Liraglutide: novità nella gestione del diabete tipo 2

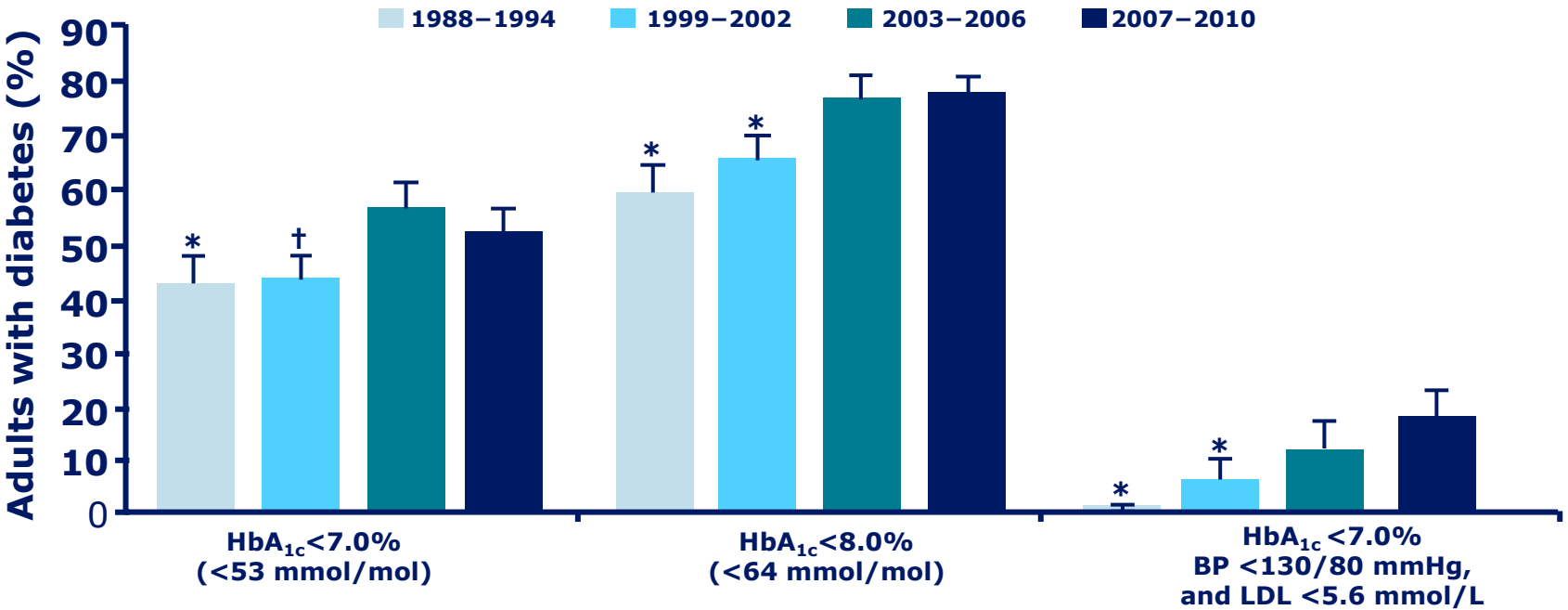
Dott. Natalino Simioni
UOC Medicina
Presidio Ospedaliero di Cittadella (PD)

- Il sottoscritto dott. Natalino Simioni
  ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato - Regione del 5 novembre 2009

  dichiara

- Che negli ultimi due anni ha avuto rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:
- Lilly
- Novonordisk

Achievement of the ABC goals has improved, but remains suboptimal among adults with diabetes (USA)



Prevalence of meeting ABC goals among 4926 adults aged ≥20 years with diagnosed diabetes, NHANES 1988–2010. Estimates are age- and sex-standardised to the 2007–2010 diabetic NHANES population (+ SE). NHANES is a stratified, multistage, probability cluster survey conducted in the non institutionalized U.S. population

*p<0.01, estimates are compared with those of 2007–2010. †p<0.05, estimates are compared with those of 2007–2010.

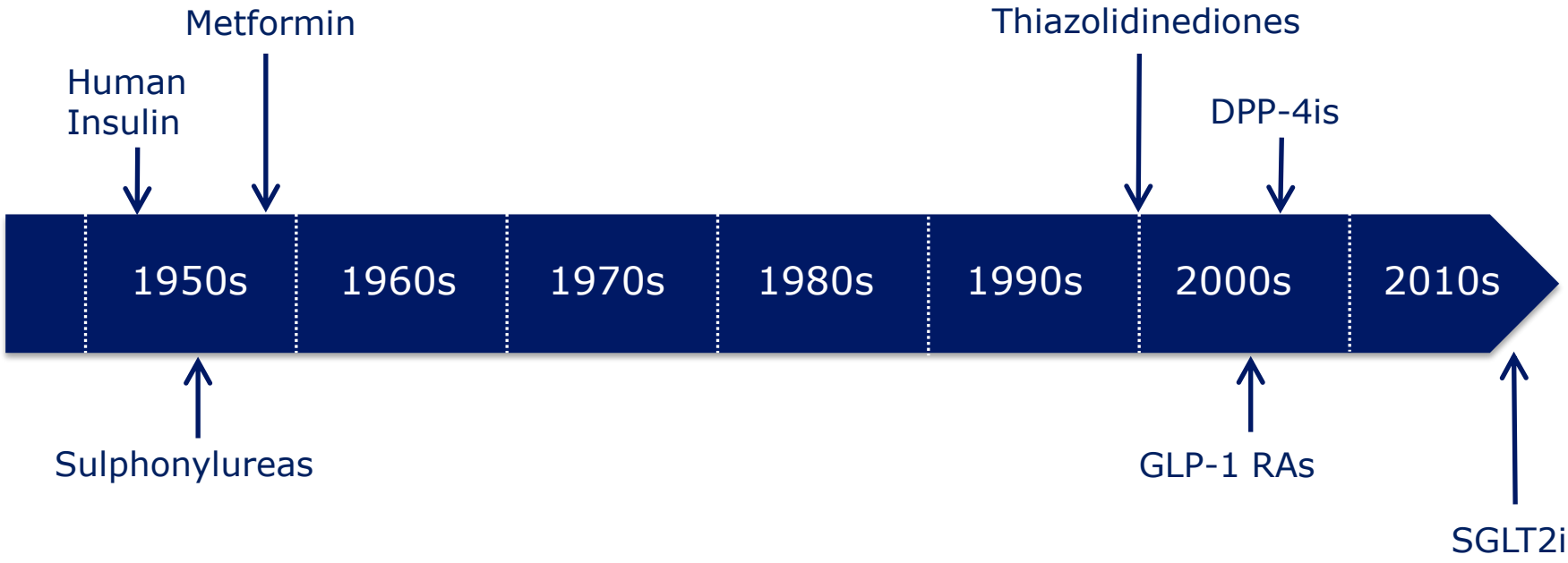
Stark Casagrande S et al. *Diabetes Care*. 2013;36(8):2271-2279.

Achievement of the HbA1c goals has improved but still remains low among adults with T2D (Italy)

Nel corso di 8 anni, è stato registrato un trend di incremento della quota di soggetti con valori di HbA1c a target, che è passata dal 39% al 44%, con un incremento percentuale relativo pari a circa il 12%. Parallelamente all'incremento della percentuale di soggetti con buon controllo metabolico, la quota di pazienti con valori di HbA1c superiori a 8% si è ridotta dal 35% al 27%, con un decremento relativo del 22%.

Annali AMD 2012

Treatment options in type 2 diabetes



DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose co-transporter-2 inhibitor

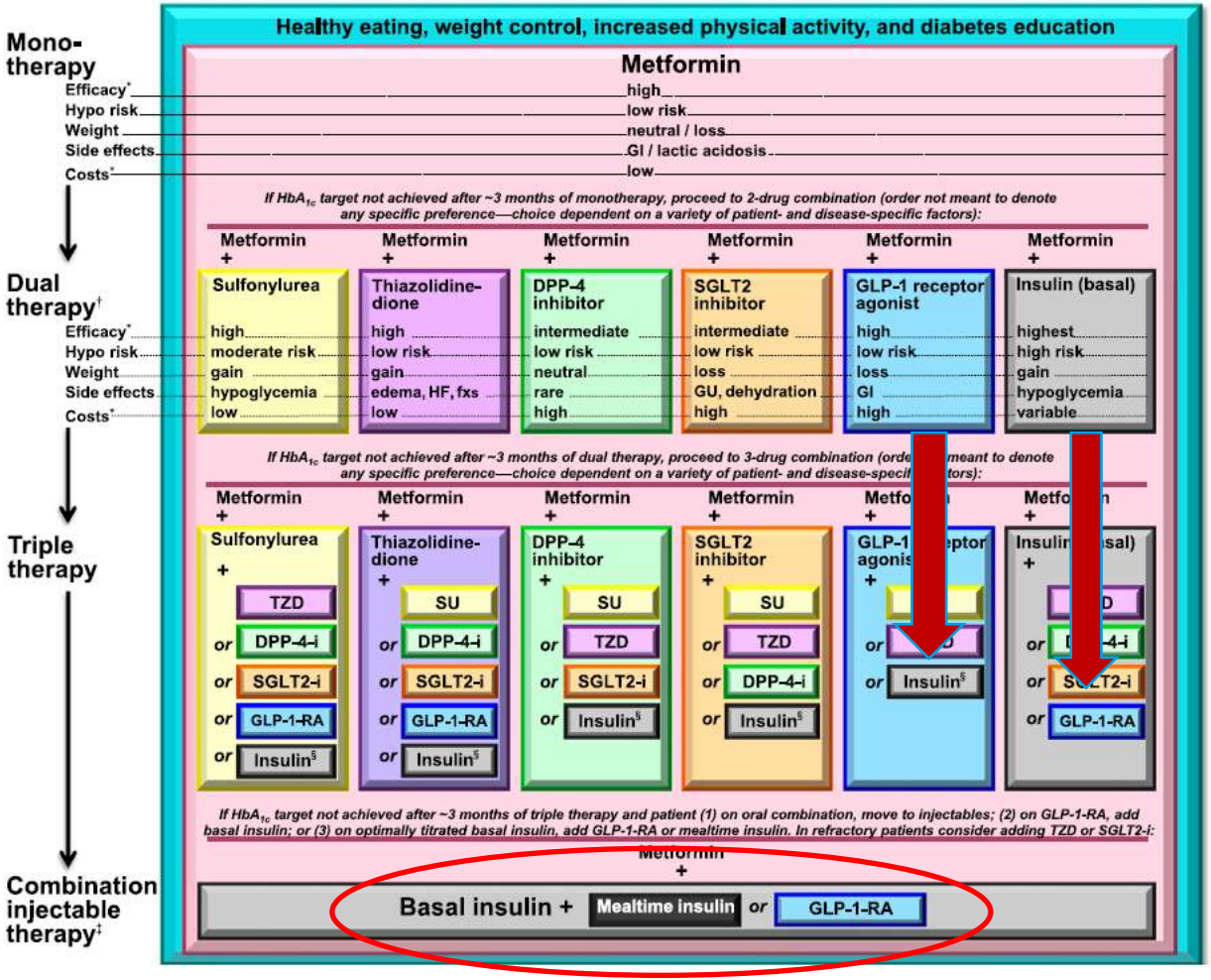
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

Silvio E. Inzucchi,[1] Richard M. Bergenstal,[2] John B. Buse,[3] Michaela Diamant,[4] Ele Ferrannini,[5] Michael Nauck,[6] Anne L. Peters,[7] Apostolos Tsapas,[8] Richard Wender,[9,10] and David R. Matthews[11,12,13]

[1]Section of Endocrinology, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT
[2]International Diabetes Center at Park Nicollet, Minneapolis, MN
[3]Division of Endocrinology, University of North Carolina School of Medicine, Chapel Hill, NC



Inzucchi et al., Diabetes Care 2015; 38:140-149

Correlation between baseline characteristics and clinical outcomes in a large population of diabetes patients treated with Liraglutide in a real-world setting in Italy

Lapolla et al… Simioni

Clinical Therapeutics *Accepted for publication November 26, 2014.*
http://dx.doi.org/10.1016/j.clinthera.2014.11.015

Anthropometrics	Values
N.	481
Age, y	57.3 (9.2)
Sex male, %	58.3
Weight, kg	106.7 (20.8)
Body mass index	37.1 (6.6)
Disease duration, y	9.5 (6.8)
Baseline HbA1c, %	8.7(1.3)
Baseline FPG, mg/dL	168.5 (45.3)

Concomitant antidiabetic medications,	%
Metformin alone	49.1
Metformin + sulfonylurea	22.8
Sulfonylurea alone	2.8
Pioglitazone (metformin or sulfonylurea or both)	1.1
Insulin	24.2

Table III. Clinical determinants of glycated hemoglobin reduction in patients under observation using a multivariate linear regression model considering the change in glycated hemoglobin from baseline to 12 months of liraglutide treatment as the dependent variable. Adjusted R^2 was 0.53.

