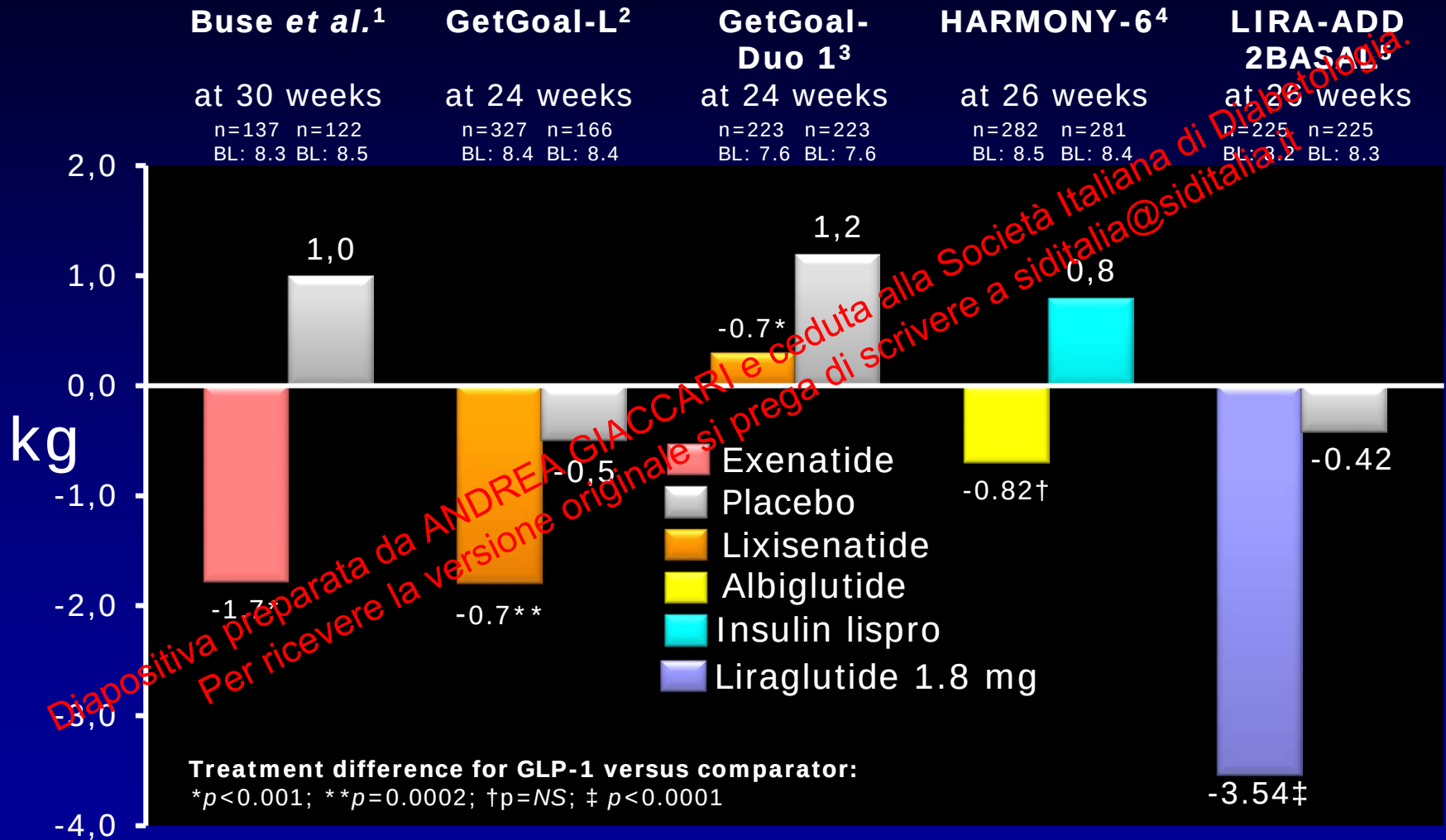


BL, baseline; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; NS, not-significant
 Caution, each study was performed in a different study population and are not for direct comparison

1. Buse *et al.* *Ann Intern Med* 2011;154:103–12; 2. Riddle *et al.* *Diabetes Care* 2013;36:2489–96; 3. Riddle *et al.* *Diabetes Care* 2013;36:2497–2503;
 4. Rosenstock *et al.* *Diabetes Care* 2014;37:2317–25; 5. Lahtela *et al.* *Diabetologia* 2014;57(Suppl. 1):Abstract 37

GLP-1 RAs added to basal insulin

body weight



BL, baseline; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; NS, not-significant
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 4. Rosenstock *et al.* *Diabetes Care* 2014;37:2317–25; 5. Lahtela *et al.* *Diabetologia* 2014;57(Suppl. 1):Abstract 37

summary

Combining a GLP-1 RA with basal insulin can reduce mean HbA_{1c} to below target levels with a low risk of hypoglycaemia

Addition of liraglutide to basal insulin results in significant weight loss

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CV outcome trials for new drugs ¹

2012 2013 2014 2015 2016 2017 2018 2019 2020

SAVOR TIMI 53
Saxagliptin
AZ/BMS (7/'13)

CAROLINA ²
interims analysis
Linagliptin
BI/Lilly (2016)

CAROLINA
Linagliptin
BI/Lilly (9/'18)

EXAMINE
Alogliptin
Takeda (12/'13)

LEADER ⁴
Liraglutide
Novo (1/'16)

Omarigliptin
Merck (10/'17)

REWIND
Dulaglutide
Lilly (4/'19)

TECOS
Sitagliptin
Merck (12/'14)

