NAPOLI, 17-20 maggio 2017

XXI CONGRESSO NAZIONALE AMD

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

GLP-1 RAs dalla ReaL Life agli scenari futuri

PER UNA DIABETOLOGIA PREDITTIVA, PREVENTIVA, PERSONALIZZATA E PARTECIPATIVA

Giuseppina T. Russo

UNIVERSITA' DEGLI STUDI DI MESSINA
DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE

DICHIARAZIONE
CONFLITTO D'INTERESSE DOCENTI

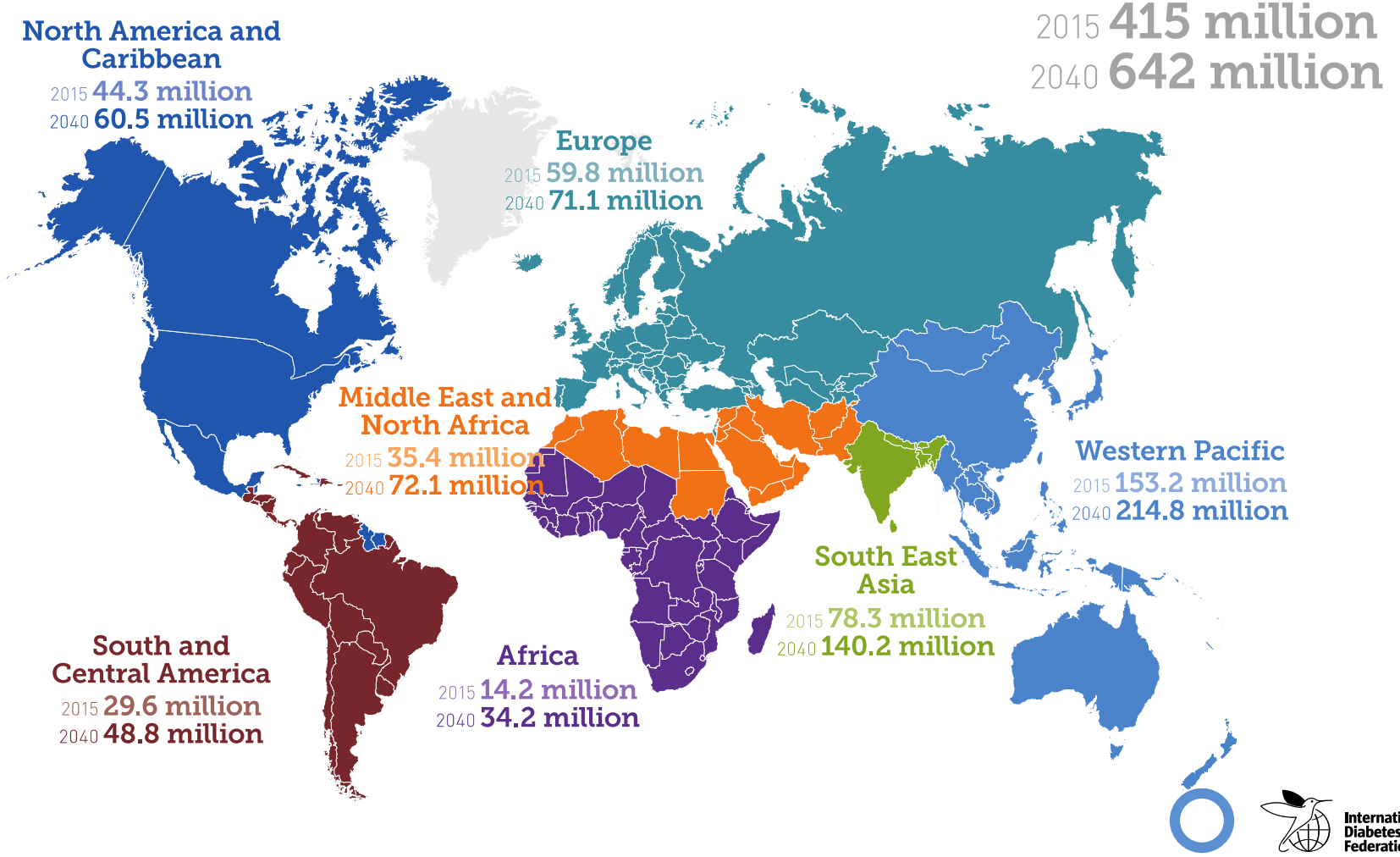
In ottemperanza alla normativa ECM ed al principio trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, il ***docente deve "rilasciare al provider o all'organizzatore la dichiarazione di conflitto d'interessi (ultimi 2 anni rapporti diretti con aziende) e che successivamente debba informare l'aula all'atto della sua presentazione o comunque prima della lezione/relazione dichiarandolo ai discenti"***.

Lecturer , Scientific consultant for:

Boehringer Ingelheim - Eli-Lilly, Novo-Nordisk- Astra Zeneca -MSD

Type 2 Diabetes: A global emergency

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



International Diabetes Federation

Type 2 Diabetes: A global emergency

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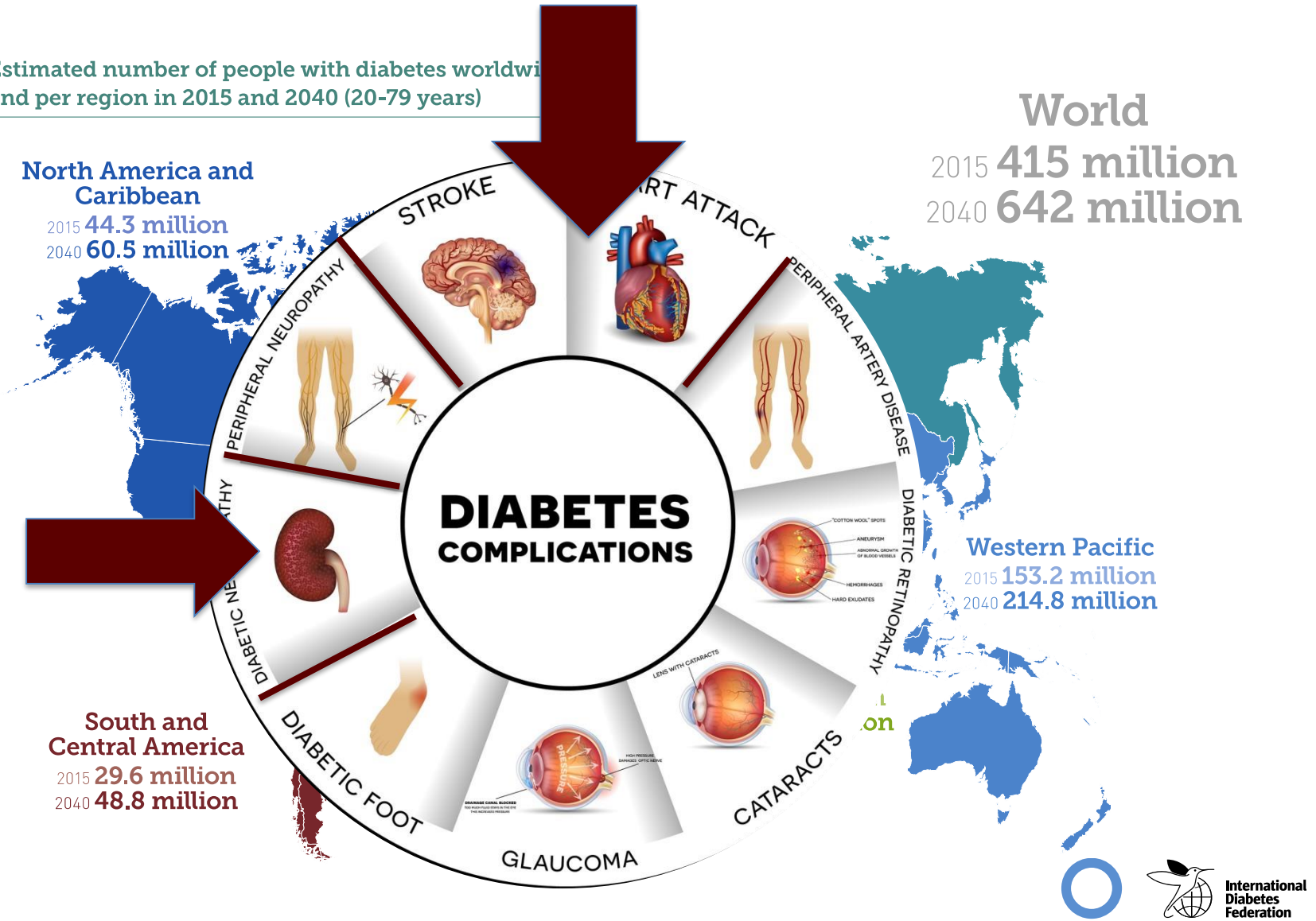
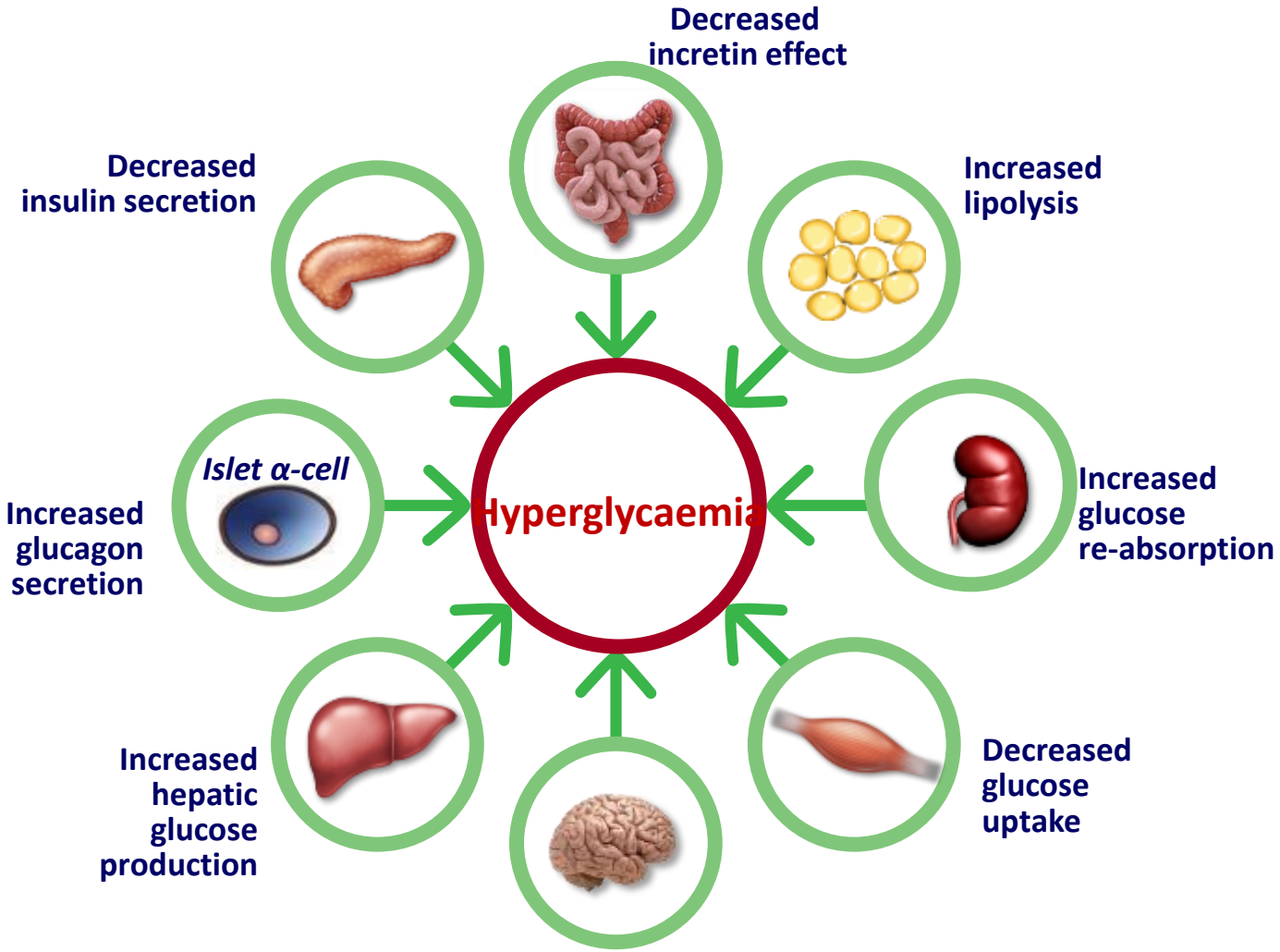


International Diabetes Federation

I meccanismi fisiopatologici "noti" alla base del DM2



T2D, Type 2 Diabetes.
Adapted from: DeFronzo RA. *Diabetes.* 2009;58:773–795; 2.
Adapted from: Tahrani AA, et al. *Lancet*. 2011;378:182–197.