Variable	Parameter Estimate	SE	t	P
Coefficient	−6.55	0.95	−6.88	<0.0001
Age	0.01	0.01	1.50	0.136
Sex	−0.01	0.14	−0.07	0.944
Duration of diabetes	−0.03	0.01	−2.95	0.004
Baseline weight	−0.01	0.001	−2.51	0.013
Baseline HbA_{1c}	0.73	0.05	13.43	<0.0001
Previous insulin therapy	−0.27	0.15	−1.80	0.073
Previous metformin monotherapy	0.45	0.14	3.11	0.002
Baseline SBP	0.01	0.001	1.54	0.117
Baseline LDL cholesterol	0.001	0.001	1.64	0.102
Baseline HDL cholesterol	−0.001	0.01	−0.18	0.854
Baseline triglycerides	−0.001	0.001	−0.34	0.732

HbA_{1c} = glycated hemoglobin; SBP = systolic blood pressure.

Table V. Clinical determinants for the probability of liraglutide treatment discontinuation due to lack of glycemic control using a multivariate logistic regression model considering treatment discontinuation within the first 12 months as the dependent variable.

Variable	Category	Odds Ratio	95% CI
Age		1.024	0.960–1.093
Sex		1.007	0.994–1.021
Duration of diabetes		1.021	0.924–1.128
Baseline HbA_{1c}		0.989	0.565–1.731
Baseline weight		1.011	0.985–1.038
Previous insulin therapy	No	1.000	–
	Yes	1.578	0.410–6.072
Previous metformin monotherapy	No	1.000	–
	Yes	3.115	0.243–39.986
Previous SU use	No	1.000	–
	Yes	3.013	1.071–9.018

HbA_{1c} = glycated hemoglobin; OR = odds ratio; SU = sulfonylurea.

Independent glucose and weight-reducing effects of Liraglutide in a real-world population of type 2 diabetic outpatients

Fadini,Simioni et al. 2013

Acta Diabetol
DOI 10.1007/s00592-013-0489-3

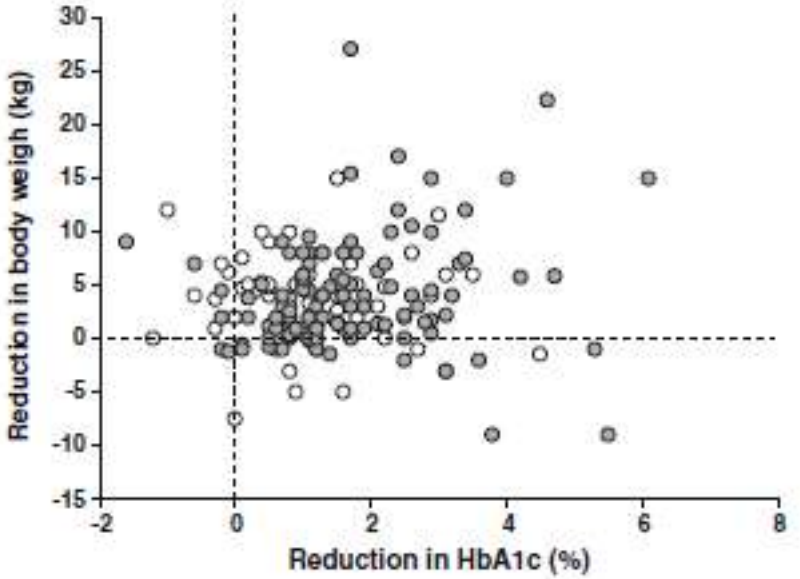
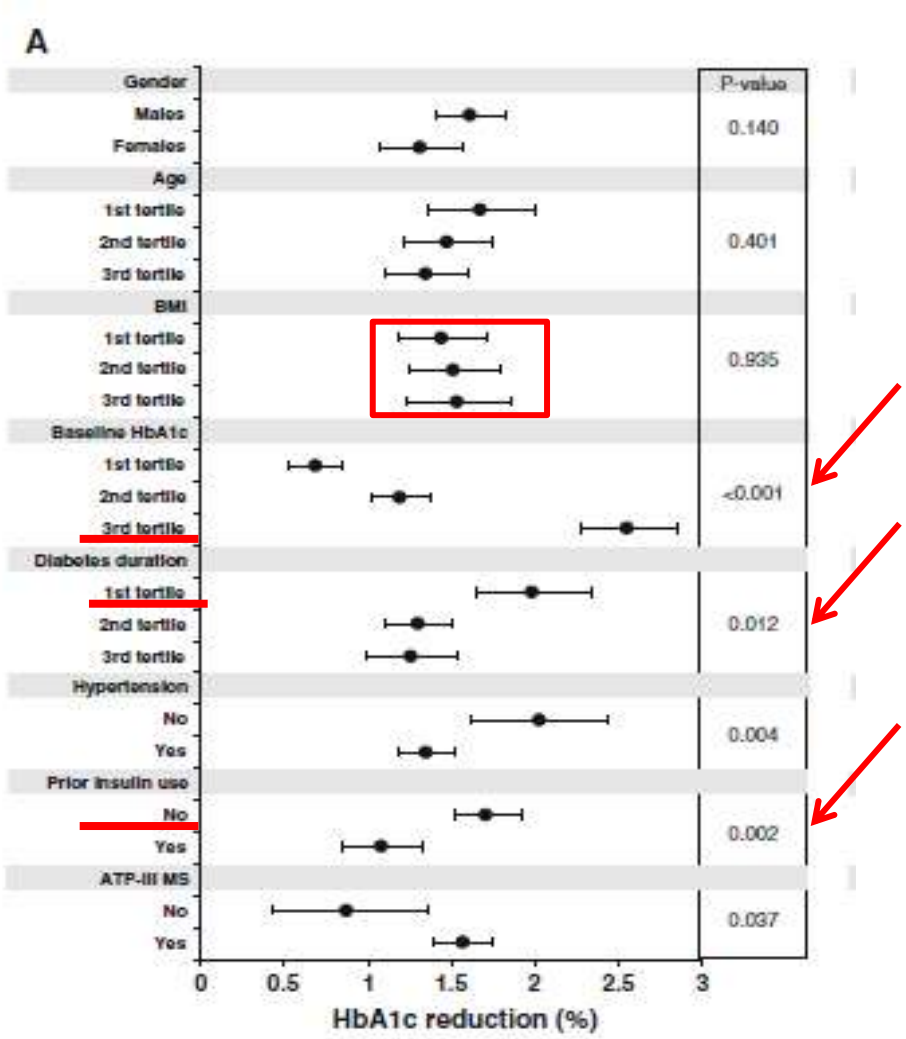
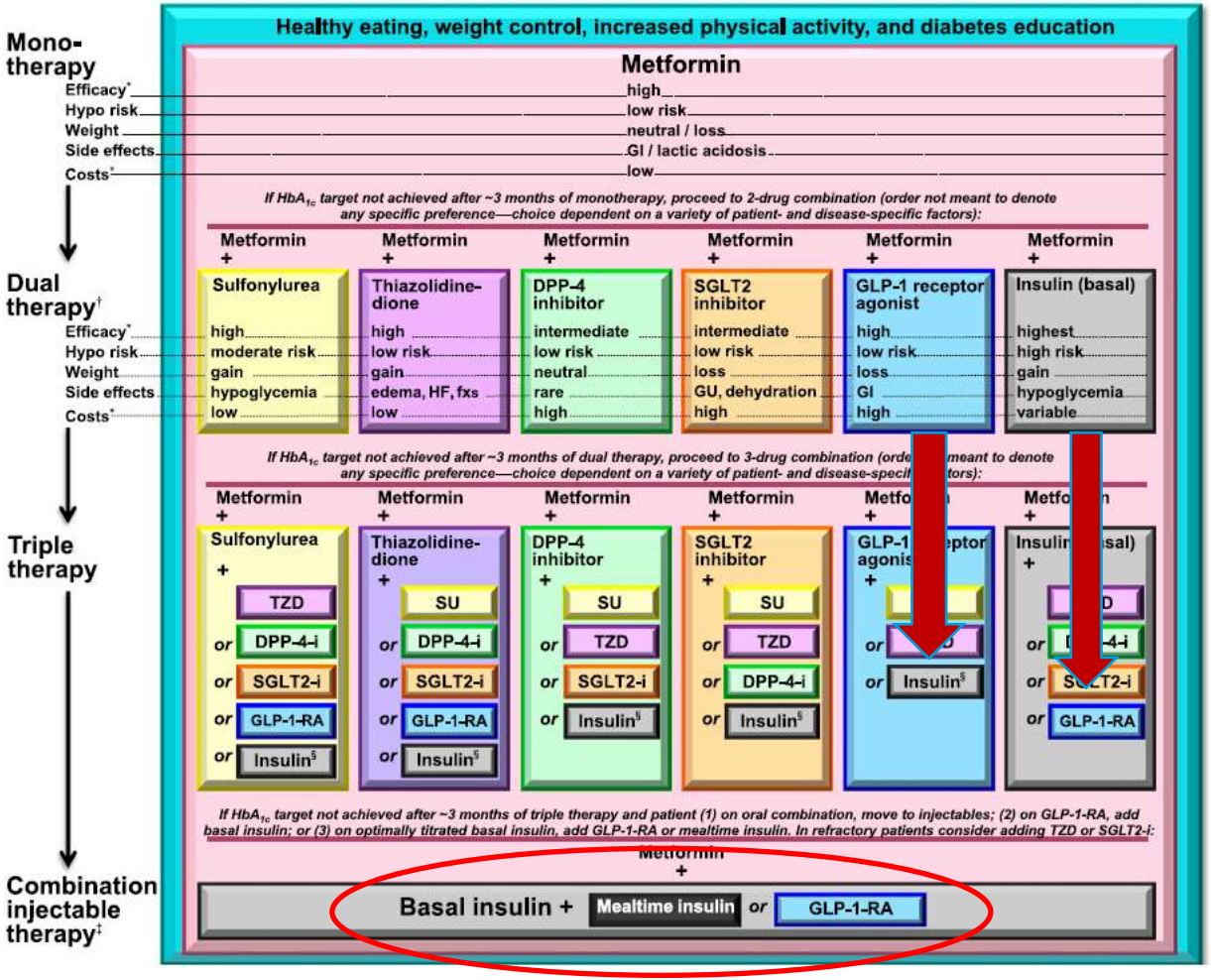


Fig. 2 The correlation between change in HbA1c and change in body weight after initiation of Liraglutide therapy. *White circles* indicate previous insulin users ($r = -0.03$; $p = 0.98$), while gray circles indicate insulin-naïve patients ($r = 0.144$, $p = 0.13$)

Forest plots reporting reduction in HbA1c in different subgroups of patients and in relation to possible determinants of glycemic efficacy and weight reduction after initiation of Liraglutide. p values are shown for t test when there are 2 conditions or for ANOVA when there are 3 tertiles





Inzucchi et al., Diabetes Care 2015; 38:140-149

New AIFA Therapeutic plan 2015

http://www.agenziafarmaco.gov.it/it/content/aggiornamento-piano-terapeutico-incretine-30032015.