SUSTAIN 6
Semaglutide
Novo (1/'16)

HARMONY
albiglutide
GSK(7/'20)

ELIXA
Lixisenatide
Sanofi (5/'14)

EXSCEL
Exenatide
BMS/AZ (3/'17)

TAK-875
Takeda (12/'18)

CANVAS (interim)
Canagliflozin
reported (FDA ACM)

CANVAS (interim) ³
Canagliflozin
J&J ('15)

CANVAS
Canagliflozin
J&J (6/'18)

DPP4

GLP1

GPR40

SGLT2

PPARa/g

AleCARDIO
Aleglitazar
Roche (5/'15)

C-SCADE 8
Empagliflozin
BI/Lilly (3/'18)

AlePREVENT
Aleglitazar
Roche (8/'18)

DECLARE
Dapagliflozin
BMS/AZ (04/'19)

¹ Expected dates for completion of primary endpoint (source: clinicaltrials.gov, accessed 04/2016)

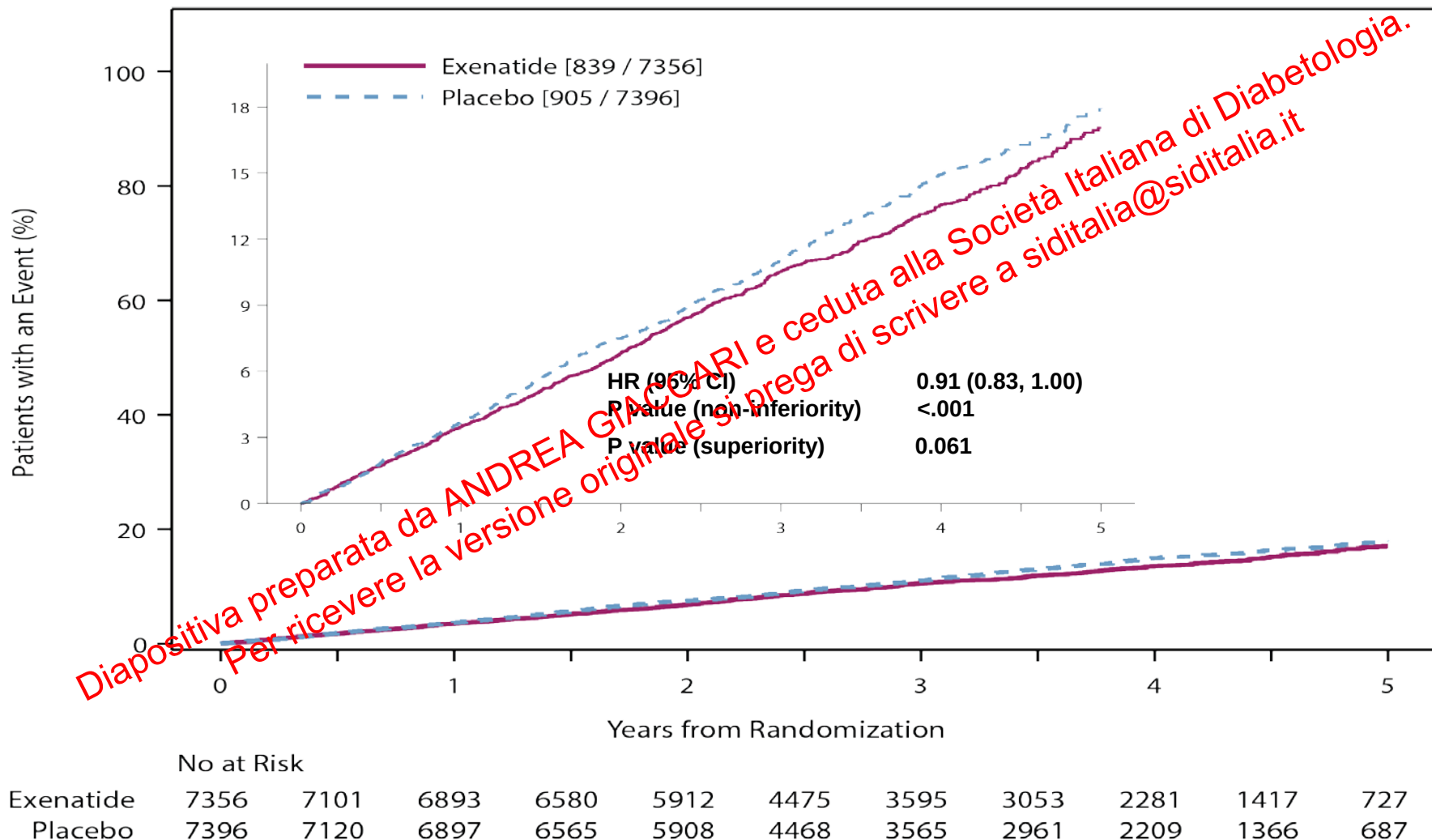
² Interims data ~2016; 2nd Linagliptin CV outcomes trial vs PBO (CARMELINA) expected to start in 2013, per primary CI (tbc) results in 2018

³ Per Janssen commentary at FDA ACM, next CV meta-analysis planned after 500 events- expected in 2015

⁴ per Novo interims analysis possible in 2014/15 if required for review of obesity sNDA