review article

DIABETES, OBESITY AND METABOLISM

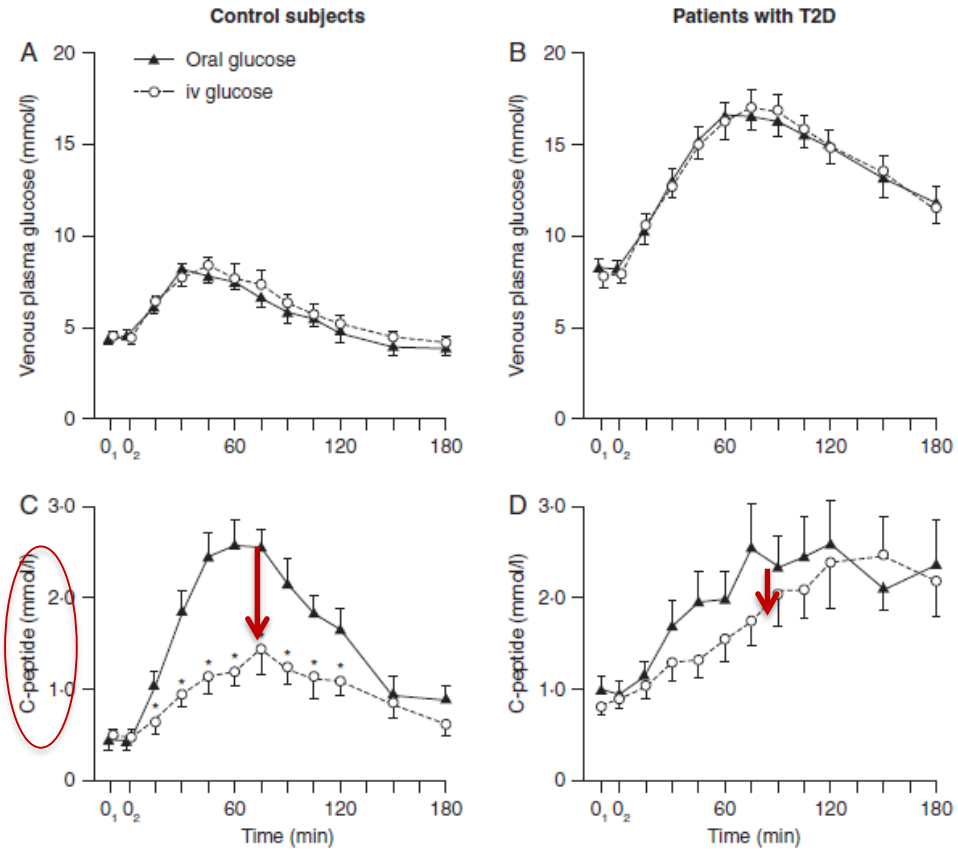
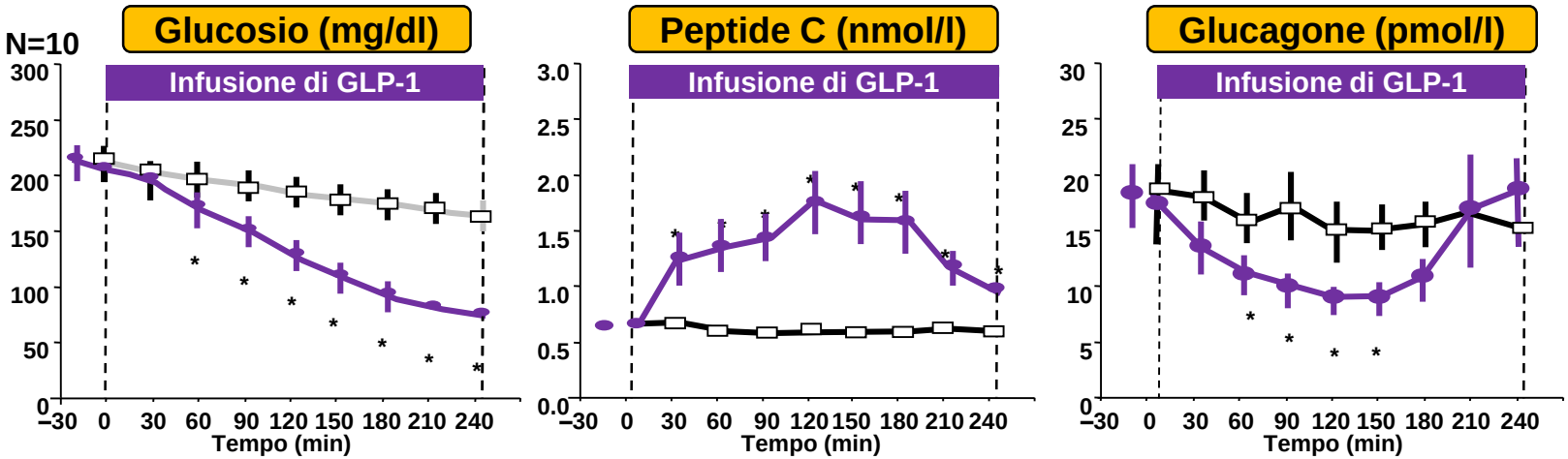


Figure 1. The incretin effect in control subjects and patients with type 2 diabetes (T2D). Venous plasma glucose and integrated incremental β-cell secretory responses to oral glucose loads (black triangles) or 'isoglycaemic' intravenous glucose infusion (open circles). After an overnight fast, oral glucose (50 g glucose/400 ml) was ingested (time 0) and blood samples taken every 15–120 min and then every 30 min for the final two samples. Isoglycaemic intravenous glucose infusions were designed to mimic glucose concentration profiles after glucose ingestion. Asterisks denote significance ($p < 0.05$) to the respective value after oral load. © Springer-Verlag 1986, reproduced with permission from Nauck et al. Diabetologia 1986; **29:** 46–52 [5]. iv, intravenous.

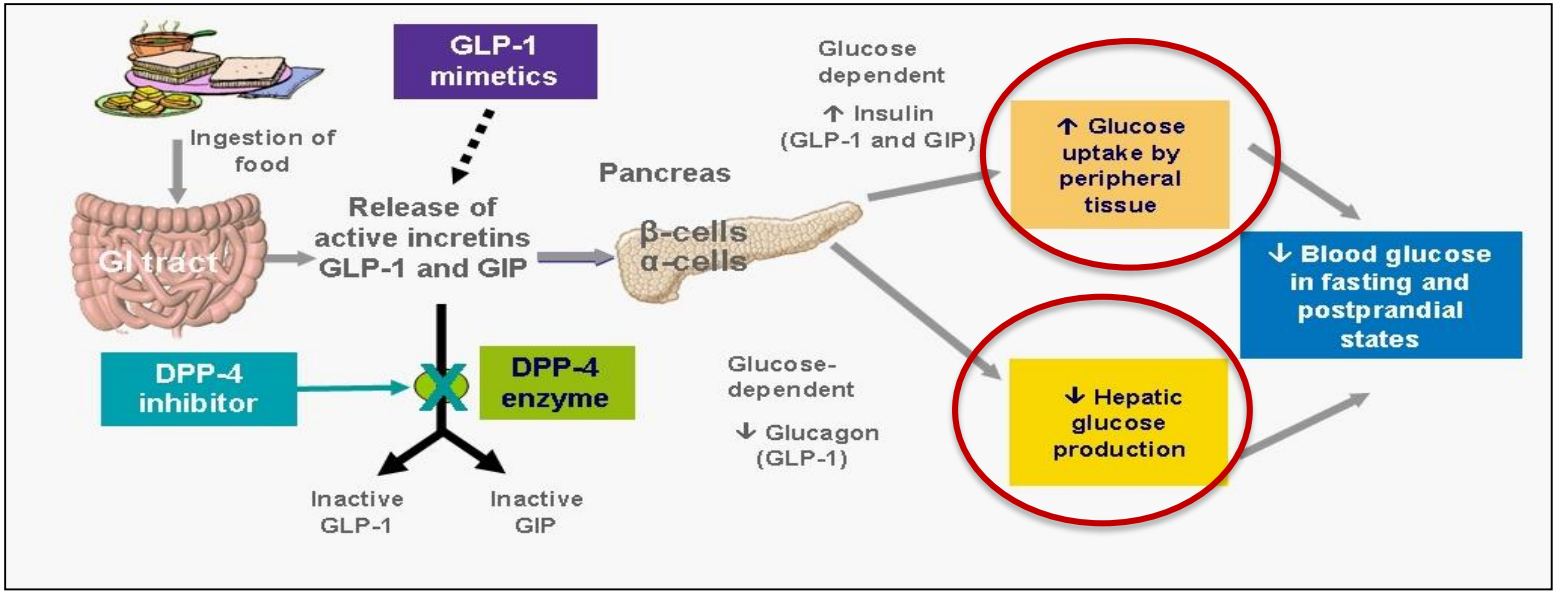
IL GLP-1 RIPRISTINA LE RISPOSTE INSULINICA E GLUCAGONICA IN MANIERA GLUCOSIO-SENSIBILE NEI PAZIENTI CON DM2



*p <0,05

†GLP-1(7-36 amide) infuso a 1,2 pmol/kg/min per 240 minuti.

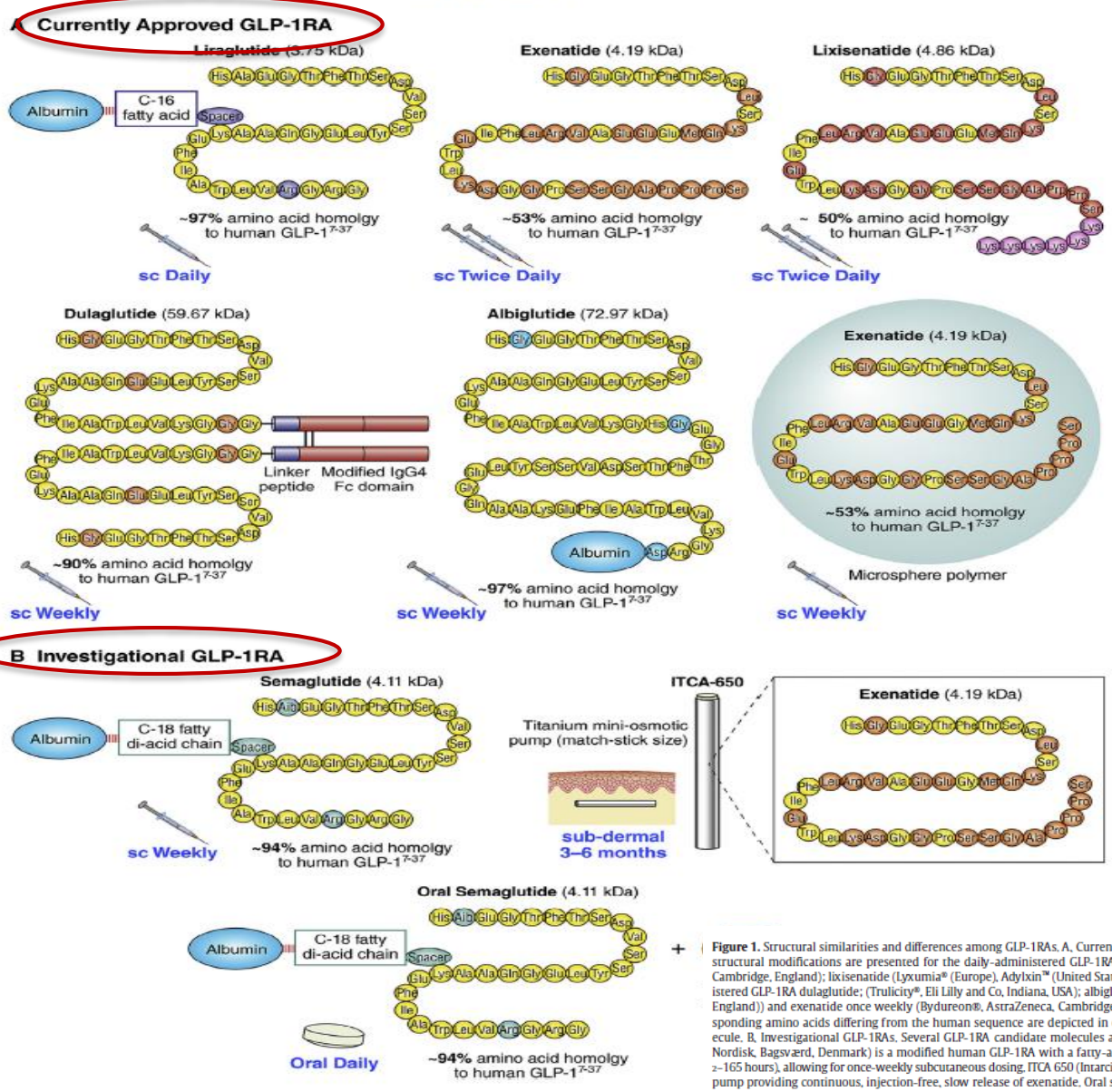
Nauck MA et al. Diabetologia 1993;36:741



Drucker DJ. Cell Metab 2006; 3:153-65

I GLP1-RAs: analogie e differenze

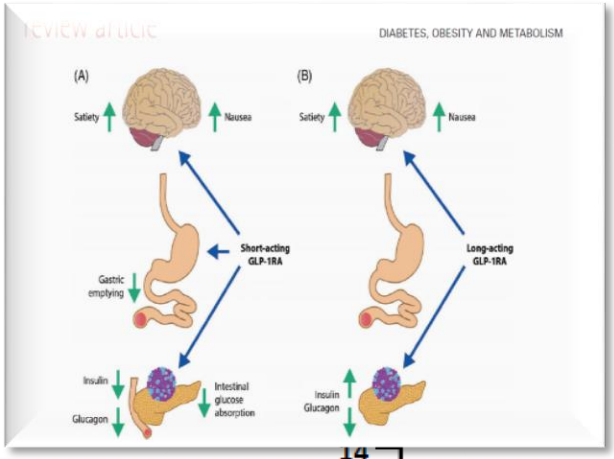
J.A. Lovshin / Can J Diabetes xxx (2017) 1–12



I GLP1 agonisti si differenziano per grado di omologia strutturale con il GLP1 nativo, strategie per prolungarne l'azione farmacologica e durata d'azione

Figure 1. Structural similarities and differences among GLP-1RAs. A, Currently approved GLP-1RAs. The primary amino acid sequences and representations of their tertiary structural modifications are presented for the daily-administered GLP-1RAs: liraglutide (Victoza®, Novo Nordisk, Bagsværd, Denmark); exenatide (Byetta®, AstraZeneca, Cambridge, England); lixisenatide (Lyxumia® (Europe), Adlyxin™ (United States), Sanofi, Gentilly, France) (not currently approved in Canada); and for the once-weekly administered GLP-1RA dulaglutide; (Trulicity®, Eli Lilly and Co, Indiana, USA); albiglutide, (Eperzan® (Canada, European Union), Tanzeum™ (United States), GlaxoSmithKline (London, England)) and exenatide once weekly (Bydureon®, AstraZeneca, Cambridge, England). The primary amino acid sequence of human GLP-1 $^{7-37}$ is depicted in yellow. Corresponding amino acids differing from the human sequence are depicted in other colours. The route of administration and dosing schedule are indicated below each molecule. B, Investigational GLP-1RAs. Several GLP-1RA candidate molecules are in late-stage clinical development for the treatment of type 2 diabetes. Semaglutide (Novo Nordisk, Bagsværd, Denmark) is a modified human GLP-1RA with a fatty-acid modification, enabling high-affinity binding to albumin and an extremely long half-life ($T_{1/2}$–165 hours), allowing for once-weekly subcutaneous dosing. ITCA 650 (Intarcia Therapeutics, Inc., Boston, USA) is a titanium, subdermal implantable (3 to 6 months) miniosmotic pump providing continuous, injection-free, slow release of exenatide. Oral semaglutide (Novo Nordisk, Bagsværd, Denmark) is a coformulation of semaglutide with an oral absorption enhancer (SNAC, Emisphere Technologies) allowing for oral delivery by a once-daily tablet. *GLP-1*, glucagon-like peptide 1; *GLP-1RA*, glucagon-like peptide-1 receptor agonist; sc, subcutaneous; *SNAC*, sodium N-[8-(2-hydroxybenyzol) amino] caprylate.