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

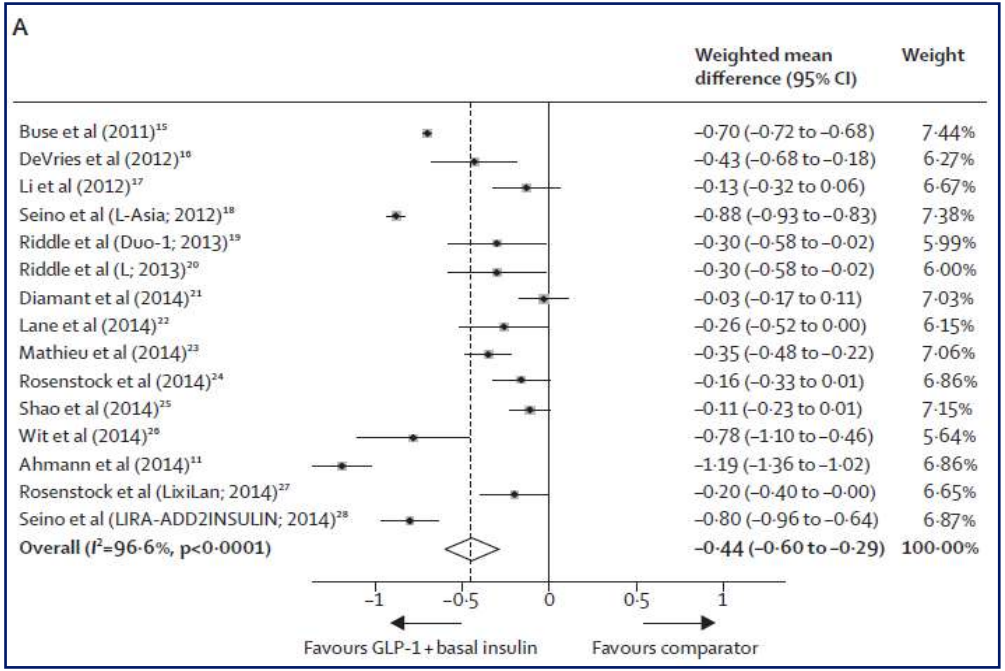
Conrad Eng, Caroline K Kramer, Bernard Zinman, Ravi Retnakaran*
***Lancet* 2014; 384: 2228–34**

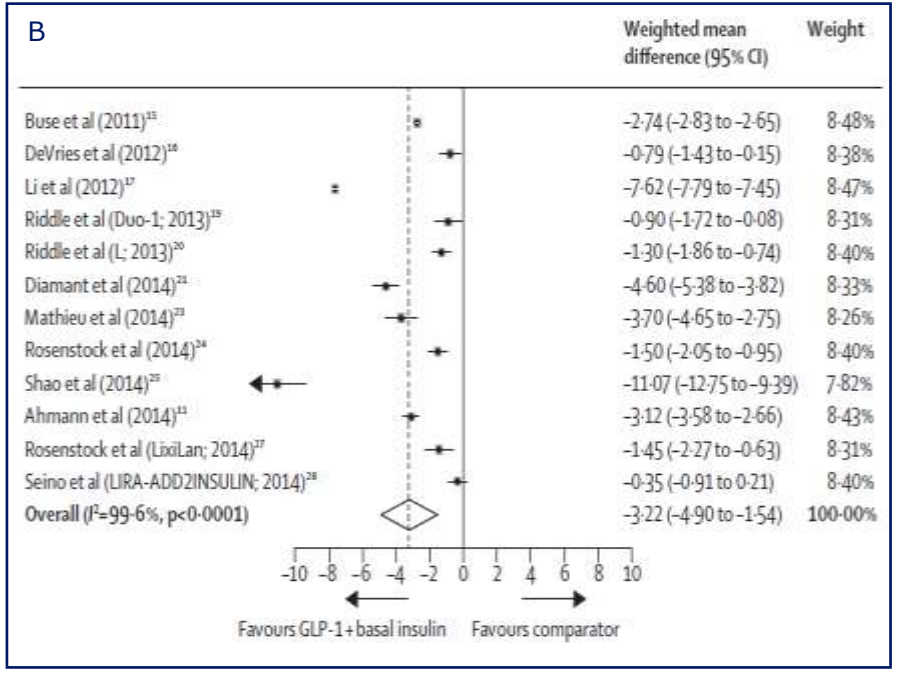
- 15 eligible studies and were included in the analysis (N=4348 participants).
- Compared with other anti-diabetic treatments, GLP-1 agonist (Liraglutide, Exenatide, Lixisenatide, Albiglutide) and basal insulin combination treatment yielded an improved mean reduction in HbA1c of –0·44% (95% CI –0·60 to –0·29)
- Improved likelihood of achieving the target HbA1c of 7·0% or lower (relative risk [RR] 1·92; 95% CI 1·43 to 2·56)
- No increased relative risk of hypoglycaemia (0·99; 0·76 to 1·29)
- Mean reduction in weight of –3·22 kg (–4·90 to –1·54).
- Furthermore, compared with basal-bolus insulin regimens, the combination treatment yielded a mean reduction in HbA1c of –0·1% (–0·17 to –0·02), with lower relative risk of hypoglycaemia (0·67, 0·56 to 0·80), and reduction in mean weight (–5·66 kg; –9·8 to –1·51).

GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes.

Meta-analyses of glucagon-like peptide-1 (GLP-1) agonist and basal insulin combination treatment versus other anti-diabetic treatments, comparing HbA1c concentrations

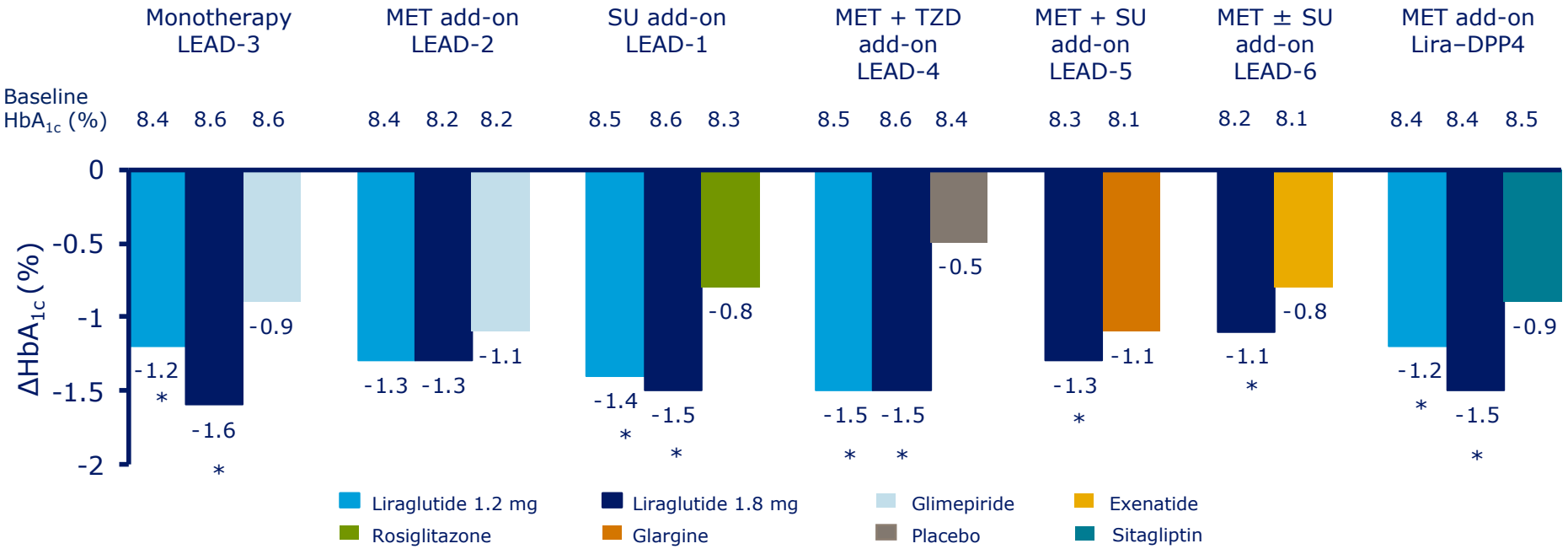
Outcome assessed is **(A) HbA1c** (%), **(B) Weight** in studies that compared combination treatment with basal-bolus insulin treatment