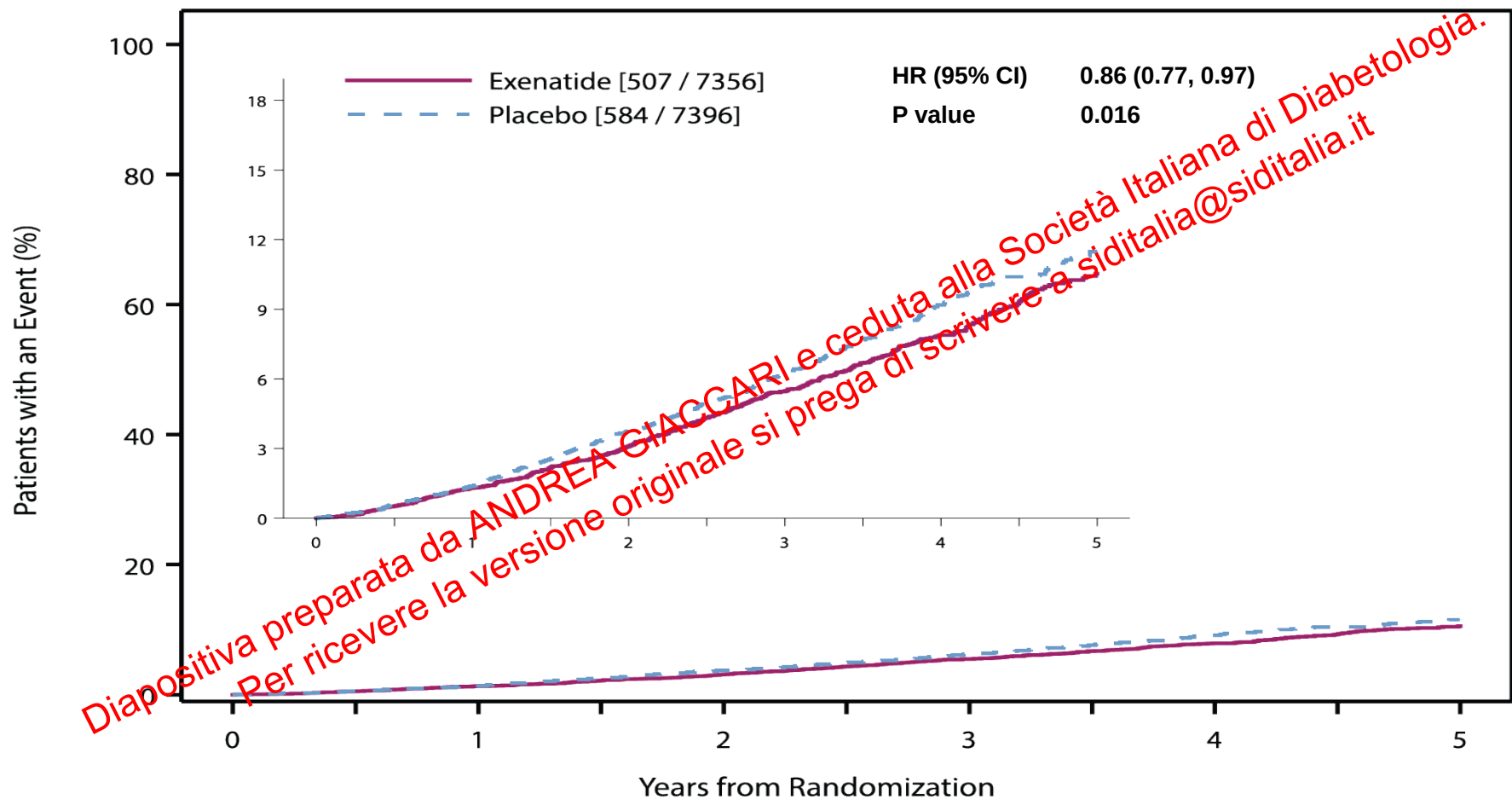
Primary Composite Cardiovascular Outcome