Studio DURATION 1: 7-point SMBG Profile



Exenatide bid *vs* Exenatide LAR

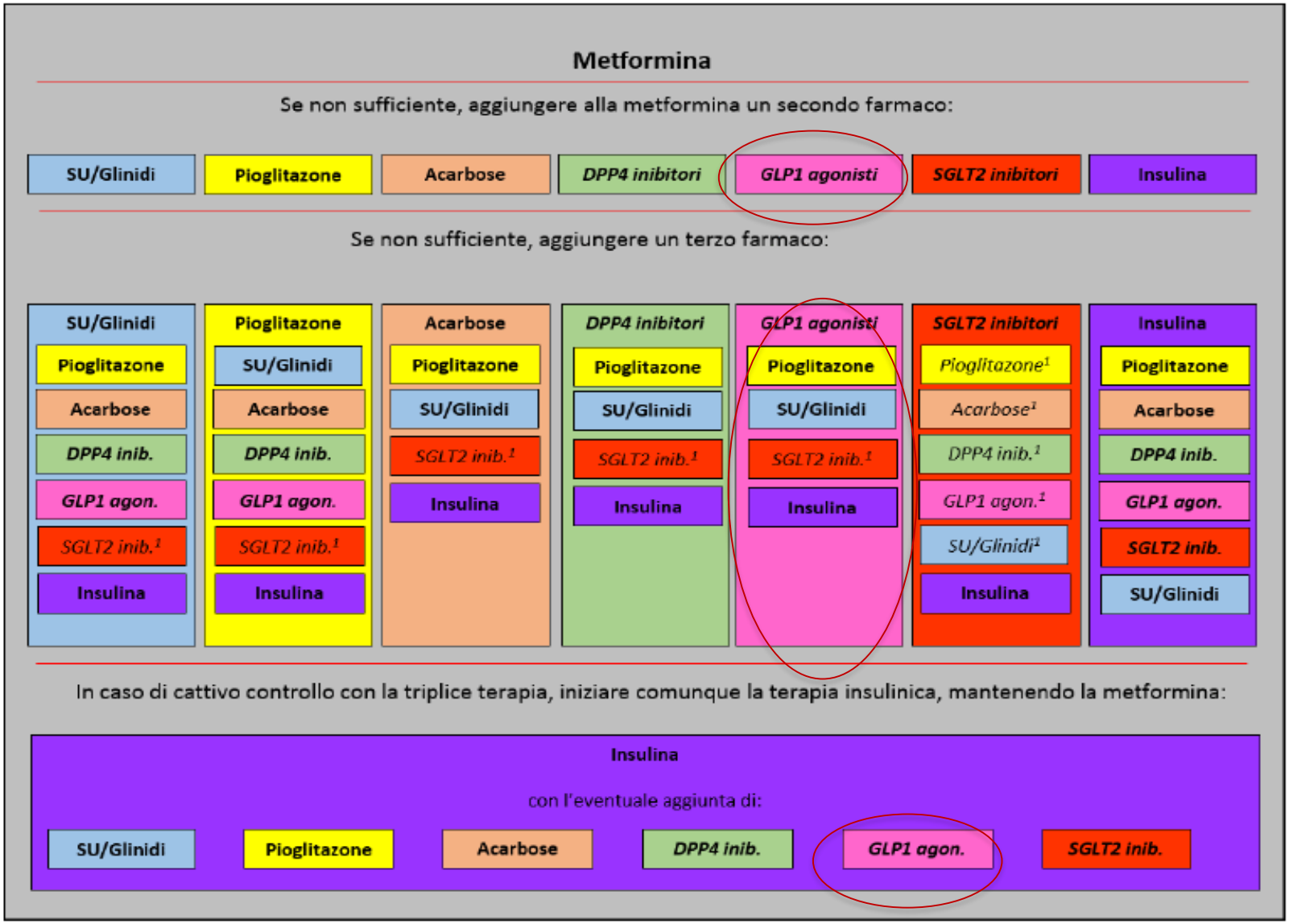
Agonista del recettore del GLP-1 long acting

Agonista del recettore del GLP-1 ad "azione prandiale"

The primary endpoint of the study was a change in HbA1C at 30 weeks.

Adapted from Drucker. *Lancet*. 2008;372:1240-1250.

Figura 2. Schema generale della terapia farmacologica del diabete di tipo 2



Standard Italiani per la cura del diabete 2016

Efficacy of GLP1RAs on glucose control

Efficacy GLP1RAs vs. other classes of hypoglycaemic agents

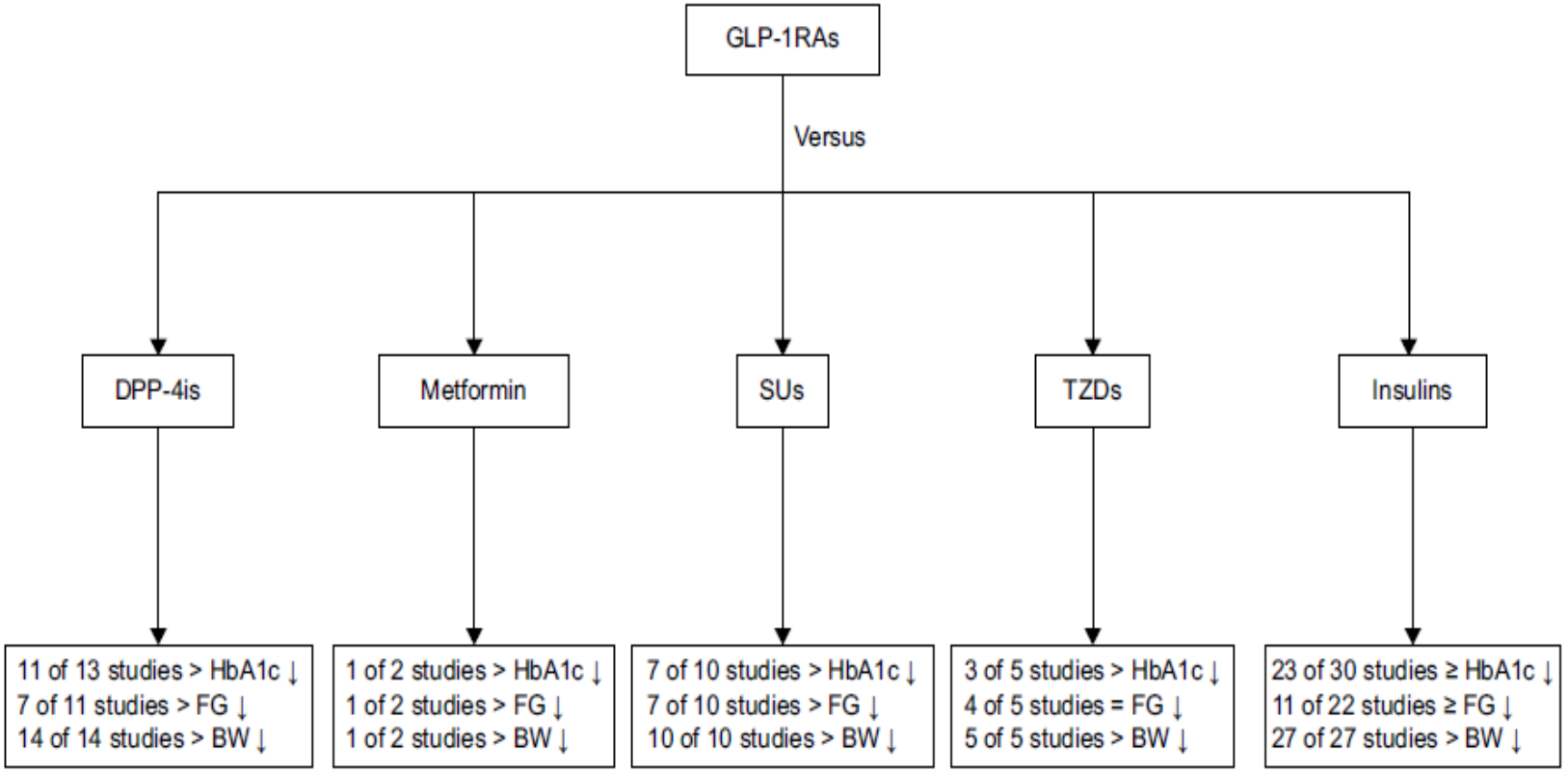
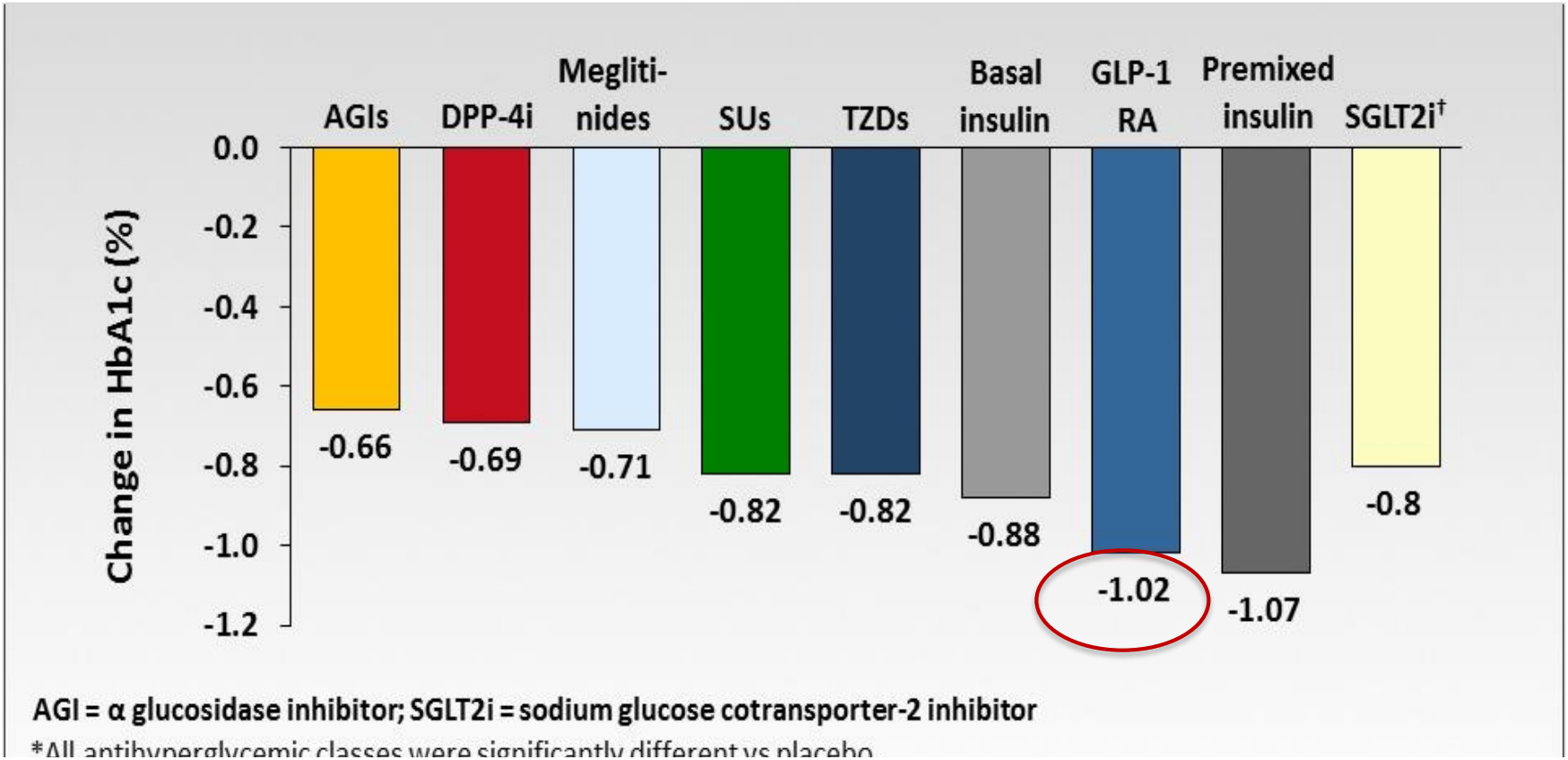


Figure 3 Comparison of efficacy of GLP-1RAs with other glucose-lowering treatments in type 2 diabetes. General trends in glycemic parameters and body weight (BW) in comparative trials of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and other glucose-lowering therapies. The total number of studies includes studies that reported these parameters.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; FG, fasting glucose; HbA1c, glycated hemoglobin; SU, sulfonylurea; TZD, thiazolidinedione.