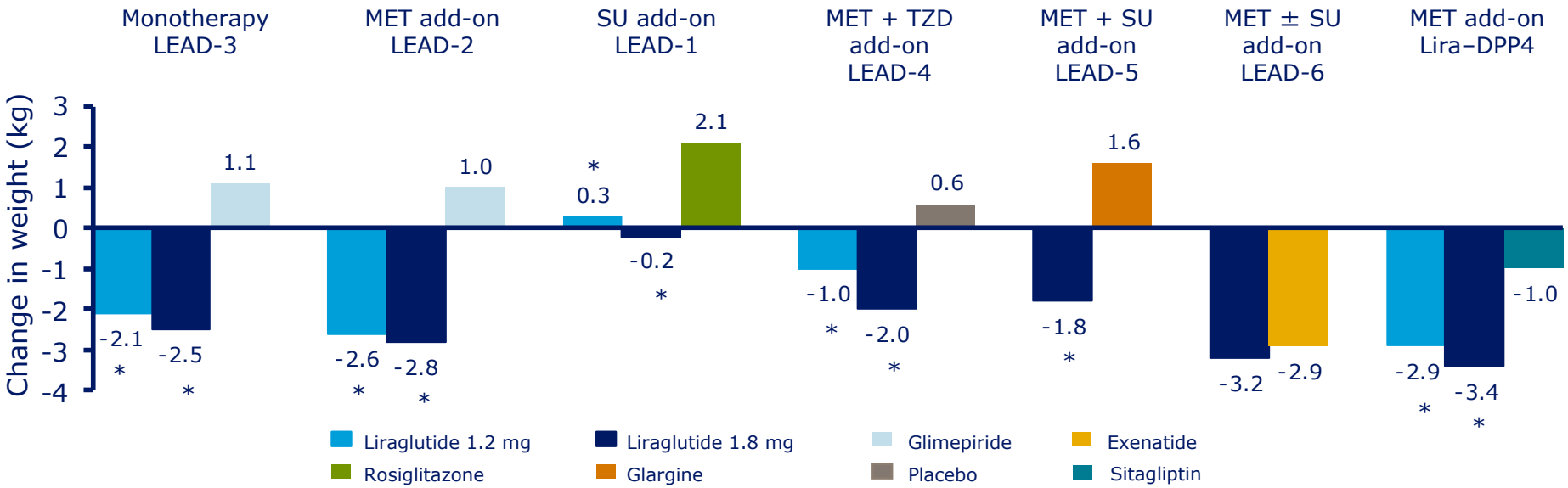
Eng et al., Lancet 2014; 384: 2228–34

HbA_{1c} effects in the LEAD programme



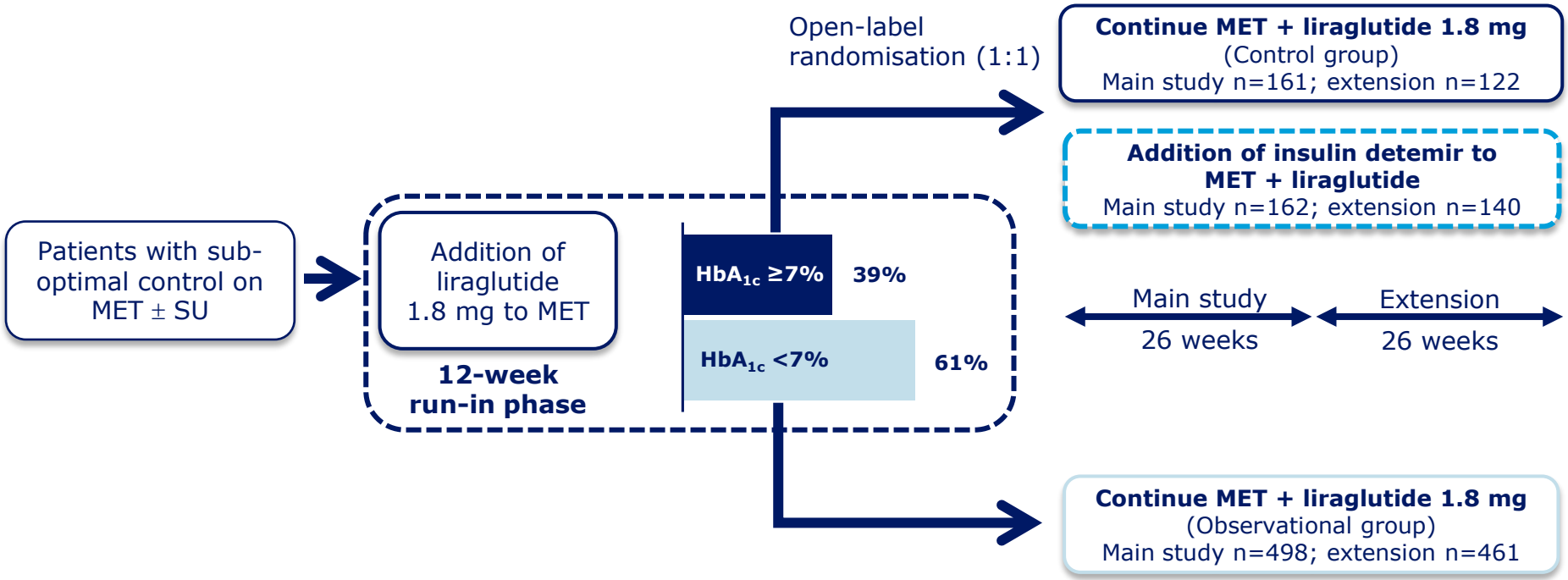
Significant *vs. comparator; change in HbA_{1c} from baseline for overall population (LEAD-4,-5); add-on to diet and exercise failure (LEAD-3); or add-on to previous oral anti-diabetic drug (OAD) monotherapy (LEAD-2,-1).
HbA_{1c}, glycosylated haemoglobin; MET, metformin; Sita, sitagliptin; SU, sulphonylurea; TZD, thiazoladinedione
Marre *et al. Diabet Med* 2009;26;268–278 (LEAD-1); Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2); Garber *et al. Lancet* 2009;373:473–481 (LEAD-3); Zinman *et al. Diabetes Care* 2009;32:1224–1230 (LEAD-4); Russell-Jones *et al. Diabetologia* 2009;52:2046–2055 (LEAD-5); Buse *et al. Lancet* 2009;374:39–47 (LEAD-6); Pratley *et al. Lancet* 2010:375;1447–1456 (lira vs. sita)

Weight reduction with liraglutide in people with type 2 diabetes



*Significant vs. comparator
Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione
Marre *et al. Diabet Med* 2009;26;268–78 (LEAD-1); Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2); Garber et al. *Lancet* 2009;373:473–81 (LEAD-3); Zinman *et al. Diabetes Care* 2009;32:1224–30 (LEAD-4); Russell-Jones *et al. Diabetologia* 2009;52:2046-2055 (LEAD-5); Buse *et al. Lancet* 2009;374:39–47 (LEAD-6); Pratley *et al. Lancet* 2010;375:1447–56 (LIRA-DPP4i)

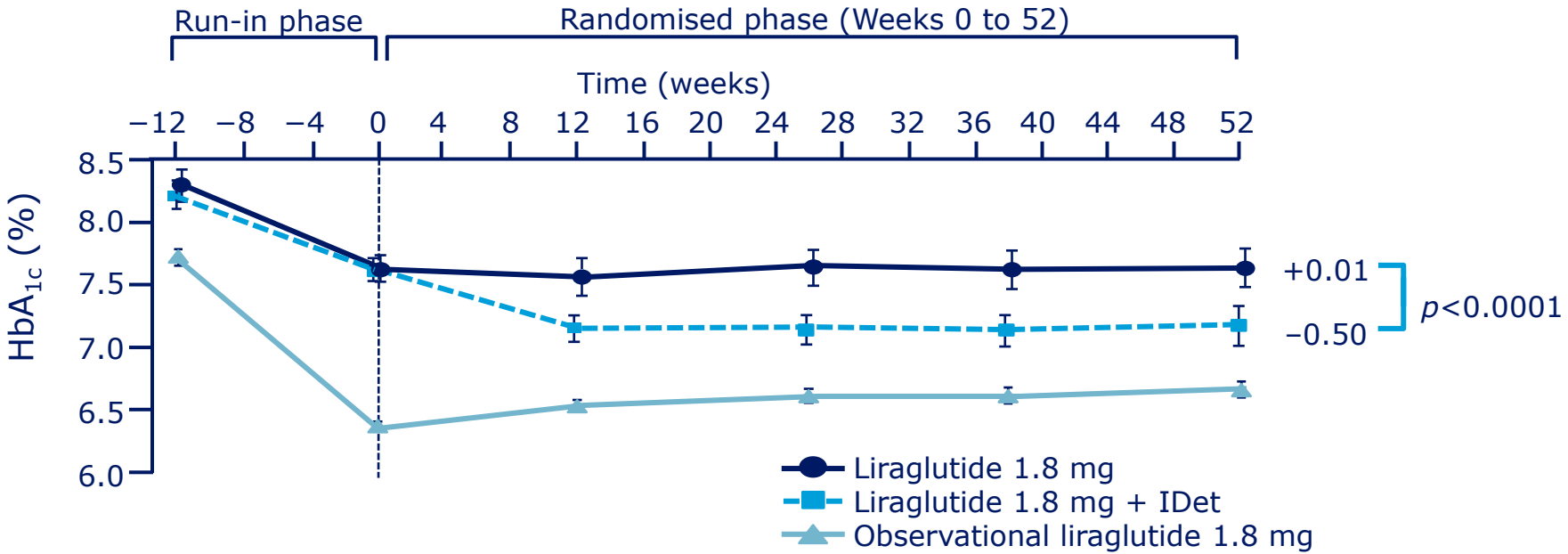
Basal insulin added to GLP-1 receptor agonist: LIRA-DETEMIR study design



MET, metformin; SU, sulphonylurea

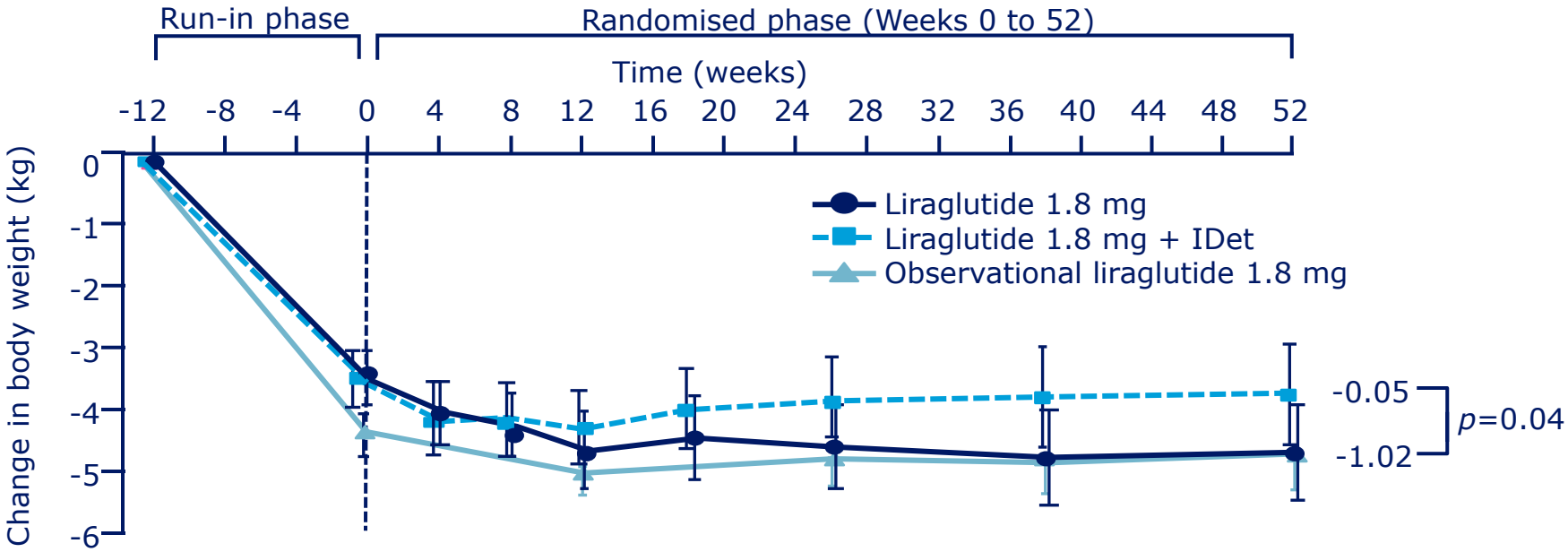
DeVries *et al. Diabetes Care* 2012;35:1446–1454

Addition of insulin detemir to liraglutide: Change in HbA_{1c} (%)



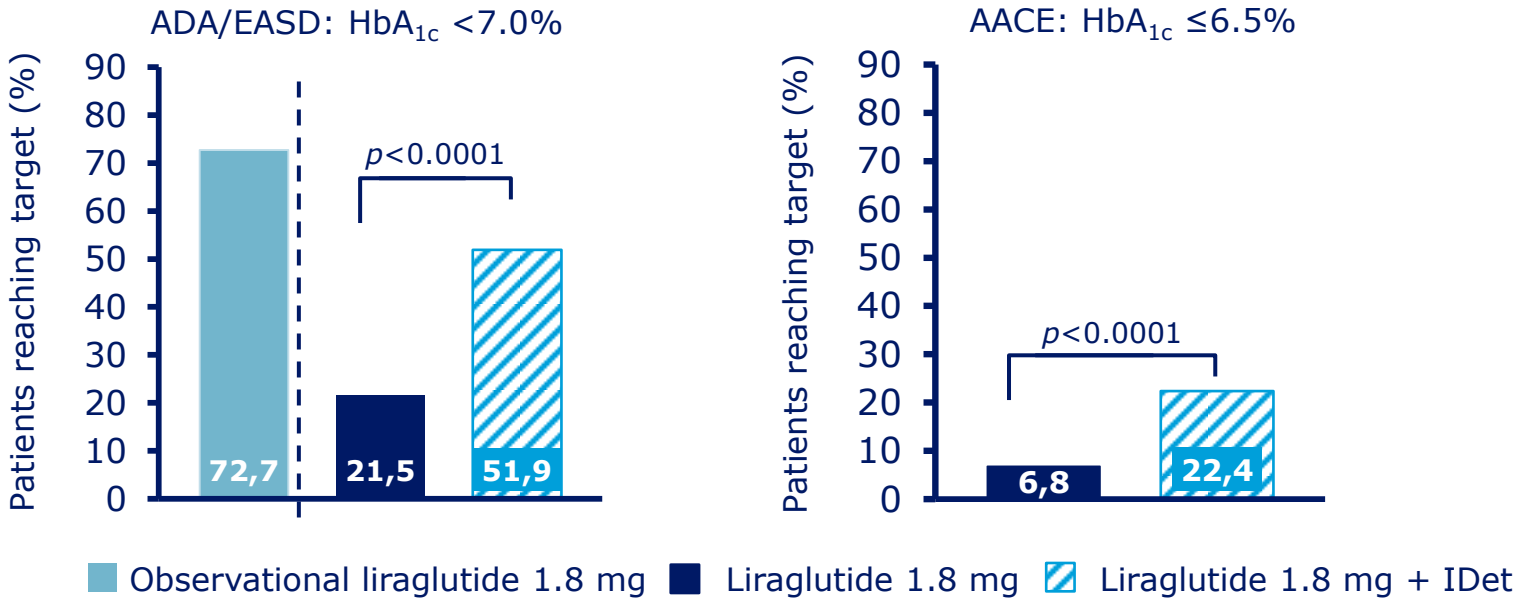
Mean (2SE); data are LOCF
Last observation before intensification is included as LOCF in the initial treatment group; ANCOVA on FAS LOCF for difference in randomised phase
ANCOVA, analysis of covariance; FAS, full analysis set; HbA_{1c}, glycosylated haemoglobin; IDet, insulin detemir; LOCF, last observation carried forward; SE, standard error
Rosenstock *et al. J Diabetes Complications* 2013;27:492–500

Addition of insulin detemir to liraglutide: Mean change in body weight



Mean (2SE); data are LOCF
Last observation before intensification is included as LOCF in the initial treatment group; ANCOVA on FAS LOCF for difference in randomised phase
ANCOVA, analysis of covariance; FAS, full analysis set; IDet, insulin detemir; LOCF, last observation carried forward; SE, standard error
DeVries *et al. Diabetes Care* 2012;35:1446–1454

Addition of insulin detemir to liraglutide: Subjects meeting targets at week 52

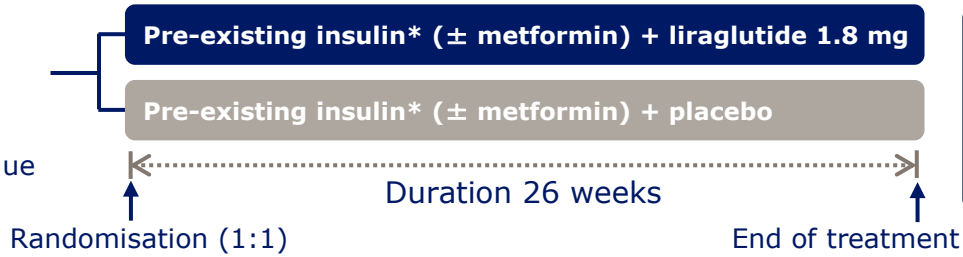


Data for the randomised groups are estimates from logistic regression analyses for the FAS LOCF. Data for the observational group are for the FAS LOCF; logistic regression analyses were not performed. Patients in the extension IDet-intensified group are included in their initial treatment groups until they received IDet
AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes

DeVries *et al. Diabetes Care* 2012;35:1446–1454

LIRA-ADD2BASAL: Study design

446 patients
- T2DM
- HbA_{1c} 7–10%
- BMI 20–45 kg/m^2
- Basal insulin analogue therapy



Trial information
- Initiation: September 2012
- Double blinded
- Patients stratified by screening HbA_{1c}; OAD treatment; type of basal insulin analogue

Trial objective

To investigate the effect of liraglutide vs. placebo when added to basal insulin analogues ± metformin in subjects with T2DM.