Intention-to-Treat Analysis for Non-inferiority & Superiority



All-Cause Mortality

Intention-to-Treat Analysis

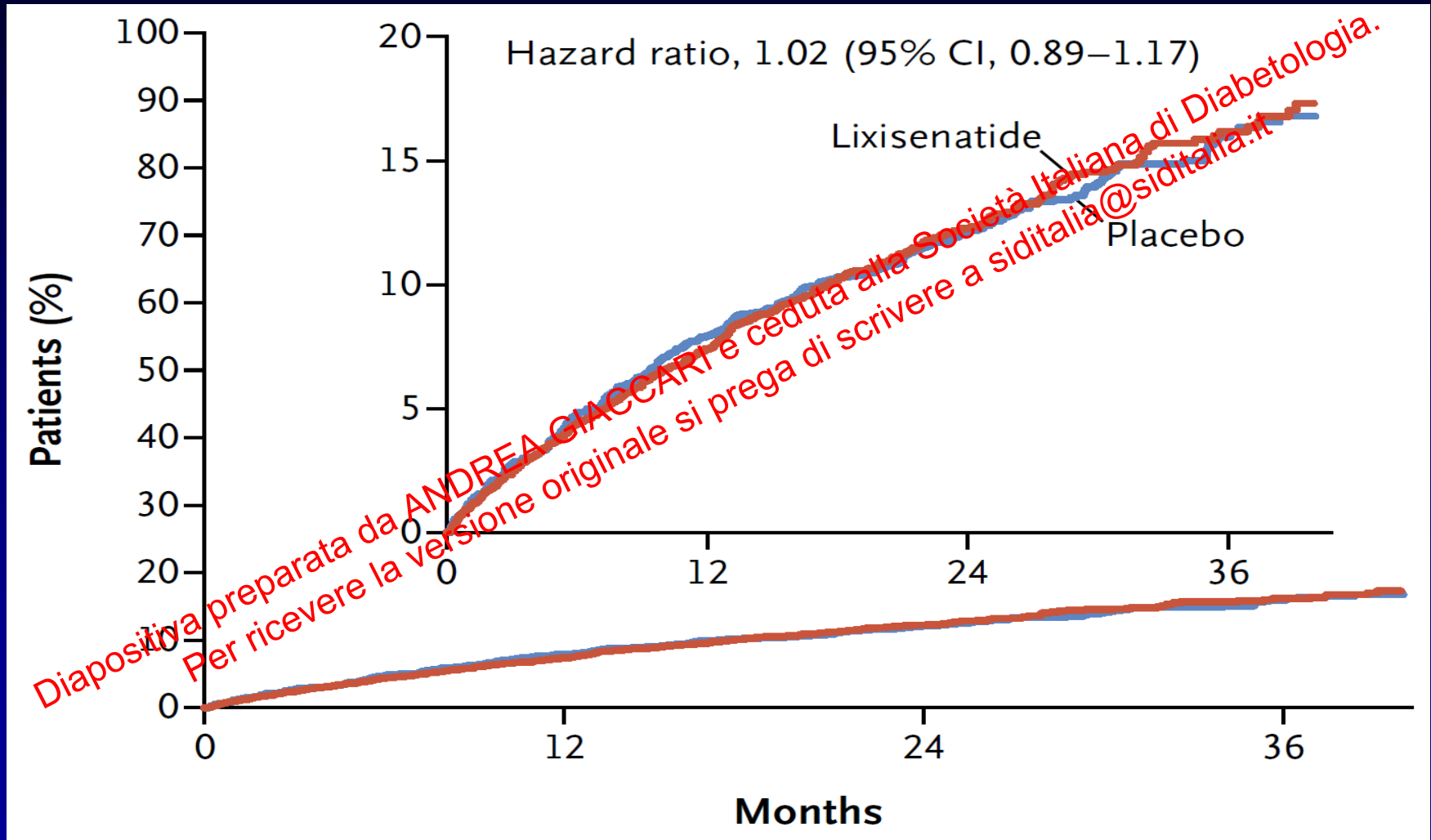


No at Risk

Exenatide	7356	7304	7234	7028	6433	4991	4095	3518	2698	1726	907
Placebo	7396	7344	7278	7058	6470	5019	4091	3478	2666	1695	892

ELIXA: primary endpoint

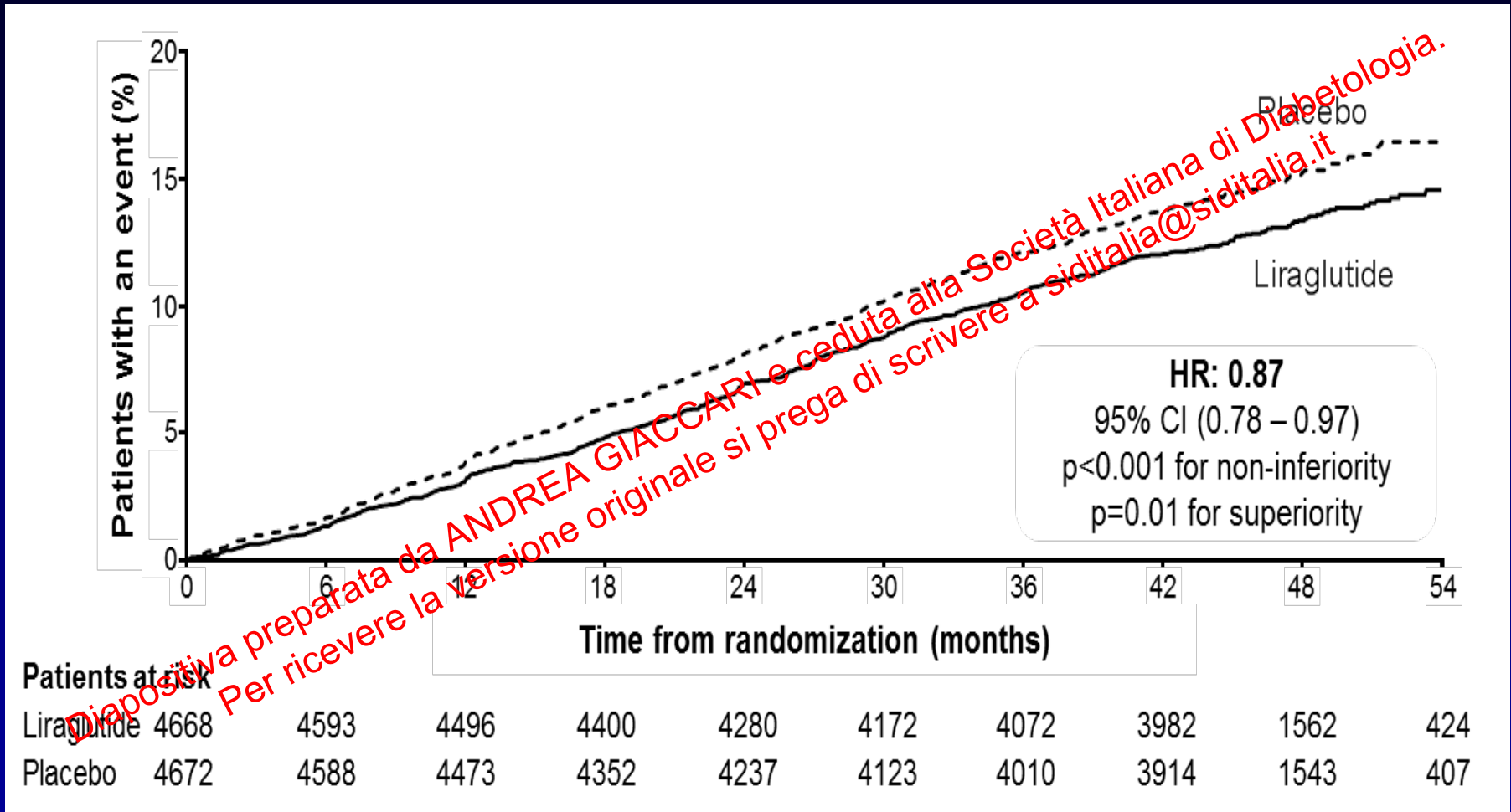
4-MACE: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina



Pfeffer MA et al.: NEJM 373:2247, 2015

M... CD... NEJM 375:211, 2016

LEADER: Primary outcome (MACE) CV death, non-fatal MI, or non-fatal stroke



The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Marso SP et al.: NEJM 375:311, 2016

summary

Combining a GLP-1 RA with basal insulin can reduce mean HbA_{1c} to below target levels with a low risk of hypoglycaemia

Addition of liraglutide to basal insulin results in significant weight loss

Liraglutide is, at the moment, the only available GLP-1 RA demonstrating CV superiority

summary of pooled indirect analysis

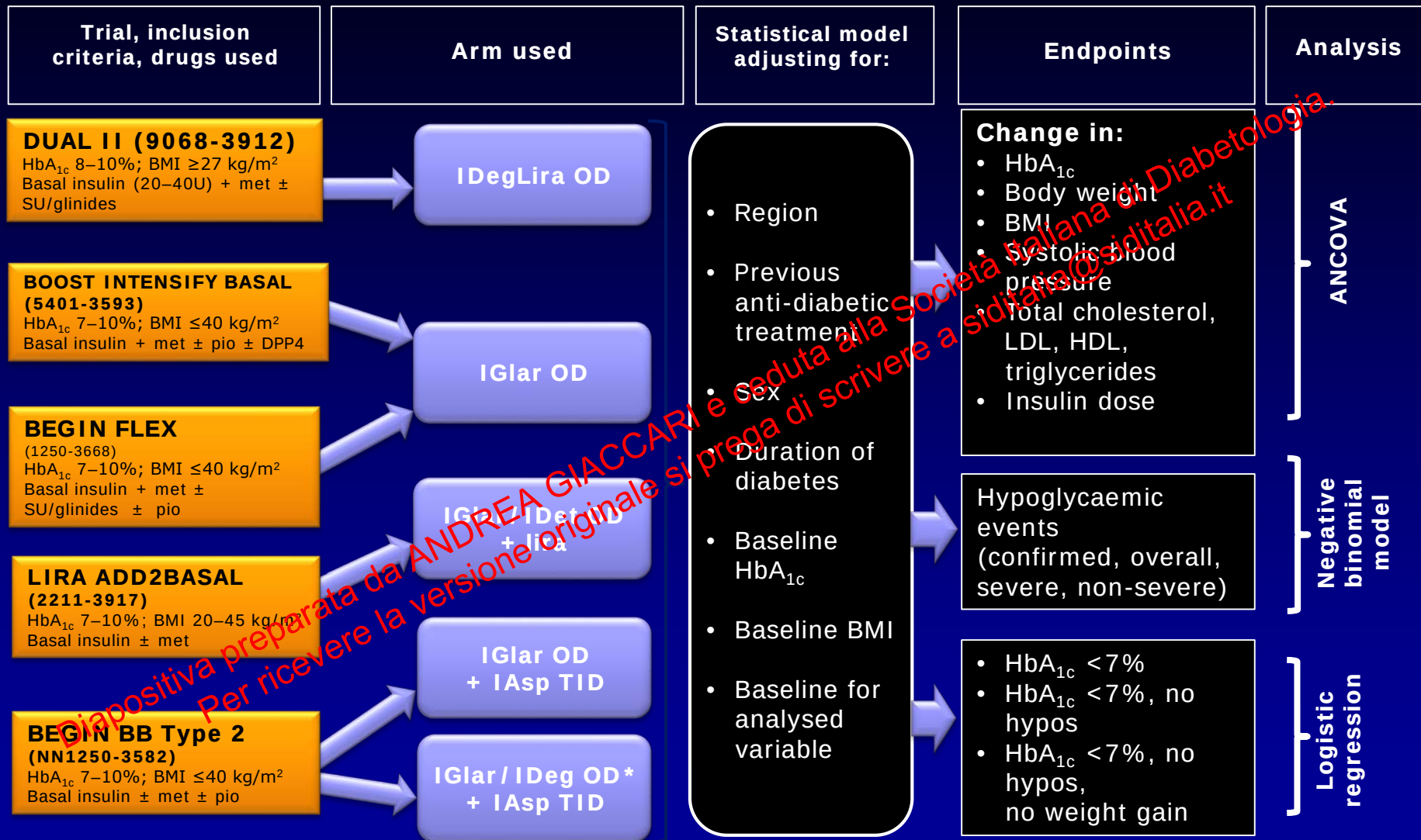


Figure 1. Summary of method: pooled indirect analysis of IDegLira OD versus other insulin intensification strategies in patients uncontrolled on basal insulin