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: mean change from baseline in A1C



AGI = α glucosidase inhibitor; SGLT2i = sodium glucose cotransporter-2 inhibitor

*All antihyperglycemic classes were significantly different vs placebo

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

DIABETES, OBESITY AND METABOLISM

review article

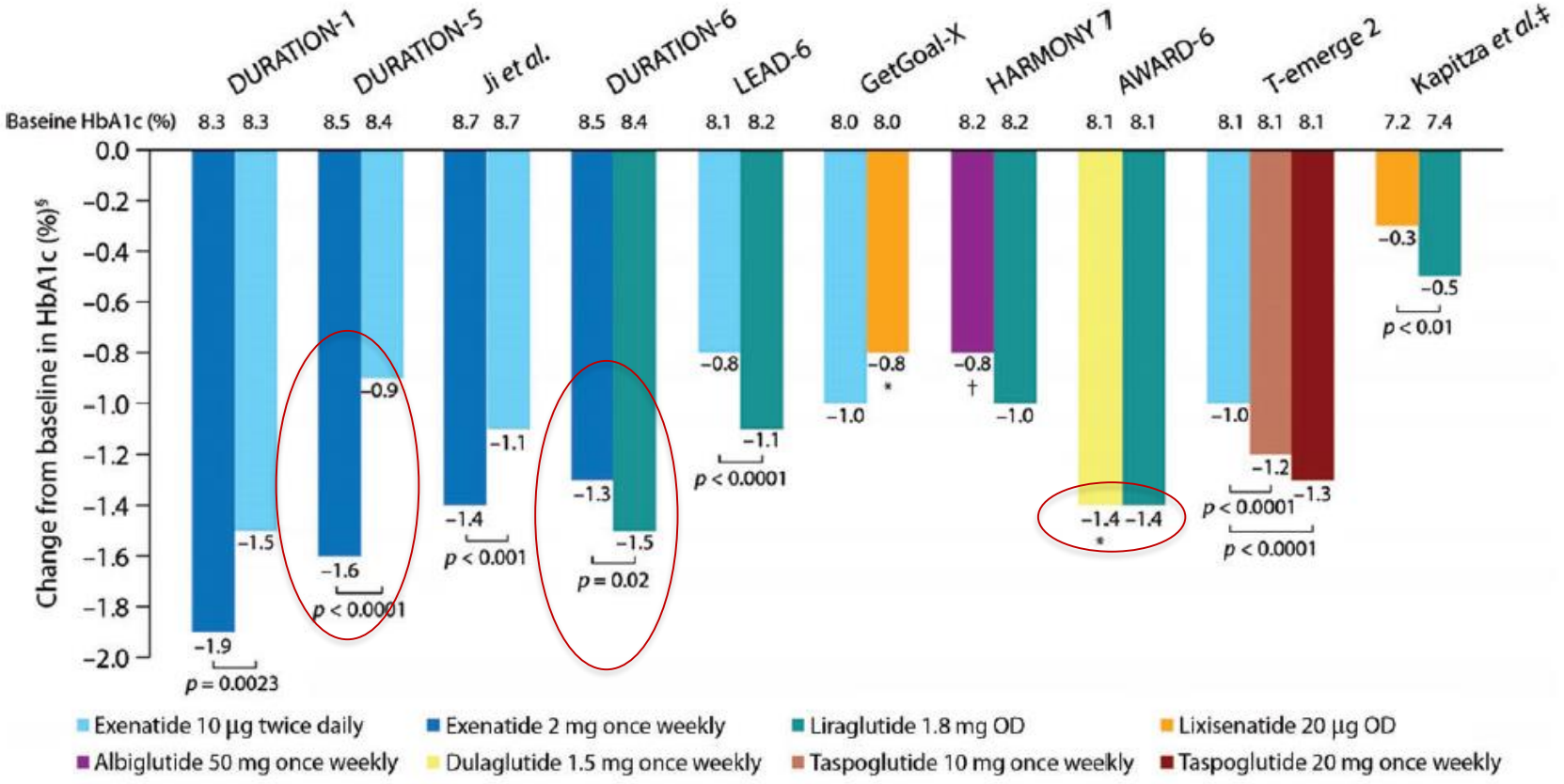
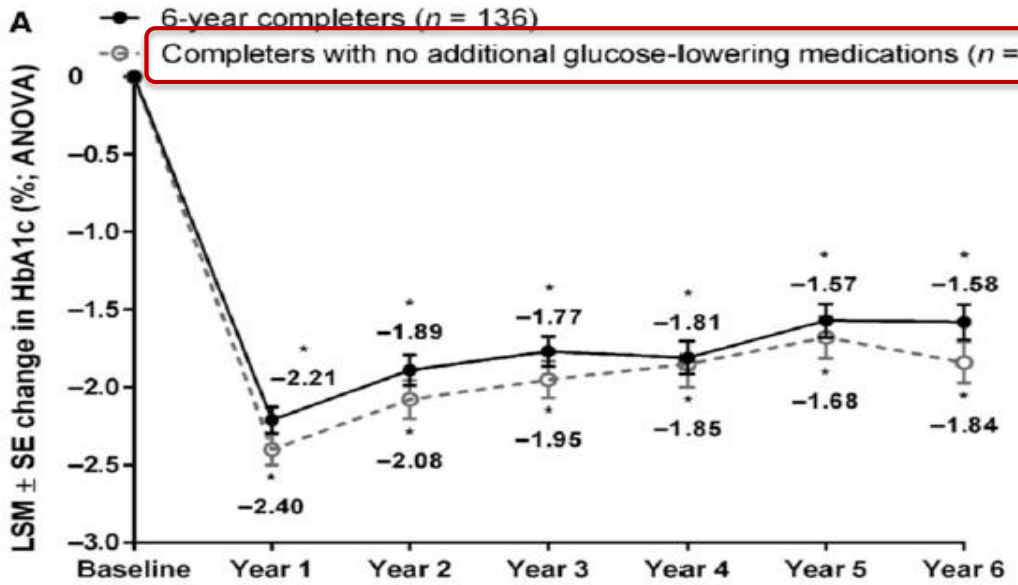


Figure 2. Reductions in glycated haemoglobin (HbA1c) in published phase III (and one phase II) randomized head-to-head studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes. *Non-inferiority criteria met. †Non-inferiority criteria not met. ‡Phase II study. §A 1% change in HbA1c corresponds to a 10.93 mmol/mol change in The International Federation of Clinical Chemistry units.

Efficacy and Tolerability of Exenatide Once Weekly Over 6 Years in Patients with Type 2 Diabetes: An Uncontrolled Open-Label Extension of the DURATION-1 Study

Robert R. Henry, MD,[1] Eric J. Klein, MD,[2] Jenny Han, MS,[3] and Nayyar Iqbal, MD[4]

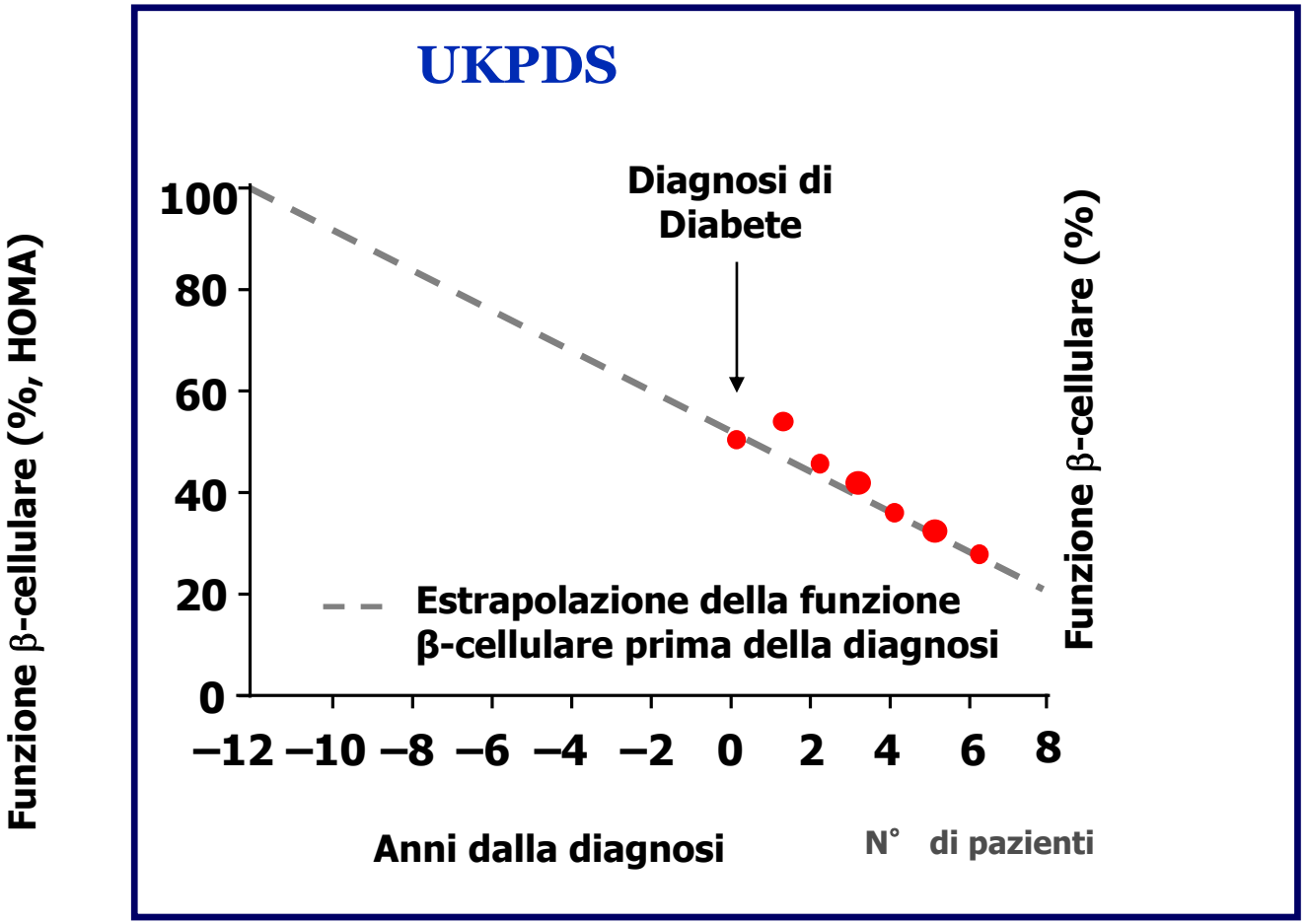


Absolute values (%)							
Completers	8.14	6.49	6.81	6.90	6.81	7.01	7.07
Completers, no medications added	8.16	6.38	6.63	6.71	6.72	6.84	6.86

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 10, 2016

DOI: 10.1089/dia.2016.0107

Il deficit β-cellulare è un evento precoce



UKPDS 16. Diabetes 44:1249–1258 1995

OPEN ACCESS Freely available online

PLOS ONE

Factors Associated with Beta-Cell Dysfunction in Type 2 Diabetes: The BETADECLINE Study

Giuseppina T. Russo[1]*, Carlo Bruno Giorda[2], Stefania Cercone[3], Antonio Nicolucci[4], Domenico Cucinotta[1], on behalf of BetaDecline Study Group¶

1 Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, 2 Metabolism and Diabetes Unit ASL TO5, Chieri, Italy, 3 MSD, Rome, Italy, 4 Department of Clinical Pharmacology and Epidemiology Fondazione Mario Negri Sud, S. Maria Imbaro, Italy

Abstract

Aims: Beta-cell dysfunction is an early event in the natural history of type 2 diabetes. However, its progression is variable and potentially influenced by several clinical factors. We report the baseline data of the BetaDecline study, an Italian prospective multicenter study on clinical predictors of beta-cell dysfunction in type 2 diabetes.

Materials and Methods: Clinical, lifestyle, and laboratory data, including circulating levels of inflammatory markers and non-esterified fatty acids, were collected in 507 type 2 diabetic outpatients on stable treatment with oral hypoglycemic drugs or diet for more than 1 year. Beta-cell dysfunction was evaluated by calculating the proinsulin/insulin ratio (P/I).

Results: At baseline, the subjects in the upper PI/I ratio quartile were more likely to be men and receiving secretagogue drugs; they also showed a borderline longer diabetes duration (P = 0.06) and higher serum levels of glycated hemoglobin (HbA_{1c}), fasting blood glucose, and triglycerides. An inverse trend across all PI/I quartiles was noted for BMI and serum levels of total cholesterol (T-C), LDL-C, HDL-C and C reactive protein (CRP), and with homeostatic model assessment (HOMA-B) and HOMA of insulin resistance (HOMA-IR) values (P<0.05 for all). At multivariate analysis, the risk of having a P/I ratio in the upper quartile was higher in the subjects on secretagogue drugs (odds ratio [OR] 4.2; 95% confidence interval [CI], 2.6–6.9) and in the males (OR 1.8; 95% CI, 1.1–2.9).

Conclusions: In the BetaDecline study population, baseline higher PI/I values, a marker of beta-cell dysfunction, were more frequent in men and in patients on secretagogues drugs. Follow-up of this cohort will allow the identification of clinical predictors of beta-cell failure in type 2 diabetic outpatients.