Key inclusion criteria

Stable insulin detemir or insulin glargine ≥20 U/day for 8 weeks (± metformin ≥1500 mg/day).

Primary endpoint
- Change in HbA_{1c} from baseline to week 26

Key secondary endpoints
- Change in body weight from baseline to week 26
- Change in FPG from baseline to week 26
- Change in 7-point SMPG profile from baseline to week 26
- Number of hypoglycaemic episodes

*Insulin detemir or insulin glargine ≥20 U/day; if HbA_{1c} ≤8%, insulin dose was reduced by 20%
BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; SMPG, self-measured plasma glucose; T2DM, type 2 diabetes mellitus; U, units of insulin
Lahtela *et al. Diabetologia* 2014;57(Suppl 1):Abstract 37

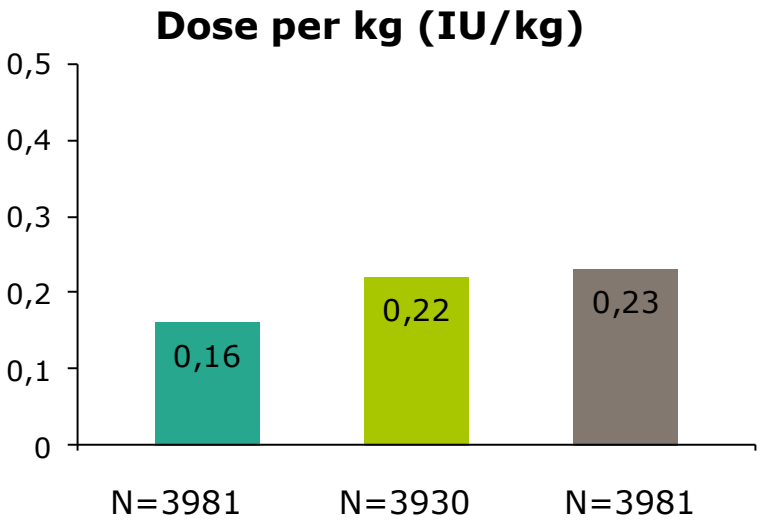
Baseline characteristics

	Liraglutide 1.8 mg (N=225)	Placebo (N=225)
Age (years)	59.3	57.5
Duration of diabetes (years)	12.1	12.1
Female ; Male (%)	46.7% ; 53.3%	39.6% ; 60.4%
Weight (kg)	90.2	91.9
BMI (kg/m^2)	32.3	32.2
HbA_{1c}, % (mmol/mol)	8.2% (66.1)	8.3% (67.2)
Metformin (No ; Yes)	8.0% ; 92.0%	6.7% ; 93.3%
Basal insulin analogue (%) (detemir ; glargine)	33.3% ; 66.7%	32.0% ; 68.0%
Pre-trial insulin dose, U	48.3*	45.9*

*Geometric means 40.5 U for both groups
Data are means. Percentages are presented for gender and stratification factors (metformin and basal insulin analogue)
BMI, body mass index; HbA_{1c}, glycosylated haemoglobin

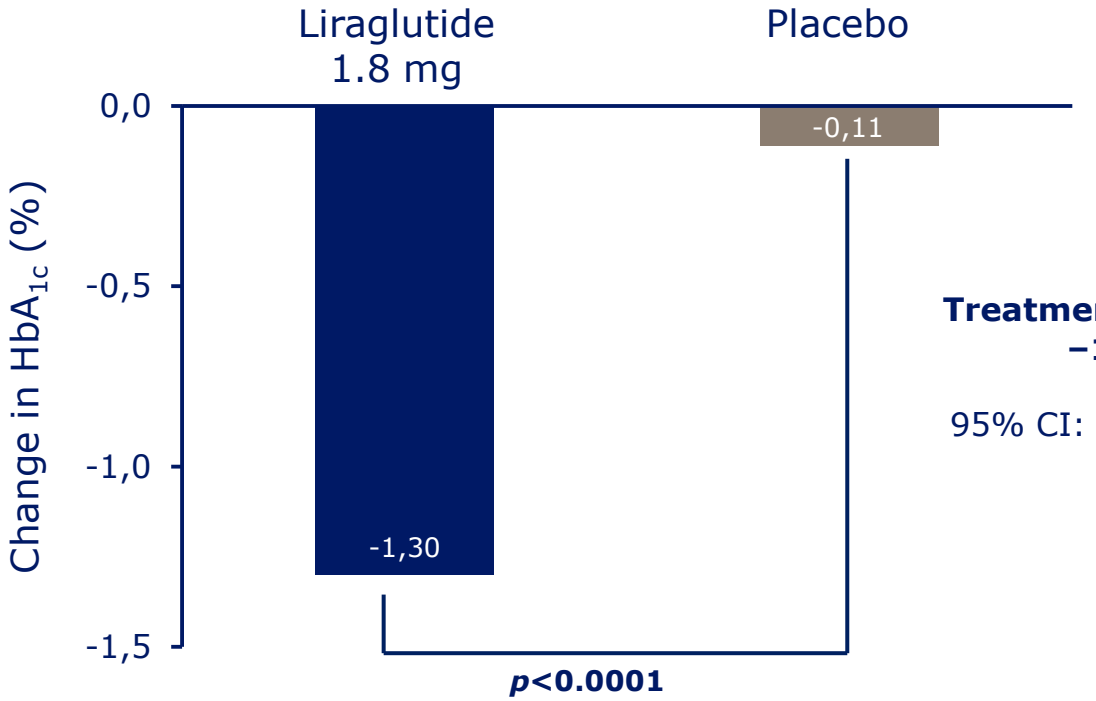
Study of Once Daily Levemir (SOLVE™): insights into the timing of insulin initiation in people with poorly controlled type 2 diabetes in routine clinical practice

	Total cohort N=17374
Gender (% male)	53
Age (yrs)	61.1 ± 11.5
Diabetes duration (yrs)	9.8 ± 7.0
OAD therapy duration (yrs)	8.5 ± 6.6
Weight (kg)	80.8 ± 17.6
BMI (kg/m^2)	29.3 ± 5.4



K. Khunti *Diabetes, Obesity and Metabolism* 14: 654–661, 2012.

LIRA-ADD2BASAL: HbA_{1c} change from baseline to week 26

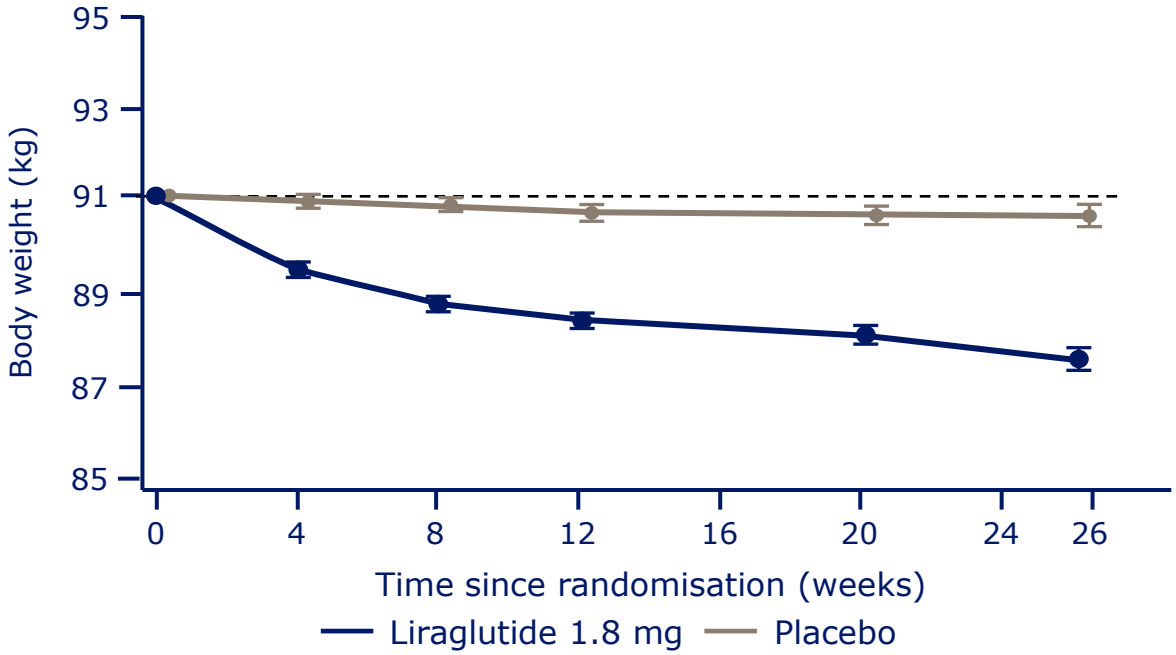


Treatment difference: –1.19%

95% CI: [–1.39;–0.99]

Estimated means from mixed model for repeated measurements
CI, confidence interval; HbA_{1c}, glycosylated haemoglobin
Lahtela *et al. Diabetologia* 2014;57(Suppl 1):Abstract 37