*Supplementary analysis

OD, once-daily; IGlar, insulin glargine, IAsp, insulin aspart; TID, three times daily; met, metformin; pio, pioglitazone; SU, sulfonylureas

baseline characteristics

Trial(s) from which data were sourced	DUAL II	LIRA-ADD2BASAL	BEGIN BB	BEGIN Flex and BOOST Intensive Basal	Supplementary analysis: BEGIN BB
Arm used	IDegLira (N=199)	Lira 1.8 mg added to basal insulin (IGlar/IDeg) (N=225)	Basal-bolus (IGlar + IAsp) (N=330) ^{a,b}	Up-titrated IGlar (N=329) ^b	Basal-bolus (IGlar or IDeg + IAsp) (N=210) ^b
Sex (male), %	56.3	53.3	57.1	52.3	50.0
Age, years	56.8 (8.9)	59.3 (9.2)	57.7 (10.9)	58.3 (9.4)	59.5 (9.3)
Body weight, kg	95.4 (19.4)	90.2 (20.0)	93.4 (16.0)	83.3 (18.3)	92.7 (17.8)
BMI, kg/m ²	33.6 (5.7)	32.3 (5.6)	32.4 (4.5)	30.0 (5.0)	32.7 (4.7)
Disease duration, years	10.3 (6.0)	12.1 (7.1)	12.3 (6.5)	11.9 (7.2)	12.70 (6.36)
HbA _{1c} , %	8.7 (0.7)	8.2 (0.8)	8.5 (0.9)	8.4 (0.9)	8.4 (0.8)
Race (Caucasian/other), %	78.9/21.1	76.4/23.6	80.4/19.6	64.4/35.6	78.1/21.9

^aData are from the subgroup of non-insulin-naïve patients who were treated with IGlar + 3x IAsp; ^bObserved results for basal-bolus and basal-only arms are on subsets of patients from the original trials (non-insulin-naïve patients) and therefore values cannot be found in the trial publications; ^cCalculated values
 BMI, body mass index; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine; SD, standard deviation

efficacy outcomes

	IDegLira (N=199)		GLP-1RA add-on to basal insulin (N=225)		Basal-bolus, IGlir as basal (N=56)		Basal only, up-titrated IGlir (N=332)	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
EOT HbA _{1c} , %	6.74 (0.94)	[6.60; 6.88]	7.09 (0.94)	[6.94; 7.24]	7.04 (0.94)	[6.78; 7.29]	7.39 (0.94)	[7.28; 7.49]
Δ HbA _{1c} , %	-1.68 (0.94)	[-1.82; -1.54]	-1.33** (0.94)	[-1.48; -1.18]	-1.39* (0.94)	[-1.64; -1.14]	-1.03** (0.94)	[-1.14; -0.93]
Δ body weight, kg	-2.88 (3.42)	[-3.39; -2.37]	-3.53 (3.42)	[-4.08; -2.97]	-4.01** (3.42)	[-5.10; -4.93]	1.16** (3.42)	[0.78; 1.55]
Δ BMI, kg/m ²	-1.02 (1.21)	[-1.19; -0.84]	-1.27 (1.21)	[-1.47; -1.08]	1.42** (1.21)	[1.10; 1.75]	0.43** (1.21)	[0.29; 0.56]
Δ SBP (mmHg)	-6.84 (12.95)	[-8.76; -4.92]	-4.68 (12.95)	[-6.75; -2.61]	1.83** (12.95)	[-1.64; 5.30]	-3.47** (12.95)	[-4.92; -2.01]
Δ cholesterol, mg/dL								
Total	-10.44 (29.67)	[-14.84; -6.05]	-13.26 (29.67)	[-18.02; -8.50]	-5.80 (29.67)	[-13.76; 2.15]	-2.88** (29.67)	[-6.24; 0.48]
LDL	-7.56 (24.07)	[-11.12; -3.99]	-9.86 (24.07)	[-13.73; -5.98]	-3.13 (24.07)	[-9.58; 3.32]	-2.73* (24.07)	[-5.45; -0.01]
HDL	8.47 (6.74)	[-0.53; 1.47]	-0.74 (6.74)	[-1.82; 0.34]	0.40 (6.74)	[-1.41; 2.20]	1.06 (6.74)	[0.30; 1.82]
Δ triglycerides, mg/dL	-18.61 (78.66)	[-30.29; -6.92]	-16.56 (78.66)	[-29.17; -3.94]	-16.14 (78.66)	[-37.22; 4.93]	-9.43 (78.66)	[-18.39; -0.47]
EOT daily basal insulin dose, U	37.80 (27.05) ^b	[33.79; 41.80]	36.63 (27.05) ^c	[32.33; 40.93]	62.43** (27.05) ^d	[55.19; 69.68]	60.65* (27.05)	[57.59; 63.72]