Citation: Russo GT, Giorda CB, Cercone S, Nicolucci A, Cucinotta D, et al. (2014) Factors Associated with Beta-Cell Dysfunction in Type 2 Diabetes: The BETADECLINE Study. PLoS ONE 9(10): e109702. doi:10.1371/journal.pone.0109702

Editor: Franco Folli, University of Texas Health Science Center at San Antonio, United States of America

Received April 14, 2014; **Accepted** September 11, 2014; **Published** October 27, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: This study was organized by AMD Foundation Rome, and was in part funded by Merck Sharp & Dohme Corp. The funds are used for the costs of laboratory and data monitoring. There is no one outside of the author SC who is employed or has relationships with Merck Sharp & Dohme. SC's contribution is in data analysis and interpretation. No additional funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: One of the authors is employed by a commercial company (MSD, Rome, Italy). This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

* Email: Giuseppina.russo@unime.it

¶ Membership of the BetaDecline Study Group is provided in the Acknowledgments.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide [1]. T2DM is sustained by insulin resistance and impaired insulin secretion. Impaired insulin secretion due to either beta-cell dysfunction and/or beta-cell loss is now recognized in the pathogenesis and progression of diabetes. The loss of beta-cell mass and the progressive decline in beta-cell function is an early feature of the natural history of diabetes and it is detectable prior to diagnosis [2]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that beta-cell function, as evaluated by the homeostatic model assessment (HOMA-B) index, was already decreased by 50% by the time of the diagnosis and that it continued to decline over the 6-year observation period, even with on-going hypoglycemic therapy [3].

The relative increase of α-cells mass, another typical defect on Langerhans islets of diabetic subjects, may even precede beta-cells loss, being already observed in normoglycaemic baboons with different degrees of obesity [4].

Beta-cell mass is influenced by a balance between proliferative and pro-apoptotic signals, which may be modulated by various growth factors, cytokines, and hormones, whose specific role in the rate of beta-cell decline remains unclear.

High levels of glucose and free fatty acids (gluco-and lipotoxicity), islet amyloid polypeptide deposition, and circulating inflammatory cytokines have been all implicated in beta-cell apoptosis [4–15] Thus, *in vitro* studies have demonstrated that

Acta Diabetol
DOI 10.1007/s00592-016-0868-7

ORIGINAL ARTICLE

Incidence and correlated factors of beta cell failure in a 4-year follow-up of patients with type 2 diabetes: a longitudinal analysis of the BETADECLINE study

Carlo B. Giorda[1] · Giuseppina T. Russo[2] · Stefania Cercone[3] · Salvatore De Cosmo[4] · Antonio Nicolucci[5] · Domenico Cucinotta[2]

Received: 15 October 2015 / Accepted: 25 April 2016

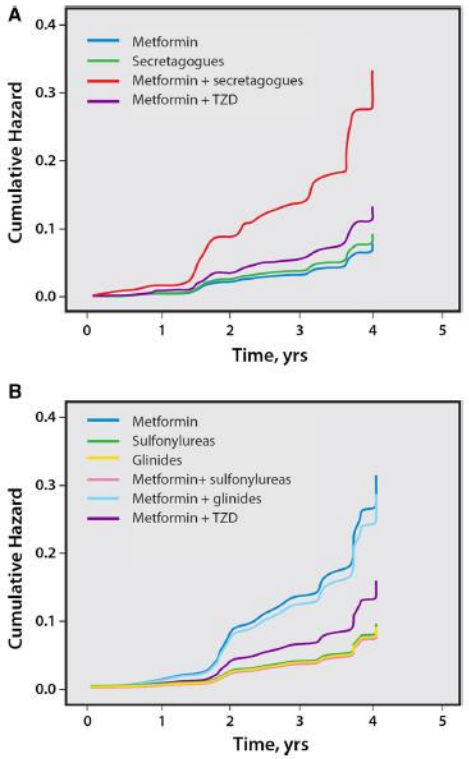
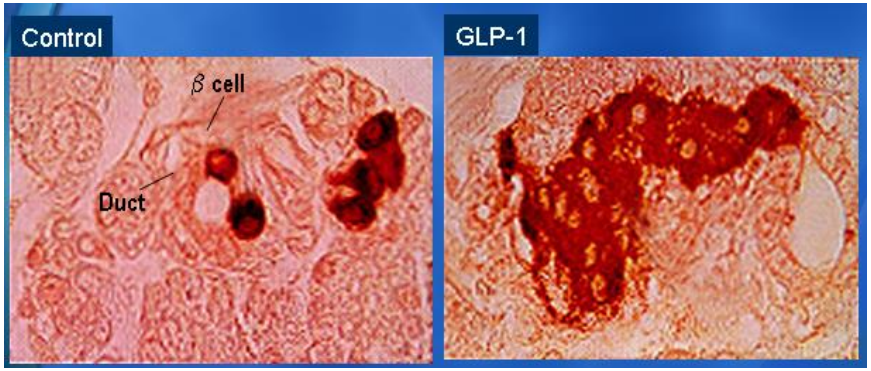


Fig. 1 Cumulative risk of insulin initiation according to diabetes therapeutic scheme at baseline (**a**), and considering individual type of secretagogues (sulfonylurea vs. glinides) (**b**). *Curves* adjusted for variables significantly associated with the initiation of insulin therapy at the multivariate Cox model (including HbA1c, IL-6, HOMA-B)

GLP-1 stimola la rigenerazione β-cellulare e aumenta la massa cellulare nei modelli animali

GLP-1 increases b-cell mass in a genetic rat model of diabetes



Increased pancreatic insulin stores and beta cell mass vs. control

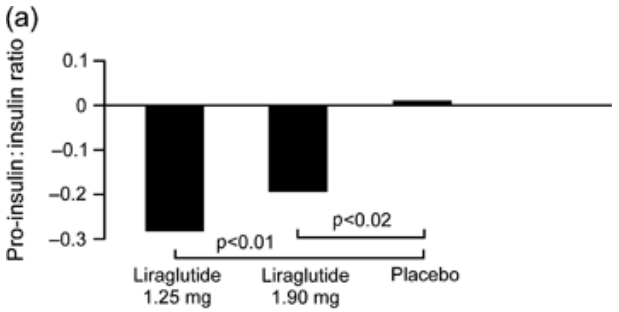
GLP-1 treatment led to a doubling of beta cell mass in 5 days.

- ↑ Proliferazione β-cellulare
- ↑ Ipertrofia β-cellulare
- ↓ Apoptosi β-cellulare
- ↑ Neogenesi β-cellulare
- ↑ Differenziazione β-cellulare

Bulotta et al. J Mol Endocrinol 2002;29:347–360
Farilla et al. Endocrinology 2003;144:5149–5158
Tourrel C. et al. *Diabetes*. 2002; 51:1443–1452

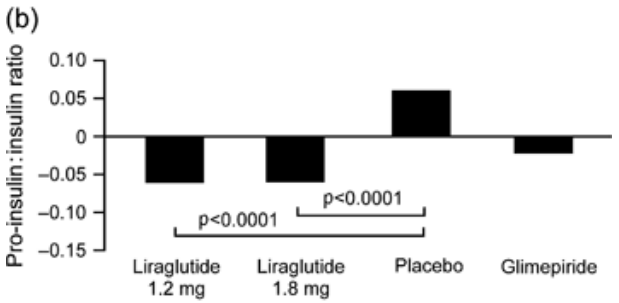
LEAD-3:
riduzione PI/I

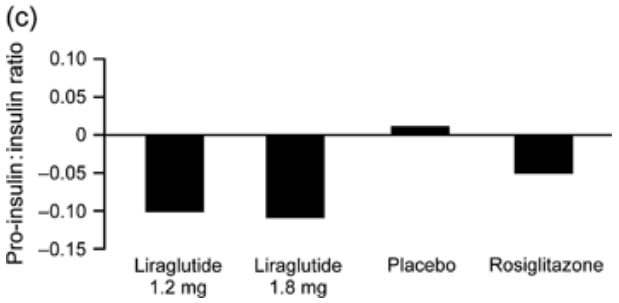
LIRA *vs.* glimepiride



LEAD-1,2,5:
riduzione PI/I

LIRA + SU and / or MET
***vs.* Glimepiride or TZD**

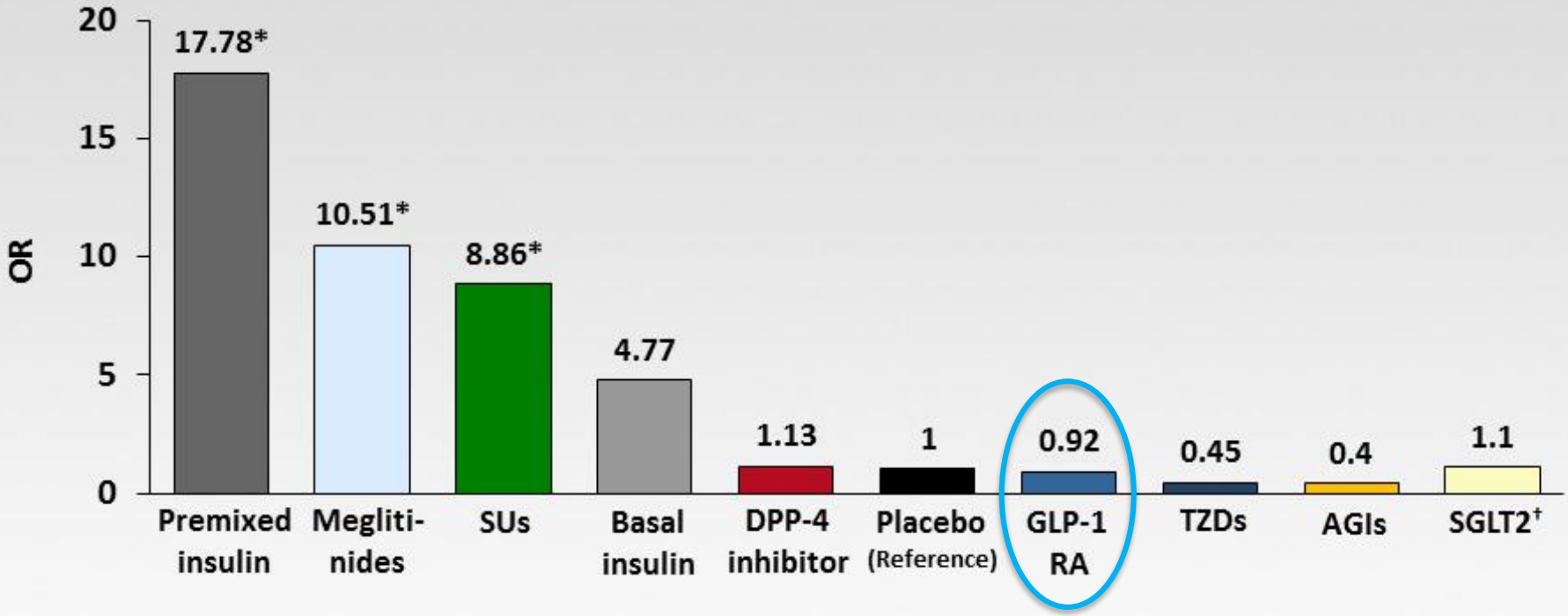




Visboll T., Diabetes, Obesity and Metabolism 2009

Hypoglycaemic risk with currently available drugs

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: At least one event of overall hypoglycaemia (odds ratio)



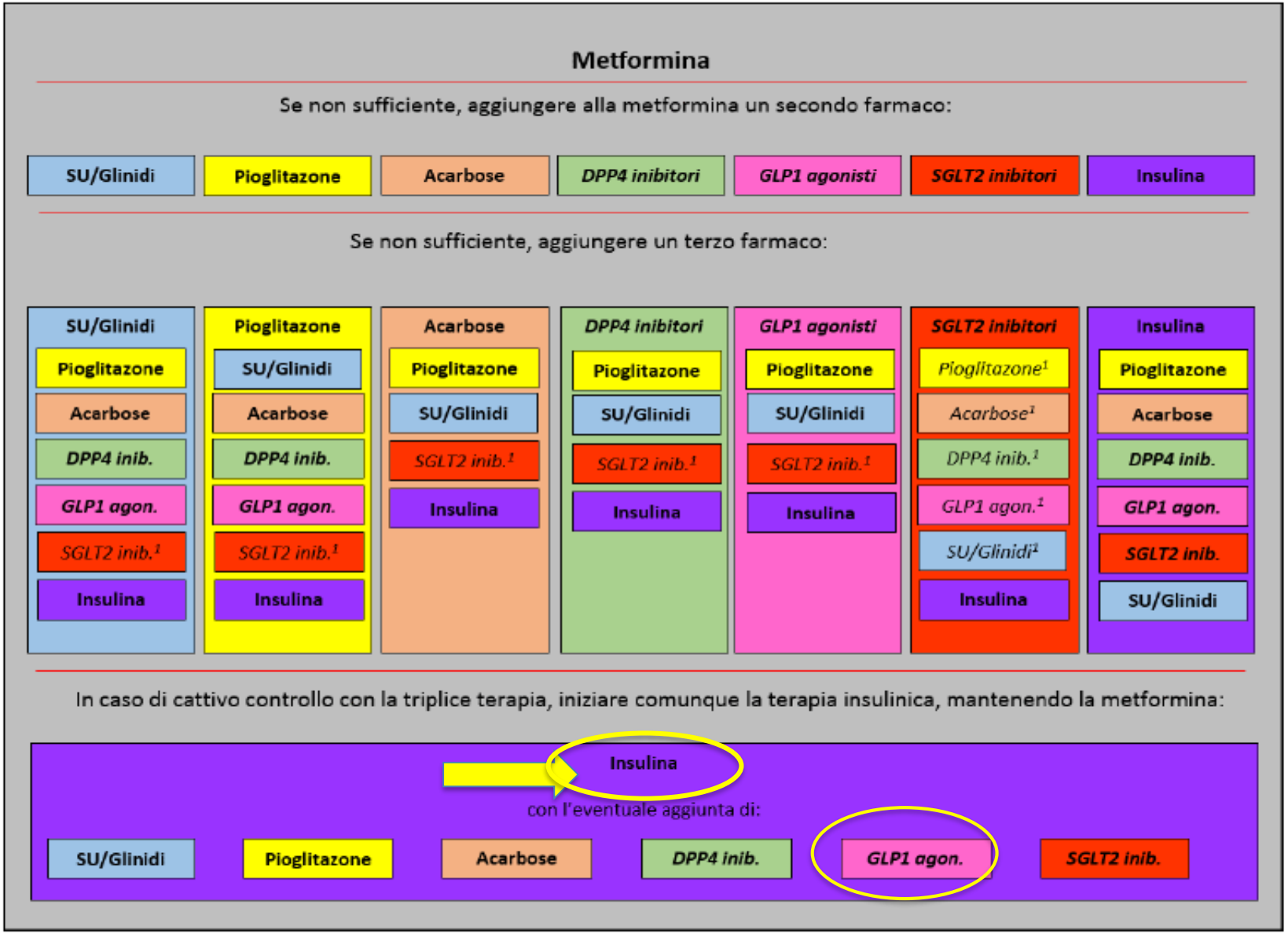
*Statistically significant vs placebo.