LIRA-ADD2BASAL: Body weight over 26 weeks



Body weight estimated mean change from baseline to Week 26

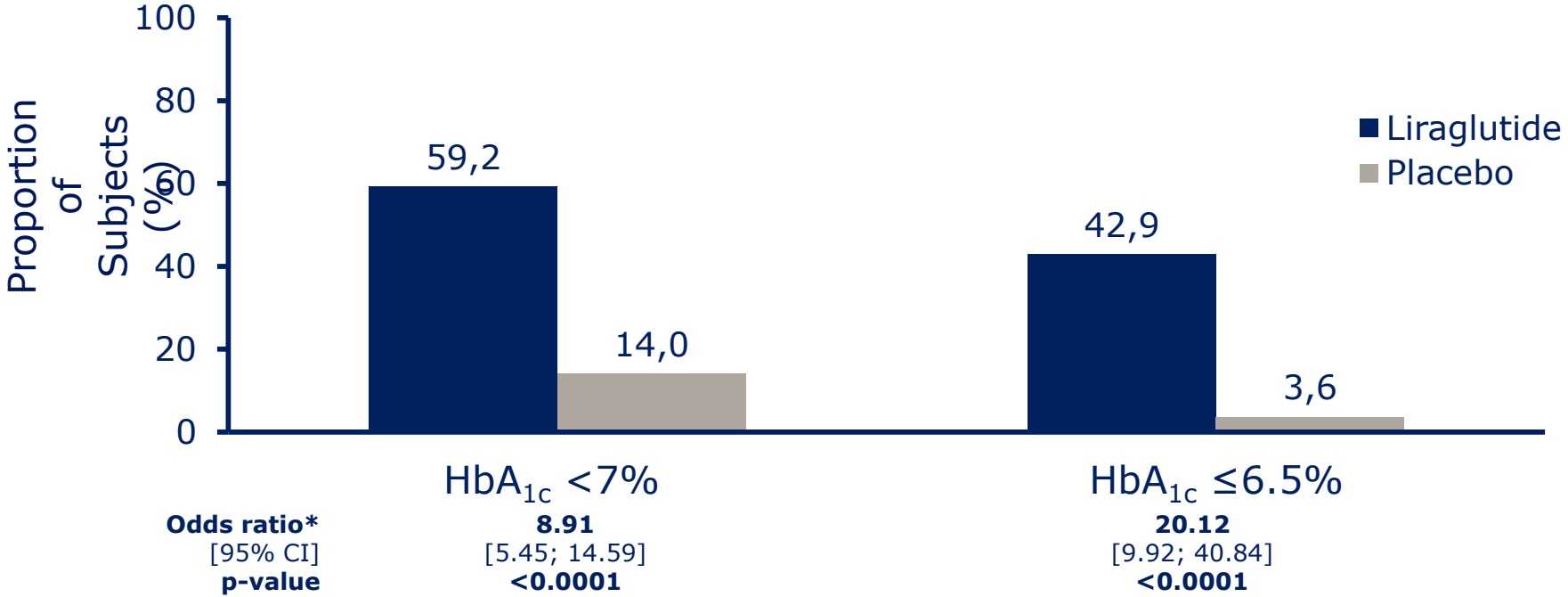
*95% CI: [–3.85;–2.37]

***p*<0.0001**

CI, confidence interval; ETD, estimated treatment difference

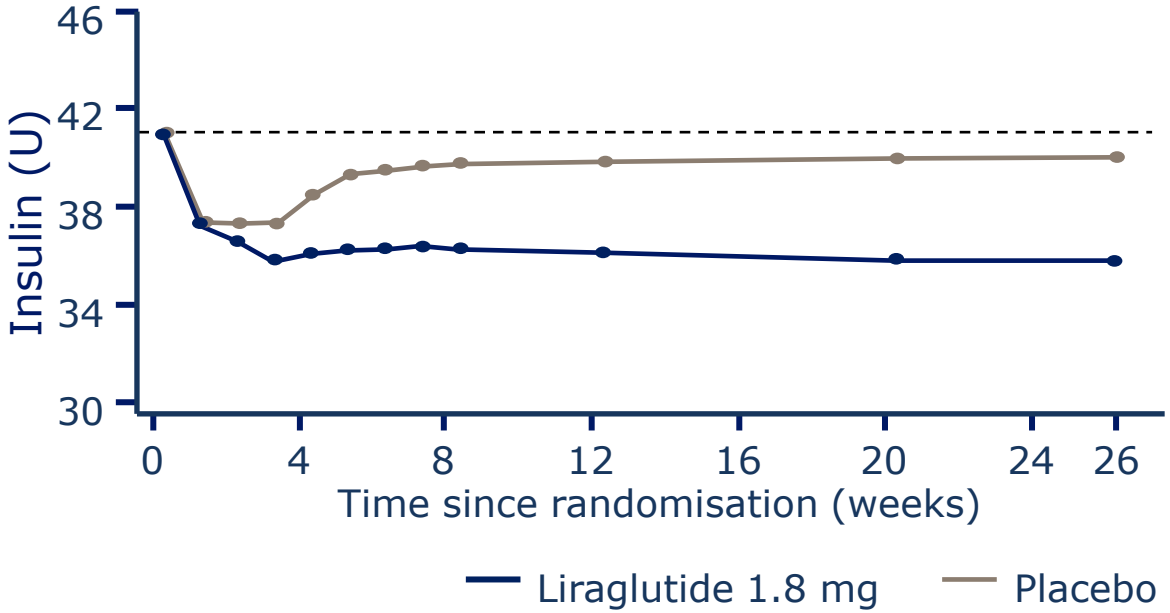
Lahtela *et al. Diabetologia* 2014;57(Suppl 1):Abstract 37

Subjects meeting targets at Week 26



*Liraglutide 1.8 mg/liraglutide placebo
The binary endpoint was analysed using a logistic regression model.
CI, confidence interval; HbA_{1c}, glycosylated haemoglobin

Change in insulin dose (U)



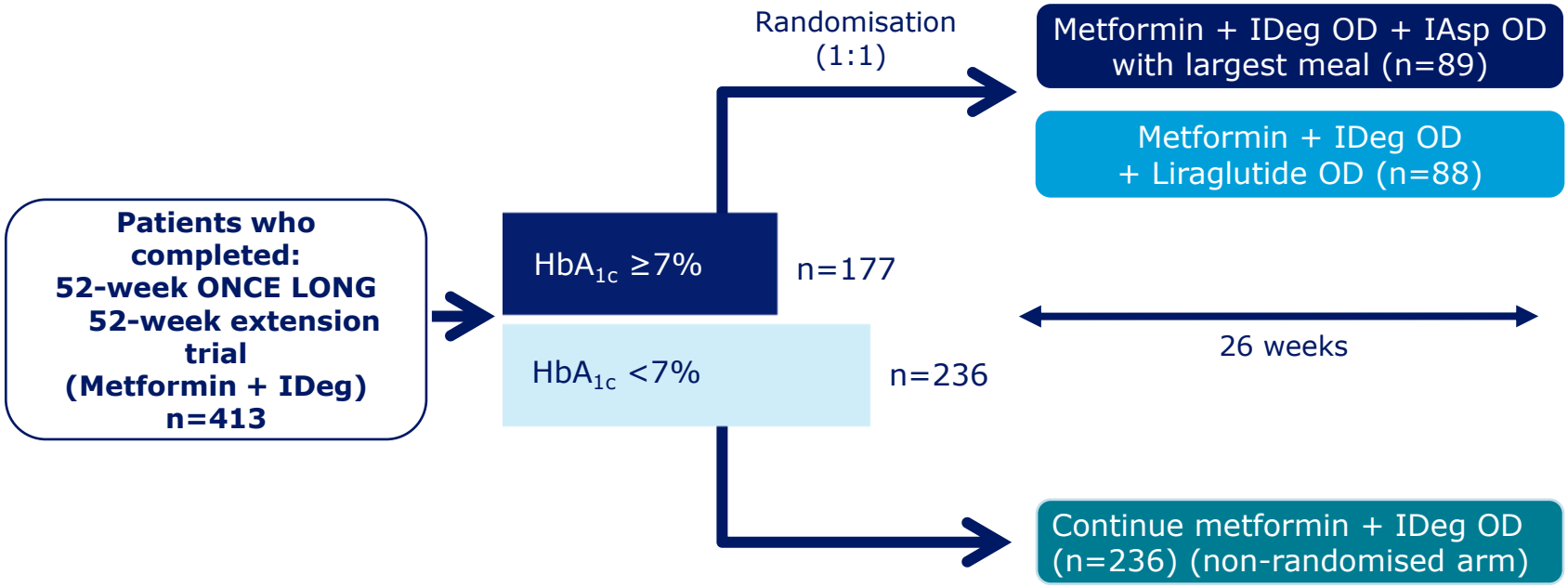
Insulin dose estimated mean ratio to baseline at week 26

*95% CI: [0.87;0.92]

***p*<0.0001**

*Mean baseline detemir or glargine dose: 40.5 U in liraglutide and placebo groups.
Data are estimated means from mixed model for log-transformed repeated measurements.
CI, confidence interval; ETR, estimated treatment ratio; HbA_{1c}, glycosylated haemoglobin; U, units of insulin

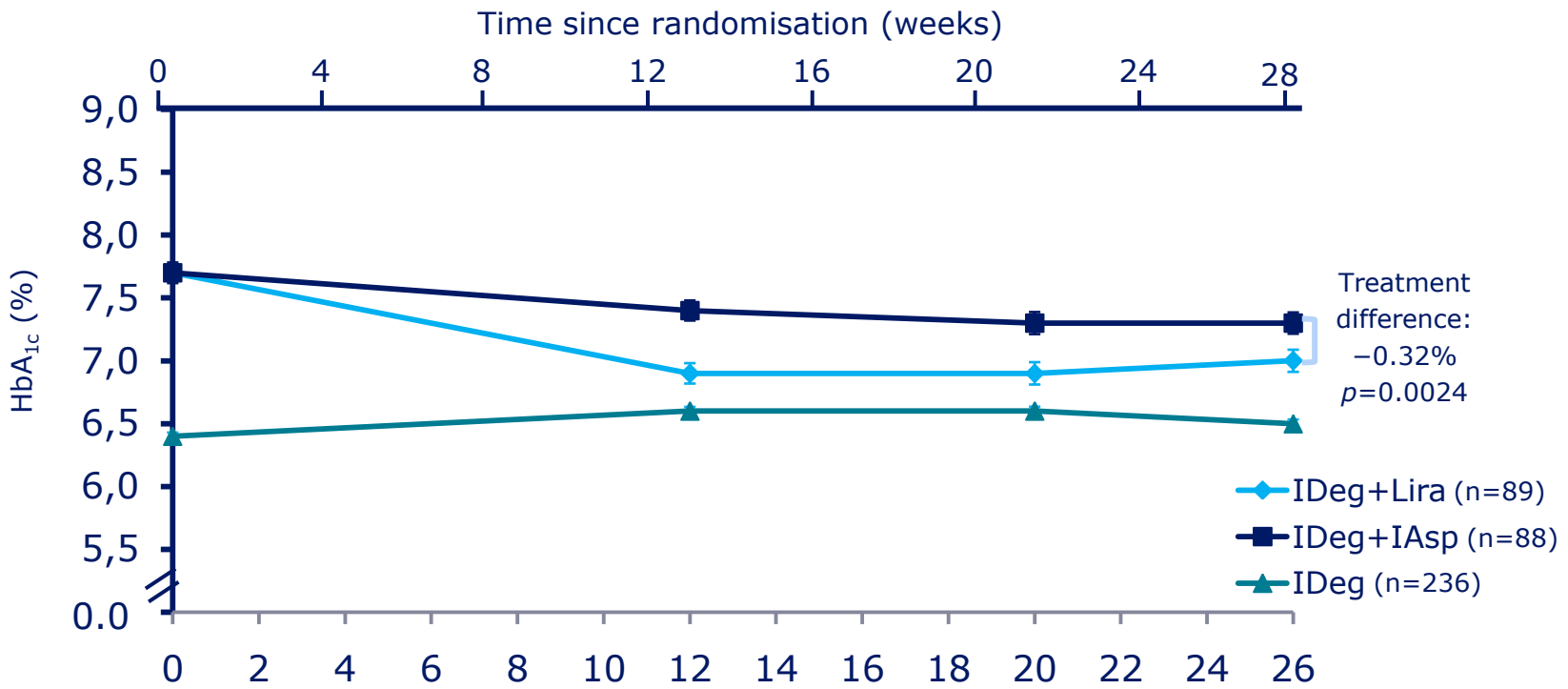
GLP-1 receptor agonist added to basal insulin: BEGIN:LIRAGLUTIDE ADD-ON study design



GLP-1, glucagon-like receptor 1; HbA_{1c}, glycosylated haemoglobin; OD, once daily