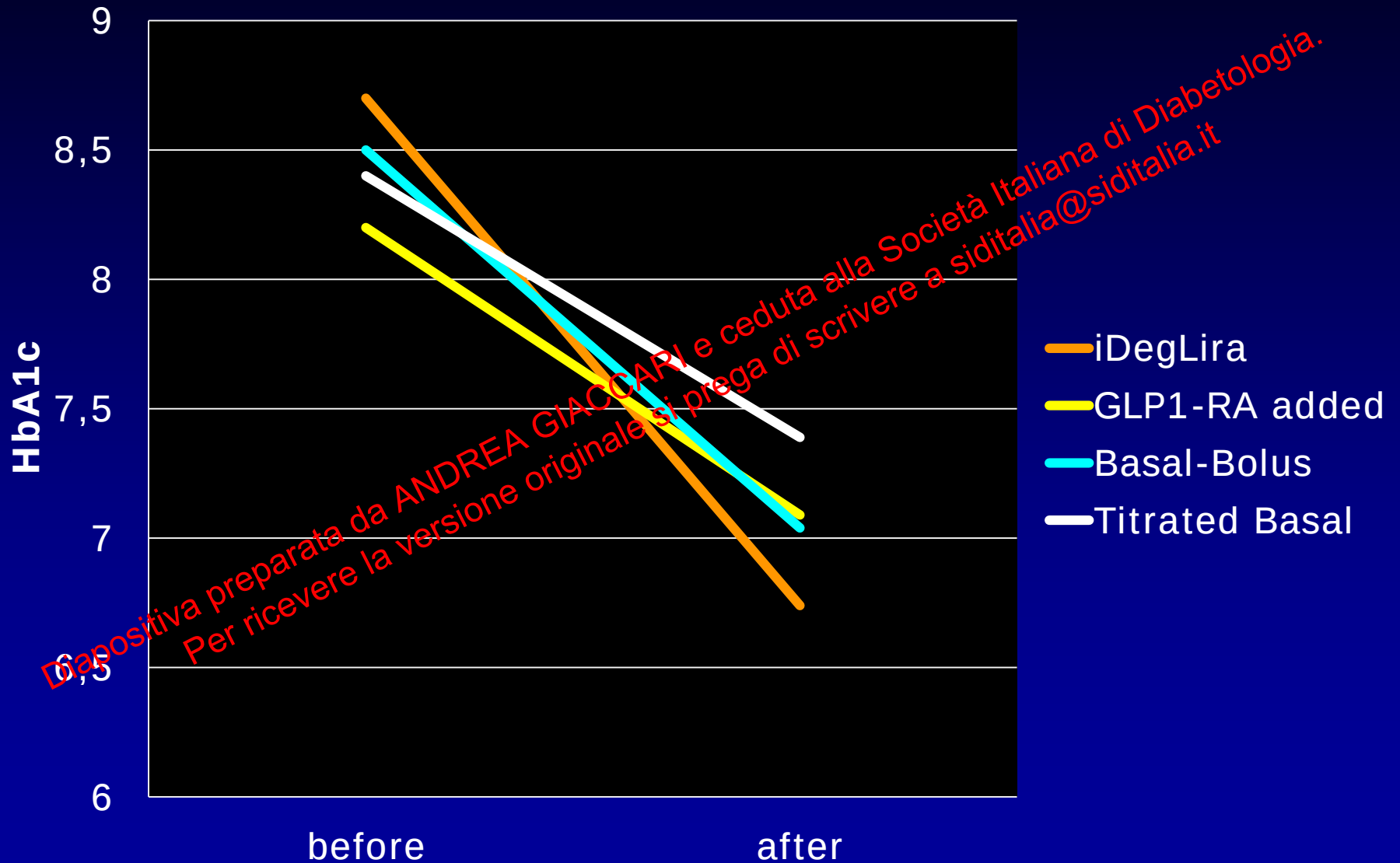
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treatment differences

	IDegLira vs. GLP-1RA add-on to basal insulin (N=199)			IDegLira vs. basal-bolus, IGlar as basal (N=56)			IDegLira vs. basal only, up-titrated IGlar (N=329)		
	Mean (SD)	95% CI	p-value	Mean (SD)	95% CI	p-value	Mean (SD)	95% CI	p-value
Δ HbA _{1c} , %	-0.35	[-0.56; -0.14]	0.0009	-0.30	[-0.58; -0.01]	0.040	-0.65	[-0.83; -0.47]	<0.0001
Δ HbA _{1c} , mmol/mol ^a	-4	[-6; -2]	0.0009	-3	[-6; 0]	0.040	-7	[-9; -5]	<0.0001
Δ body weight, kg	0.65	[-0.11; 1.40]	0.092	-6.89	[-7.92; -5.86]	<0.0001	-4.04	[-4.69; -3.40]	<0.0001
Δ BMI, kg/m ²	0.26	[-0.01; 0.52]	0.058	-2.44	[-2.80; -2.07]	<0.0001	-1.44	[-1.67; -1.21]	<0.0001
Δ SBP (mmHg)	-2.16	[-5.01; 0.69]	0.14	-8.67	[-12.58; -4.77]	<0.0001	-3.37	[-5.80; -0.94]	0.0065
Δ cholesterol, mg/dL	2.82	[-3.21; 9.34]	0.40	-4.64	[-13.60; 4.31]	0.31	-7.56	[-13.16; -1.97]	0.0081
Total	2.30	[-3.00; 7.60]	0.39	-4.43	[-11.68; 2.83]	0.23	-4.82	[-9.35; -0.30]	0.037
LDL	1.21	[-0.27; 2.70]	0.11	0.07	[-1.96; 2.10]	0.94	-0.59	[-1.86; 0.67]	0.36
Δ triglycerides, mg/dL	-2.05	[-19.36; 15.26]	0.82	-2.46	[-26.20; 21.27]	0.84	-9.18	[-24.10; 5.74]	0.23
EOT daily basal insulin dose, U	1.17	[-4.75; 7.09]	0.70	-24.64	[-32.79; -16.49]	<0.0001	-22.86	[-27.94; -17.78]	<0.0001