†An estimate of hypoglycemia risk; SGLT2 inhibitors were not included in the network meta-analysis.[b]

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012

[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

Figura 2. Schema generale della terapia farmacologica del diabete di tipo 2



Standard Italiani per la cura del diabete 2016

Efficacy of GLP1RA vs Basal insulin

Diabetes Care Volume 38, December 2015 2241

SPECIAL ARTICLE COLLECTION: INSULIN

Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2)

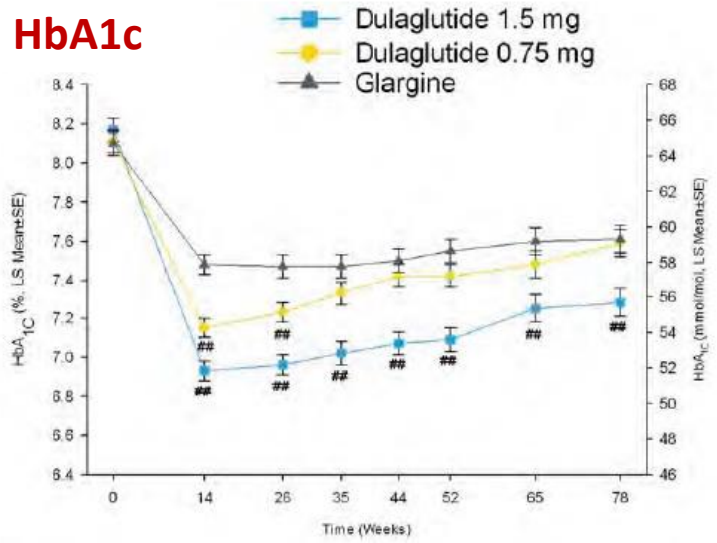
Francesco Giorgino,[1] Marian Benroubi,[2] Jui-Hung Sun,[3] Alan G. Zimmermann,[4] and Valeria Pechtner[5]

Diabetes Care 2015;38:2241–2249 | DOI: 10.2337/dc14-1625

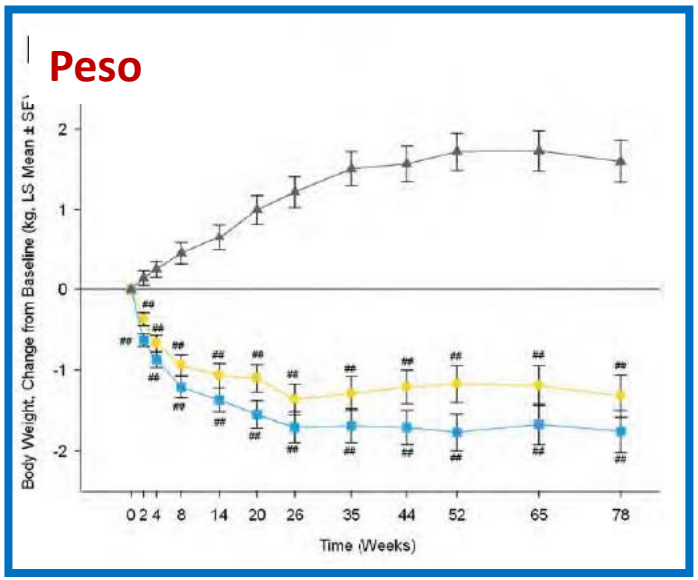
RESEARCH DESIGN AND METHODS

In this 78-week, open-label study, 810 patients were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg, or glargine.

HbA1c

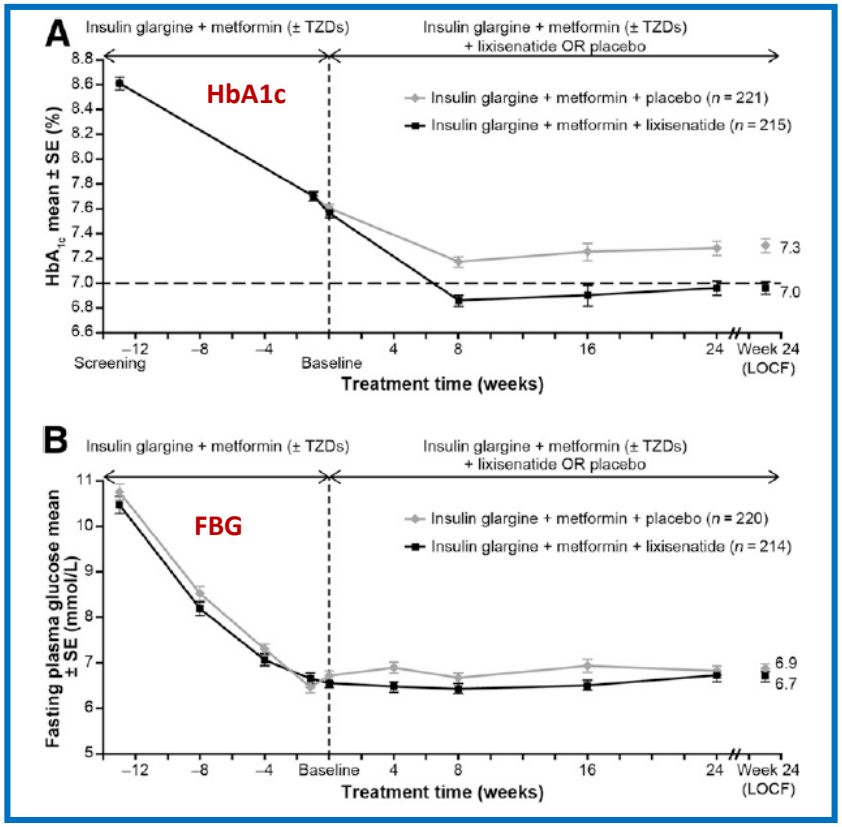


Peso

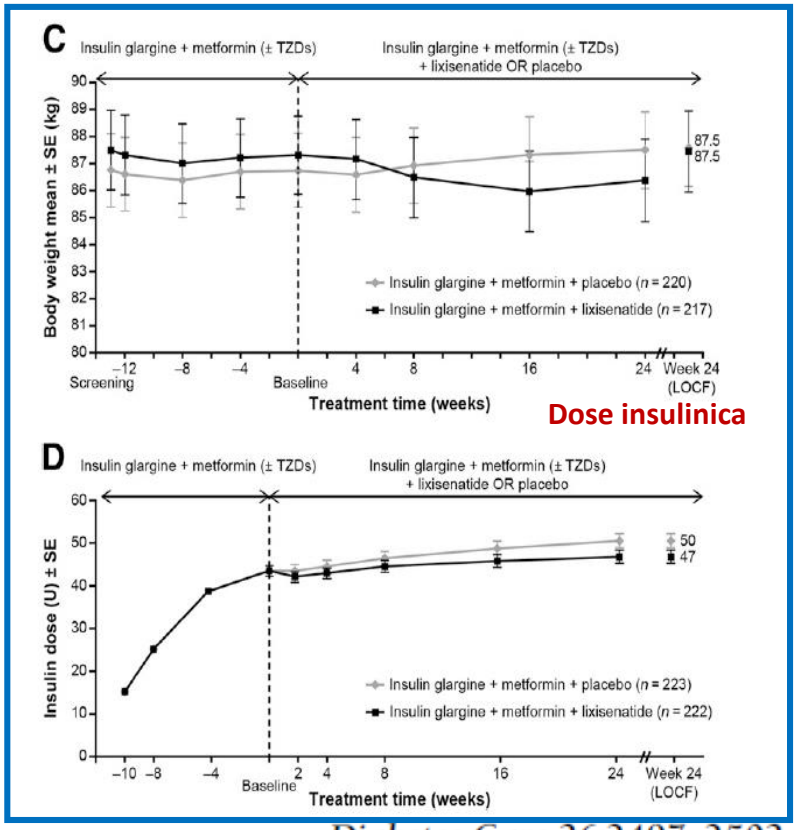


Adding Once-Daily Lixisenatide for Type 2 Diabetes Inadequately Controlled With Newly Initiated and Continuously Titrated Basal Insulin Glargine

A 24-week, randomized, placebo-controlled study (GetGoal-Duo 1)



Peso



Diabetes Care 36:2497–2503, 2013

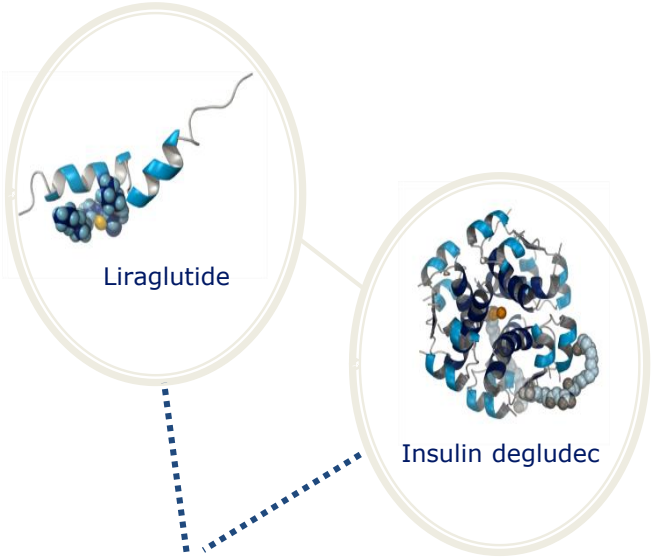
Rational drug design
Formulation feasible due to distinct, stable association forms

Unique anticipated properties of the liraglutide and insulin degludec combination

1 mL di soluzione contiene 100 unità di insulina degludec* e 3,6 mg di liraglutide*.

Una penna preriempita contiene 3 mL equivalenti a 300 unità di insulina degludec e 10,8 mg di liraglutide.

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



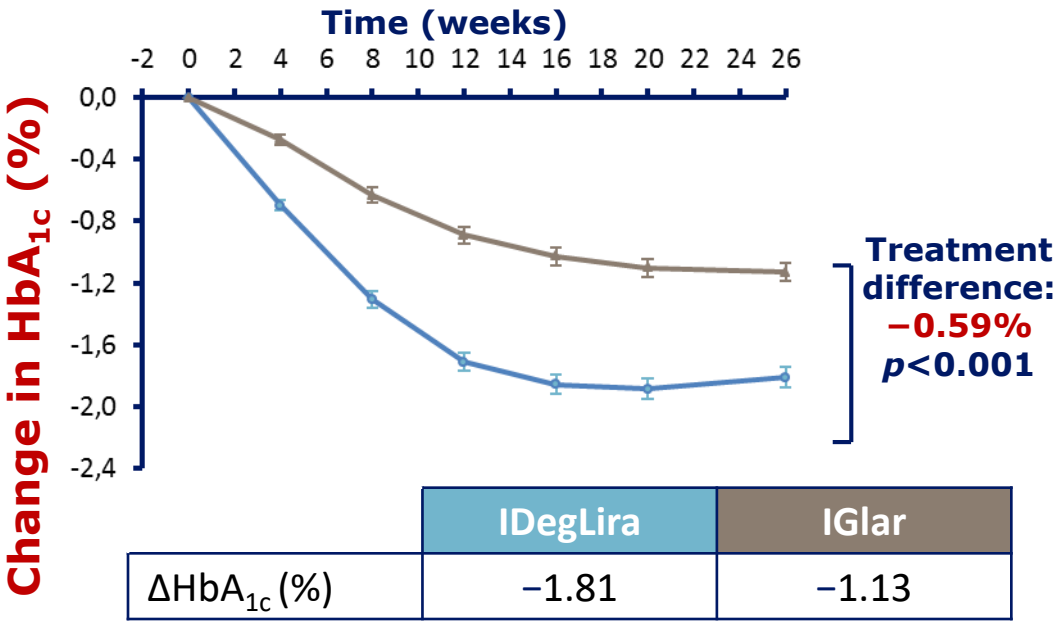
IDegLira

50 dose steps

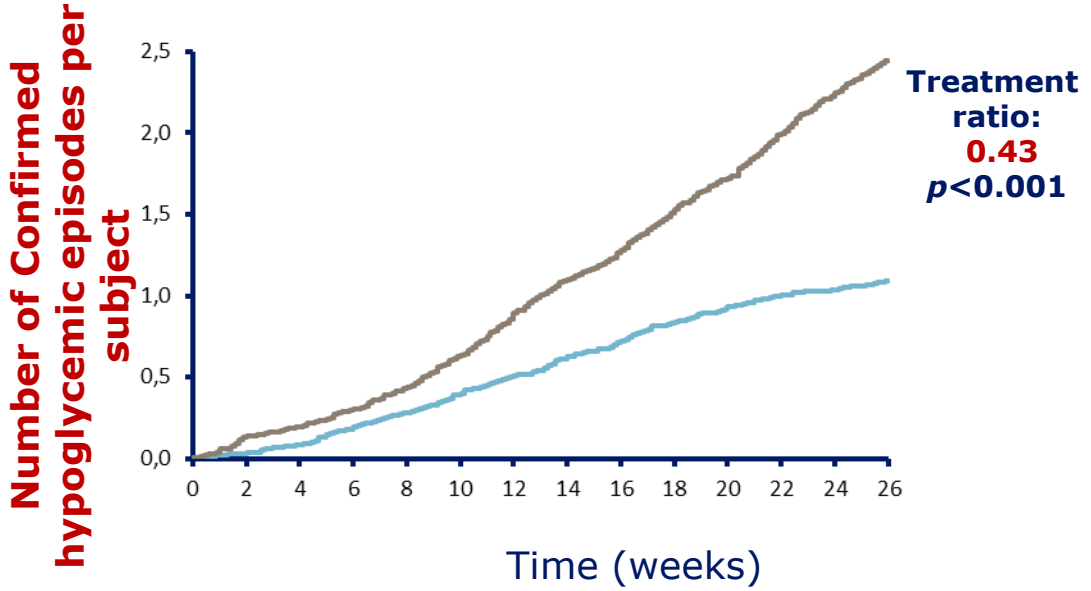
50 U insulin degludec + 1.8 mg liraglutide