Mathieu et al. *Diabetes Obes Metab* 2014;16:636–44

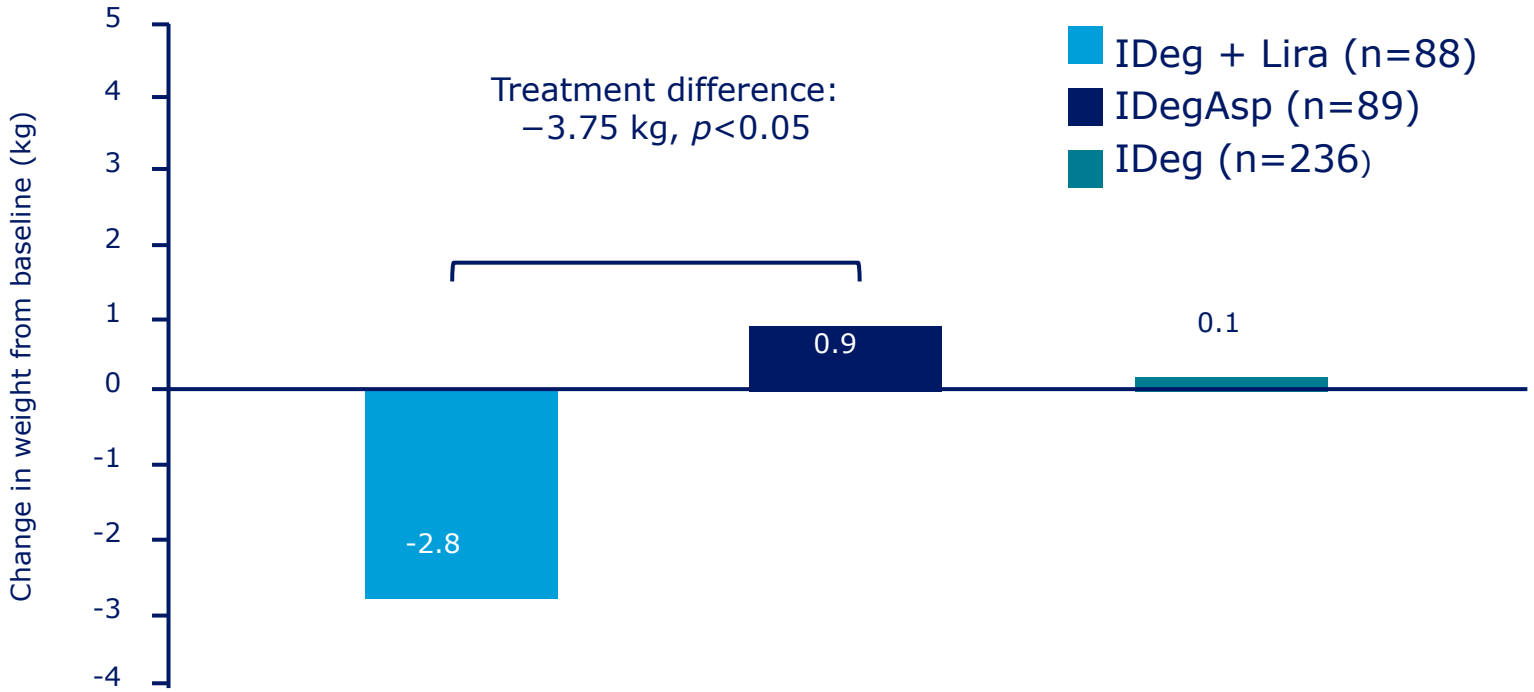
Change in HbA_{1c} (%)



Mean±SEM; FAS; NAS; LOCF; Comparisons: estimates adjusted for multiple covariates. SEM, standard error of the mean, FAS, full analysis set; NAS, non-randomised analysis set; HbA_{1c}, glycosylated haemoglobin; IDeg, insulin degludec; IAsp, insulin aspart; Lira, liraglutide; LOCF, last observation carried forward

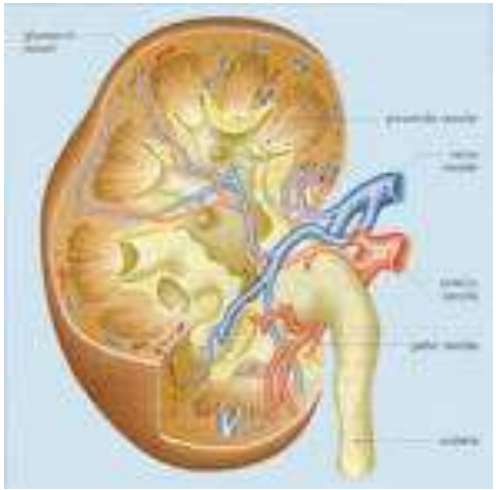
Mathieu et al. *Diabetes Obes Metab* 2014;16:636–44

Change in body weight



FAS; LOCF; Comparisons: Estimates adjusted for multiple covariates.
Mathieu et al. *Diabetes Obes Metab* 2014;16:636–44

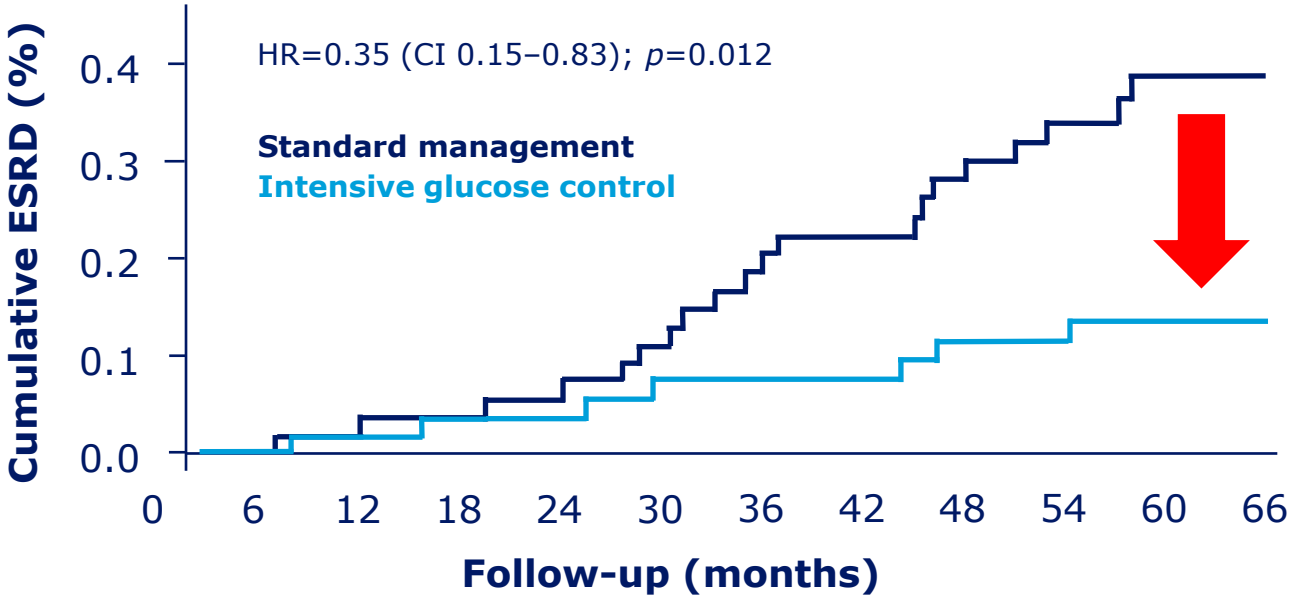
Renal impairment in type 2 diabetes



Renal Impairment in T2D
Annali AMD 2012

Non si registrano sostanziali variazioni temporali nella percentuale di soggetti con micro/macroalbuminuria o con riduzioni marcate del GFR, sebbene per quest'ultimo indicatore, così come per la concomitanza delle due forme di alterazione della funzionalità renale, sia presente un lieve trend in crescita.

Intensive glucose lowering reduces the risk of ESRD in patients with T2DM



CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; T2DM, type 2 diabetes mellitus
Perkovic V et al. *Kidney Int* 2013;83:517–523

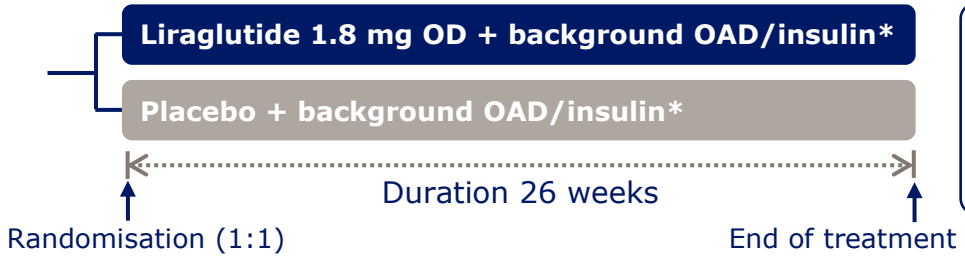
Antidiabetic therapy in CKD

Drug	Approved for moderate renal impairment	No dose adjustment	No renal excretion*
Liraglutide	√	√	√
Linagliptin	√	√	
Alogliptin	√		
Vildagliptin	√		
Saxagliptin	√		
Sitagliptin	√		
Dapaglifozin			
Exenatide LAR			
Lixisenatide			

*Absence of renal excretion defined as 0% of metabolites found in urines
SPC of: Victoza®, Tradjenta®, Vipidia™, Galvus®, Onglyza®,Januvia®, Forxiga™, Bydureon®, Lyxumia®

LIRA-RENAL: Study design

279 patients
- T2DM
- HbA_{1c} 7–10%
- BMI 20–45 kg/m^2
- Moderate renal impairment†



Trial information
- Initiation: June 2012
- Double blinded
- Patients stratified by renal function and background treatment

Trial objective

To investigate the efficacy and safety of liraglutide vs. placebo as add-on to existing diabetes medication in subjects with T2DM and moderate renal impairment.

Key inclusion criteria
- Moderate renal impairment† diagnosed more than 90 days prior to screening
- Stable diabetes treatment for 90 days prior to screening

Primary endpoint
- Change in HbA_{1c} from baseline to week 26

Key secondary endpoints
- Change from baseline in renal function
- Number of responders to HbA_{1c} <7.0% and no weight gain
- Number of responders to HbA_{1c} <7.0% and no minor or severe hypoglycaemic episodes

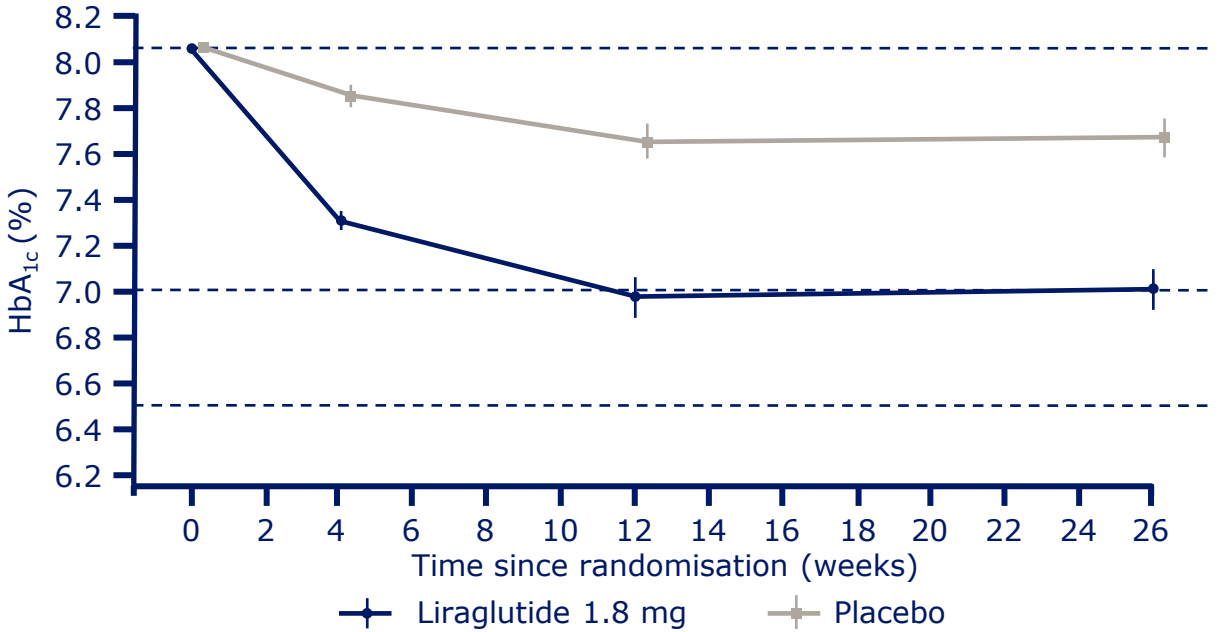
*If HbA_{1c} ≤8%, insulin dose was reduced by 20%; †eGFR (MDRD formula) was based on serum creatinine, sex, age, body size and race
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; MDRD, modification of diet in renal disease; OAD, oral anti-diabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus
Trial ID:NN2211-3916
Umpierrez G et al. *Diabetologia* 2014; 57 (Suppl 1): Abstract 182