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efficacy compared



confirmed hypoglycaemia estimated rates

	IDegLira (N=199)		GLP-1RA add-on to basal insulin (N=225)		Basal-bolus, IGlar as basal (N=56)		Basal only, up-titrated IGlar (N=329)	
	Events/ 100 PYE	95% CI	Events/ 100 PYE	95% CI	Events/ 100 PYE	95% CI	Events/ 100 PYE	95% CI
Overall confirmed hypoglycaemia	122.8	[90.71;166.]	124.4	[89.49;172.84]	1060.8* *	[680.17;1654.37]	286.1**	[231.10;354.08]
Severe hypoglycaemia	0.4	[0.04;3.68]	NA	NA	2.4	[0.38; 14.63]	2.6	[0.86; 7.94]
Non-severe hypoglycaemia	121.9	[89.90;165.23]	124.1	[89.16;172.68]	1056.3* *	[675.44;1651.96]	282.8**	[228.06;350.58]

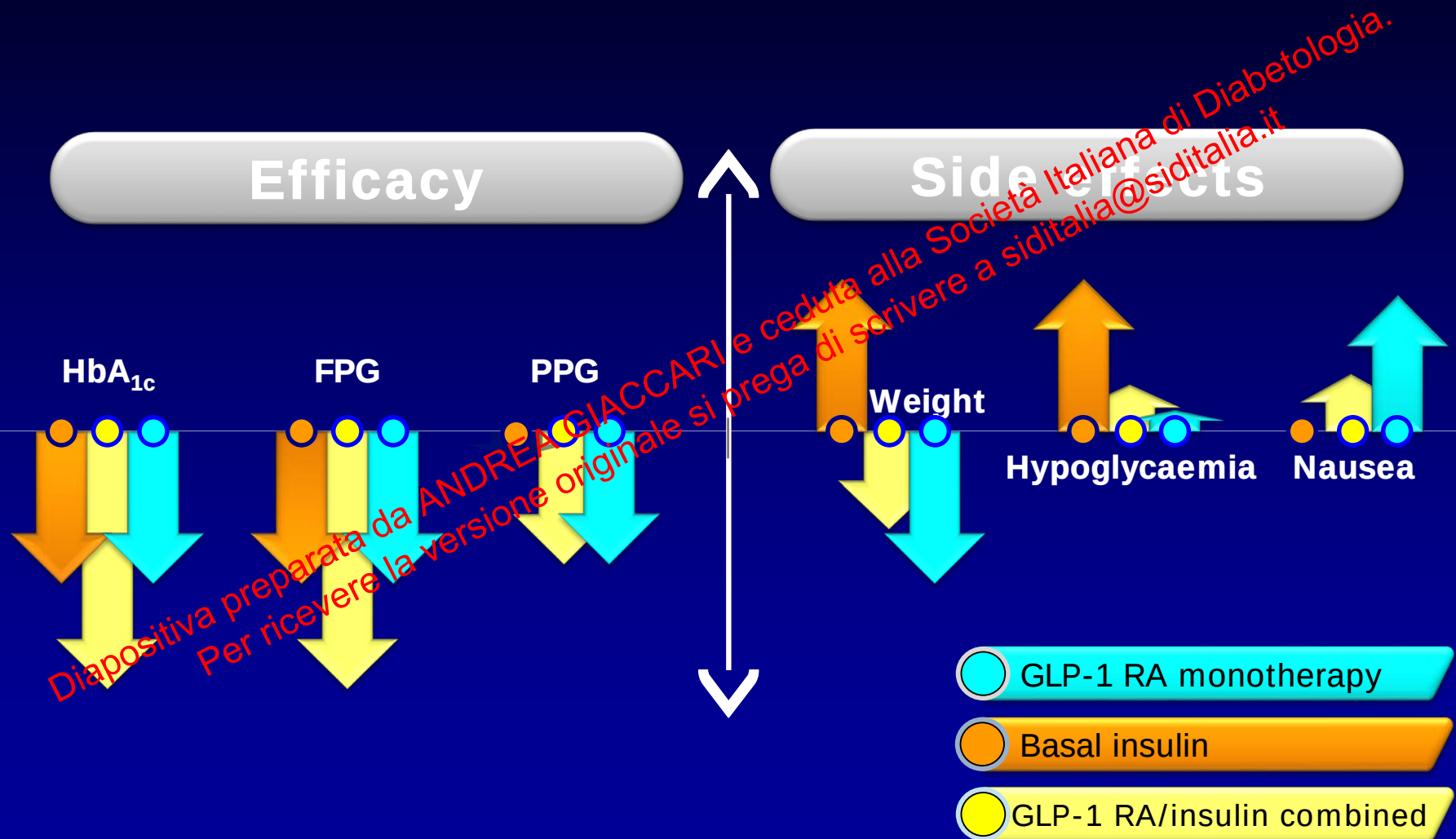
Table 4. (a) Results from the main analysis: 4-arm model with 56 patients in the basal-bolus arm. Estimated rates of confirmed hypoglycaemia per treatment arm, based on a negative binomial model

IDegLira significantly different: ** $p < 0.01$

Confirmed hypoglycaemia was defined as the occurrence of severe episodes (i.e. requiring assistance), or episodes in which plasma glucose concentration (confirmed by self-monitored blood glucose) was less than 56 mg/dL (3.1 mmol/L), irrespective of symptoms.

CI, confidence interval; IDegLira, insulin degludec/liraglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; PYE, patient-year of exposure.

what can we expect when combining a GLP-1 RA and a basal insulin in one pen?



summary

Combining a GLP-1 RA with basal insulin can reduce mean HbA_{1c} to below target levels with a low risk of hypoglycaemia.

Addition of liraglutide to basal insulin results in significant weight loss.

Liraglutide is, at the moment, the only available GLP-1 RA demonstrating CV superiority.

iDegLira sums efficacy of degludec and liraglutide, with a significant reduction of side effects of the 2 originators.