DUAL V: IdegLIRA vs Glargine

Change in HbA1c and Hypoglcemic episodes over time

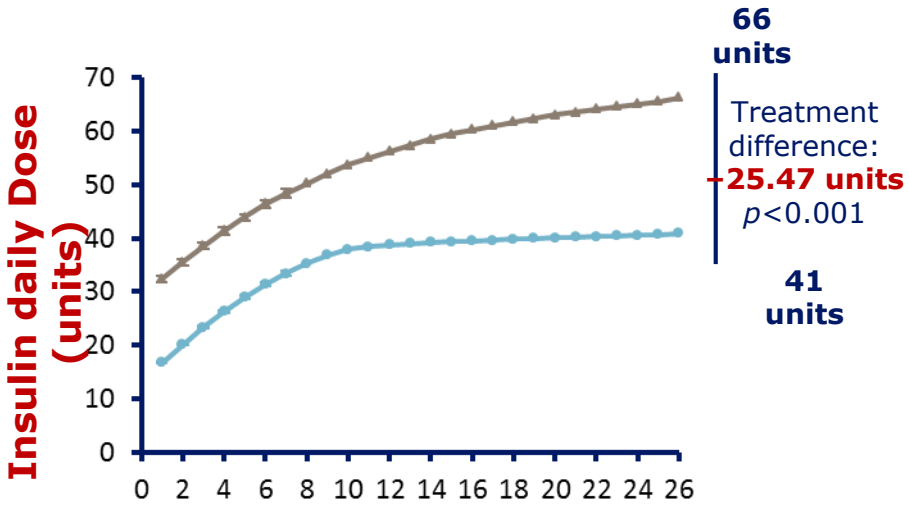


	IDegLira	IGlar
ΔHbA_{1c} (%)	−1.81	−1.13

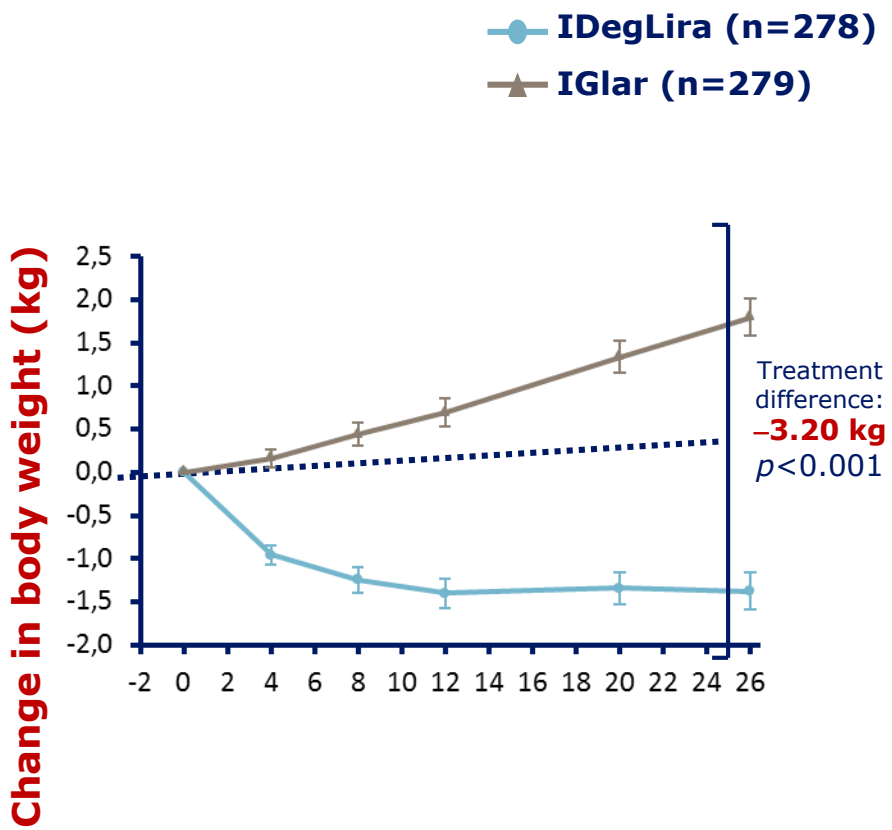


Mean observed values with error bars (standard error mean)
based on full analysis set and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis
while Δ values are observed LOCF

DUAL V: IdegLIRA vs Glargine
Change in insulin dose and body weight over time



41% of subjects on IDegLira were at maximum dose of 50 dose steps, of which 68% achieved HbA_{1c} <7%*

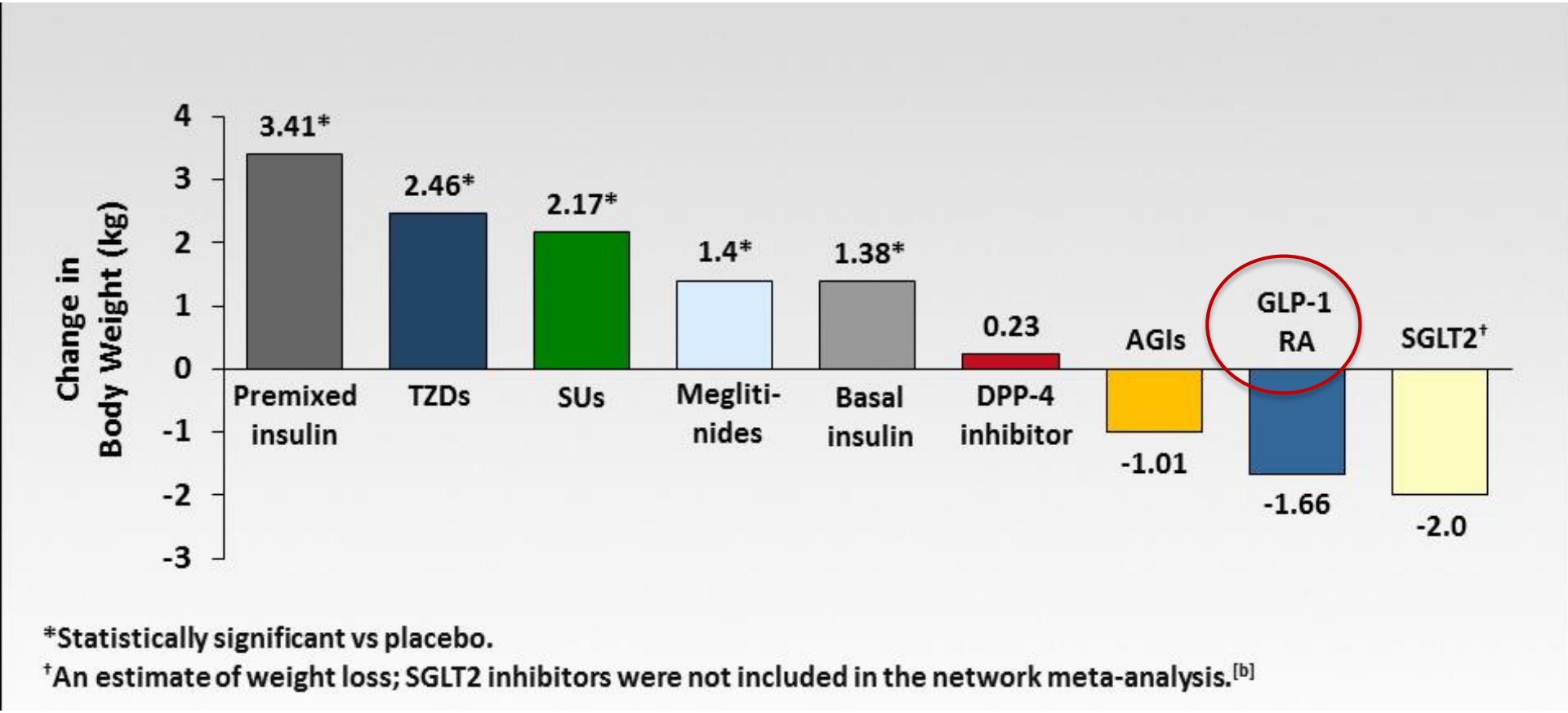


	IDegLira	IGlar
ΔBody weight (kg)	–1.4	1.8

Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis while Δ values are observed LOCF

GLP1RAs effects on CVD Risk Factors

Network meta-analysis of pairwise comparisons of randomized controlled trials evaluating the use of anti-hyperglycemic agents in addition to metformin vs. placebo: Mean change from baseline in body weight



*Statistically significant vs placebo.

†An estimate of weight loss; SGLT2 inhibitors were not included in the network meta-analysis.[b]

Liu S-C et al. Diabetes Obes and Metab 14: 810–820, 2012
[b] Fujita Y et al. J Diabetes Investing 5: 265-275, 2014

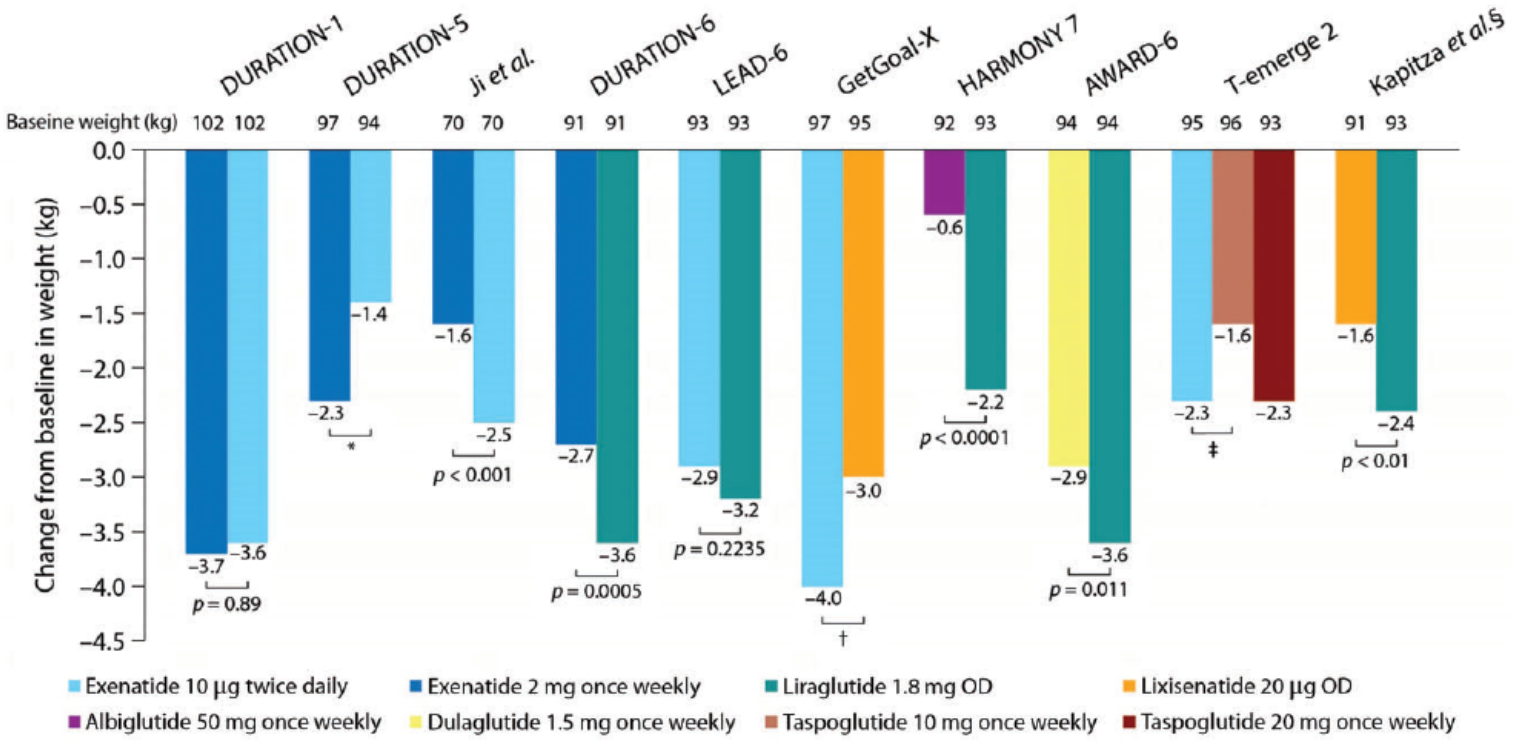


Figure 4. Reductions in weight in published phase III (and one phase II) randomized head-to-head studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes. *Difference was not significant at week 24, although it was significant at week 20. †Not stated if difference was significant. ‡Data shown at week 24; however, at week 52, weight loss was significantly lower in the taspoglutide 10 mg versus exenatide group (p = 0.01). §Phase II study.