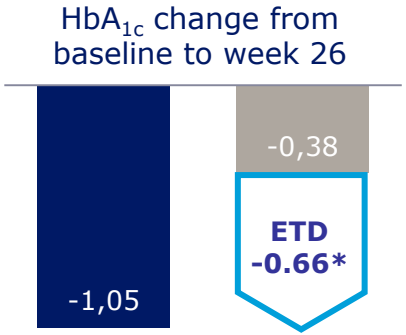
LIRA-RENAL: Baseline characteristics

	Liraglutide 1.8 mg	Placebo
Safety analysis set (N)	140	137
Age (years)	68.0	66.3
Duration of diabetes (years)	15.9	14.2
Female ; male	46% ; 54%	53% ; 47%
Weight (kg)	93.6	95.6
BMI (kg/m^2)	33.4	34.5
FPG (mmol/L)	9.5	9.3
HbA_{1c} (%)	8.1	8.0
eGFR* (mL/min/1.73 m^2)	46.6	46.9
Background anti-diabetic medication (%)		
No insulin	45.0	44.5
Basal insulin ± OAD	20.7	17.6
Premix insulin ± OAD	34.3	38.0

*MDRD; One subject had eGFR >59
Means presented, except for gender and background anti-diabetic medication
BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; MDRD, modification of diet in renal disease; OAD, oral antidiabetic drug
Umpierrez G et al. *Diabetologia* 2014; 57 (Suppl 1): Abstract 182

LIRA-RENAL: Change in HbA_{1c} (%)



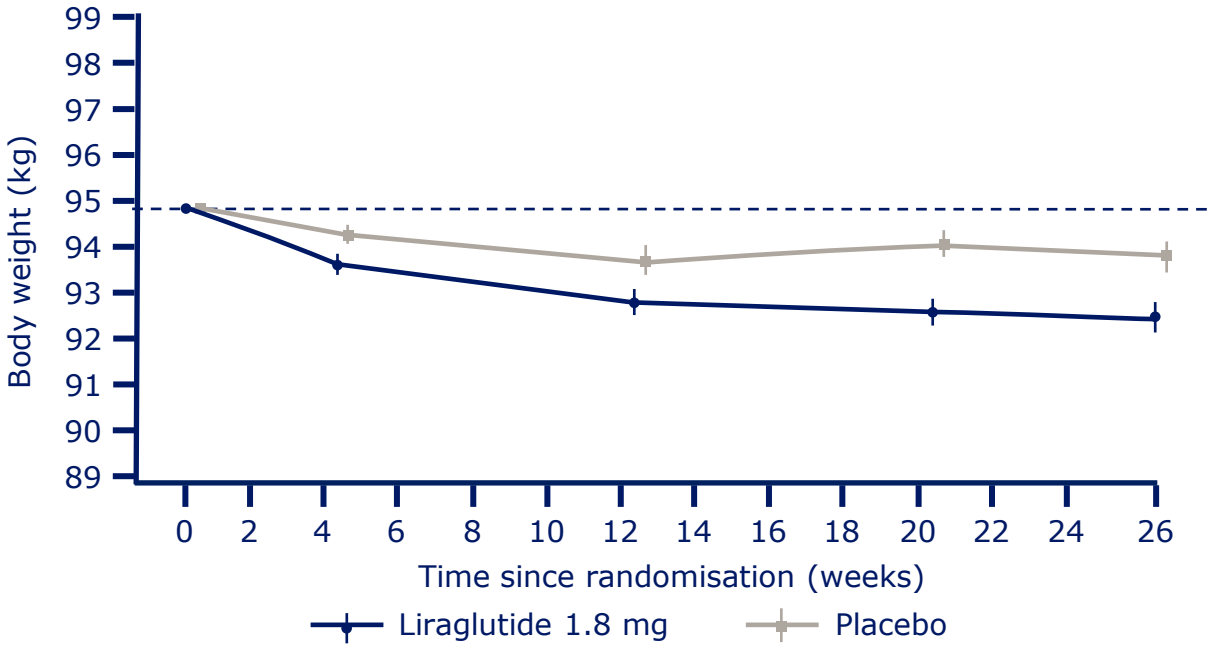


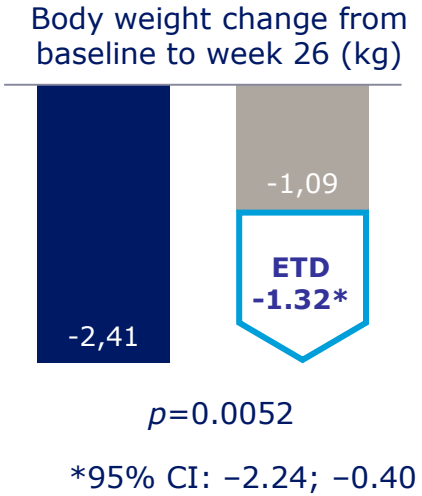
p<0.0001

*95% CI: –0.9; –0.43

Estimated means +/- standard error from mixed model for repeated measurements
CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycosylated haemoglobin
Umpierrez G et al. *Diabetologia* 2014; 57 (Suppl 1): Abstract 182

LIRA-RENAL: Change in body weight (kg)





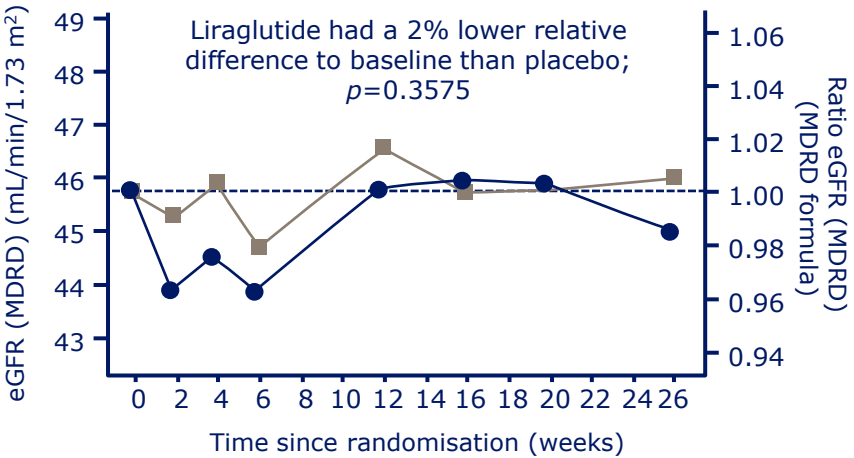
p=0.0052

*95% CI: –2.24; –0.40

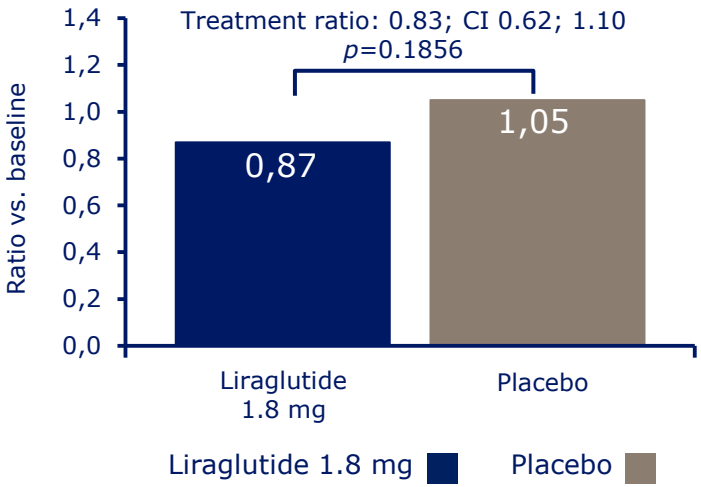
Estimated means +/- standard error from mixed model for repeated measurements
CI, confidence interval; ETD, estimated treatment difference
Umpierrez G et al. *Diabetologia* 2014; 57 (Suppl 1): Abstract 182

LIRA-RENAL: liraglutide did not result in worsening of renal function

Change in eGFR (MDRD)



Urinary albumin:creatinine



Estimated means from mixed model for log-transformed repeated measurements
eGFR, estimated glomerular filtration rate; MDRD, modified diet in renal disease; CI, confidence interval
Umpierrez G et al. Diabetologia 2014; 57 (Suppl 1): Abstract 182

Glycemic control according to glomerular filtration rate in patients with type 2 diabetes and overt nephropathy: A prospective observational study

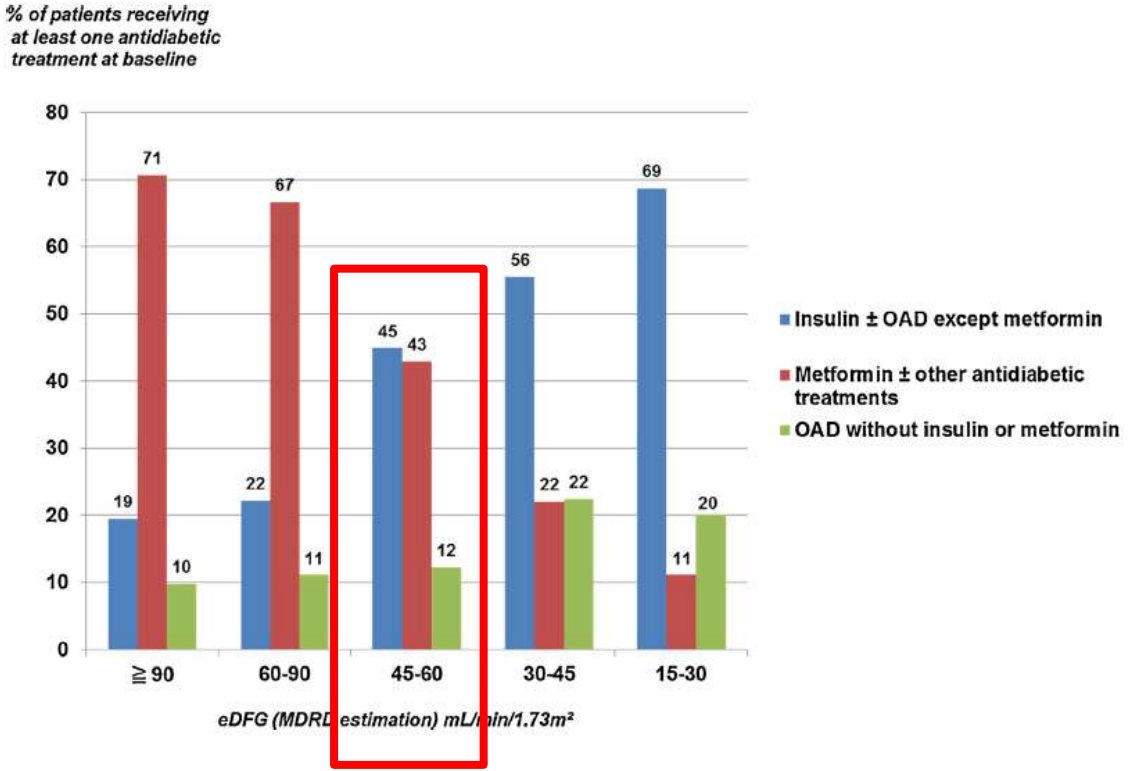


Table 3 – Glycemic control at baseline and after one year follow-up.

HbA1C at baseline (number of patients)	Evolution of the HbA1c strata after one-year follow-up (number of patients)			
	< 7% n=258	7-8% n=218	≥ 8% n=163	Total n=639
< 7%	185 (69.5%)	59 (22.2%)	22 (8.3%)	266
7-8%	50 (23.5%)	111 (52.1%)	52 (24.4%)	213
≥ 8%	23 (14.4%)	48 (30%)	89 (55.6%)	160

% are calculated in row

Glycemic control improvement

Glycemic control worsening

Conclusioni

1) Trattamento precoce con Liraglutide dopo metformina

1) Il BMI non deve essere criterio discriminante per scelta di Liraglutide

1) Liraglutide in add-on a insulina può migliorare il controllo glicemico (e insulina in add-on a Lira)

1) Nel DM2 con IRC moderata Liraglutide rappresenta una opzione terapeutica efficace e sicura

Unmet Medical Needs

(inexpletate) **Necessitates Valetudinis**

Plinio il Giovane 61-112 DC , Epistolarium Libri V, 19,9

FINE