The Journal of Clinical Investigation COMMENTARY

Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight

Laurie L. Baggio and Daniel J. Drucker

Department of Medicine, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.

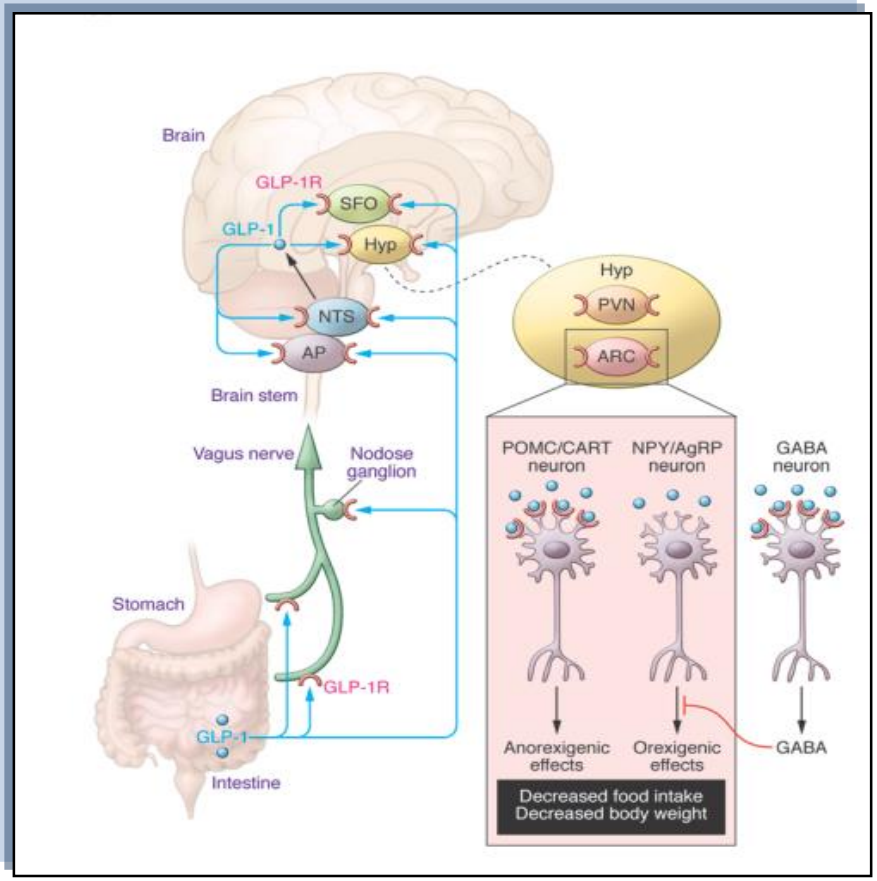
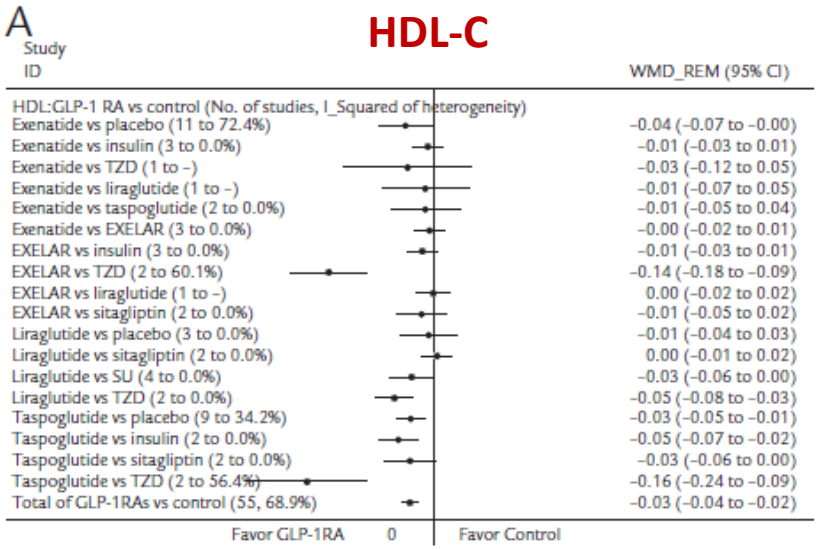
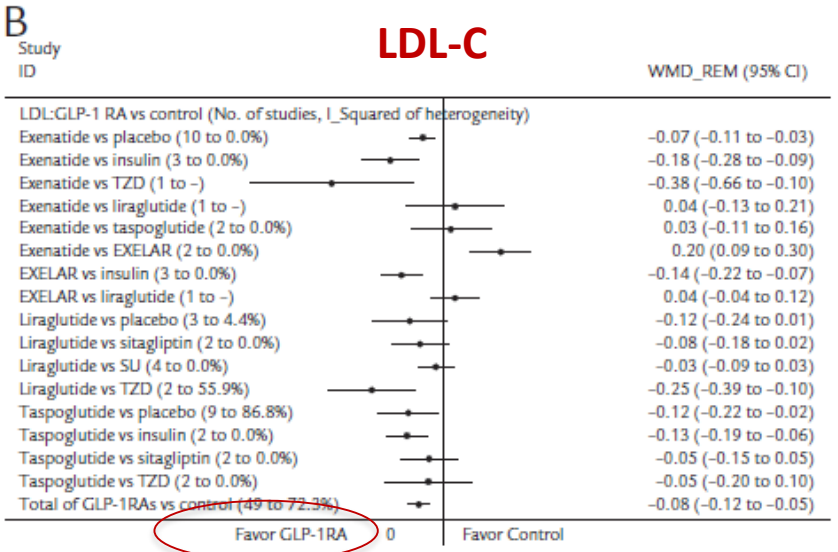
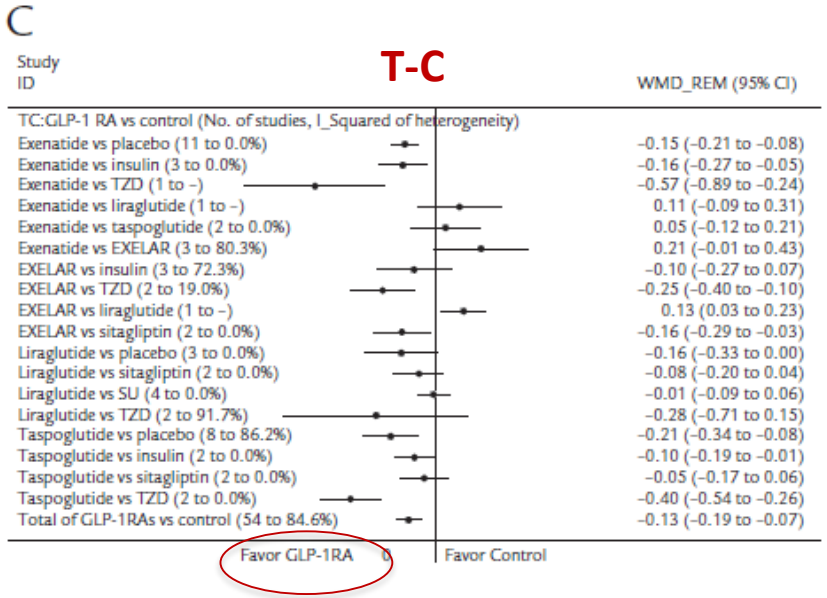


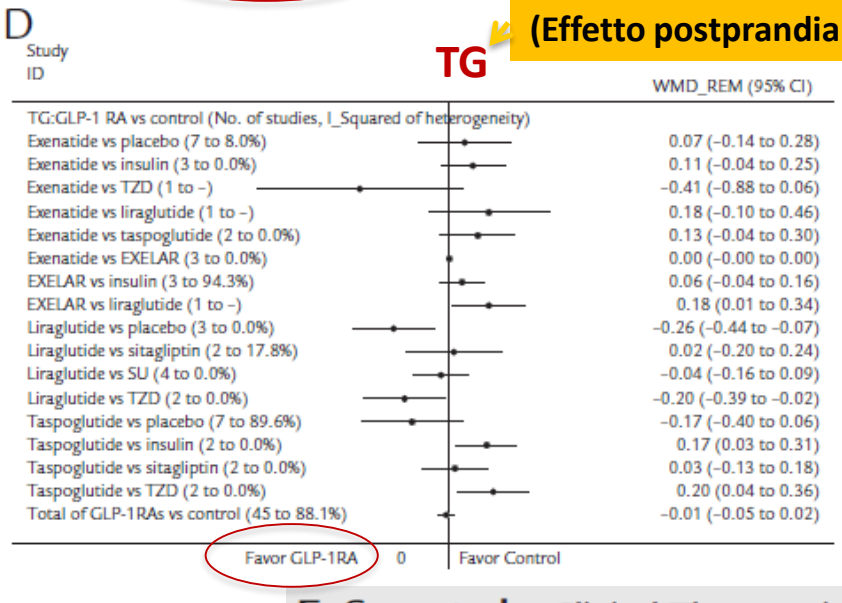
Figure 1. Peripherally administered GLP-1R agonists reduce food intake and body weight through signaling mechanisms requiring functional GLP-1Rs in the ARC of the hypothalamus. Several regions of the brain express GLP-1Rs, including the ARC, PVN, and subfornical organ (SFO), and signals from GLP-1 are transmitted through the vagus nerve or converge on the NTS and area postrema (AP). GLP-1 directly activates POMC/CART neurons and indirectly inhibits, via GABAergic transmission, the neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, which collectively results in signals that reduce food intake. Although GLP-1 generates signals that are transmitted through the vagus nerve or converge on the NTS or PVN of the hypothalamus (Hyp), these regions are not required to transduce an anorectic GLP-1R–dependent signal.

Effects of individual GLP1RAs on Lipid Profile





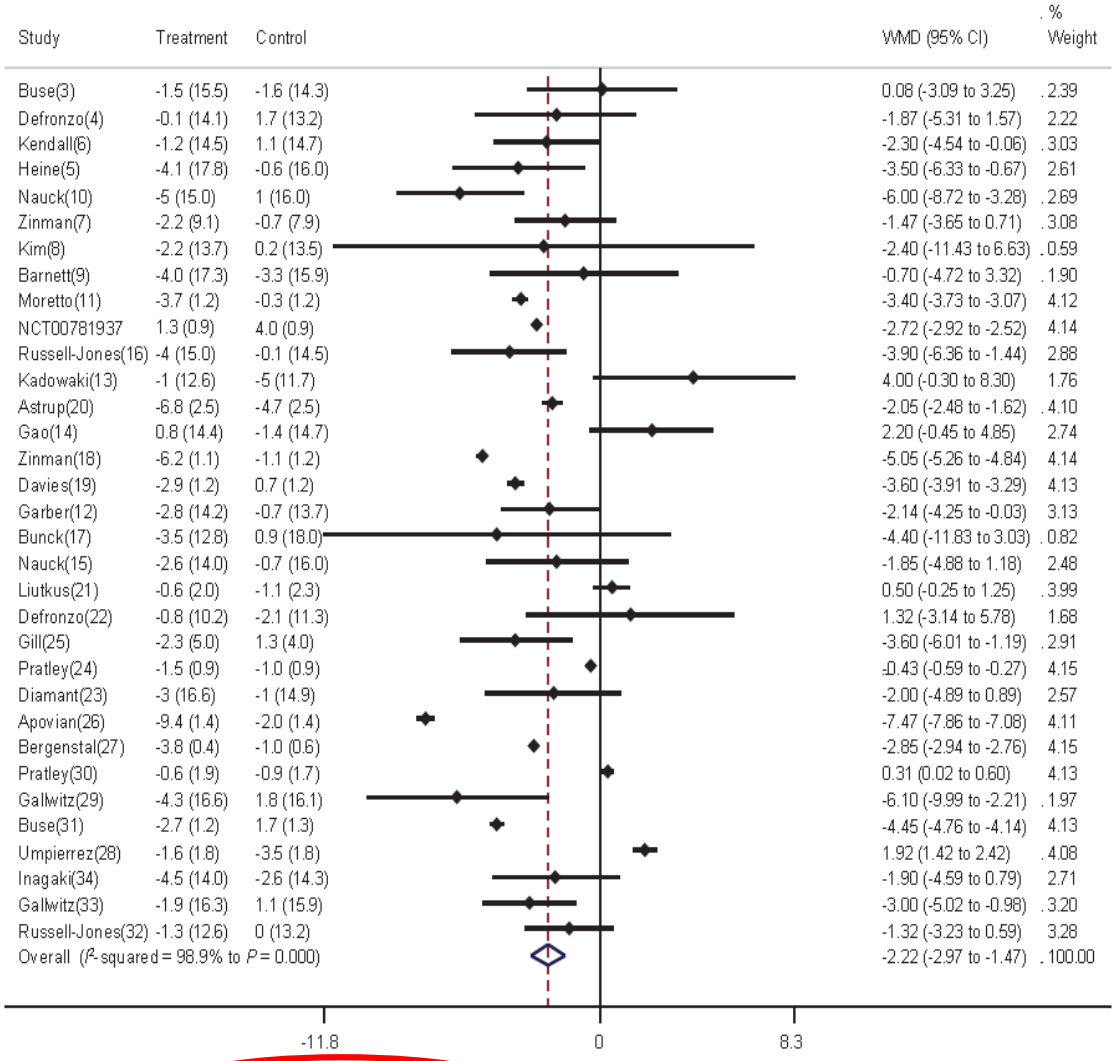




(Effetto postprandiale!)

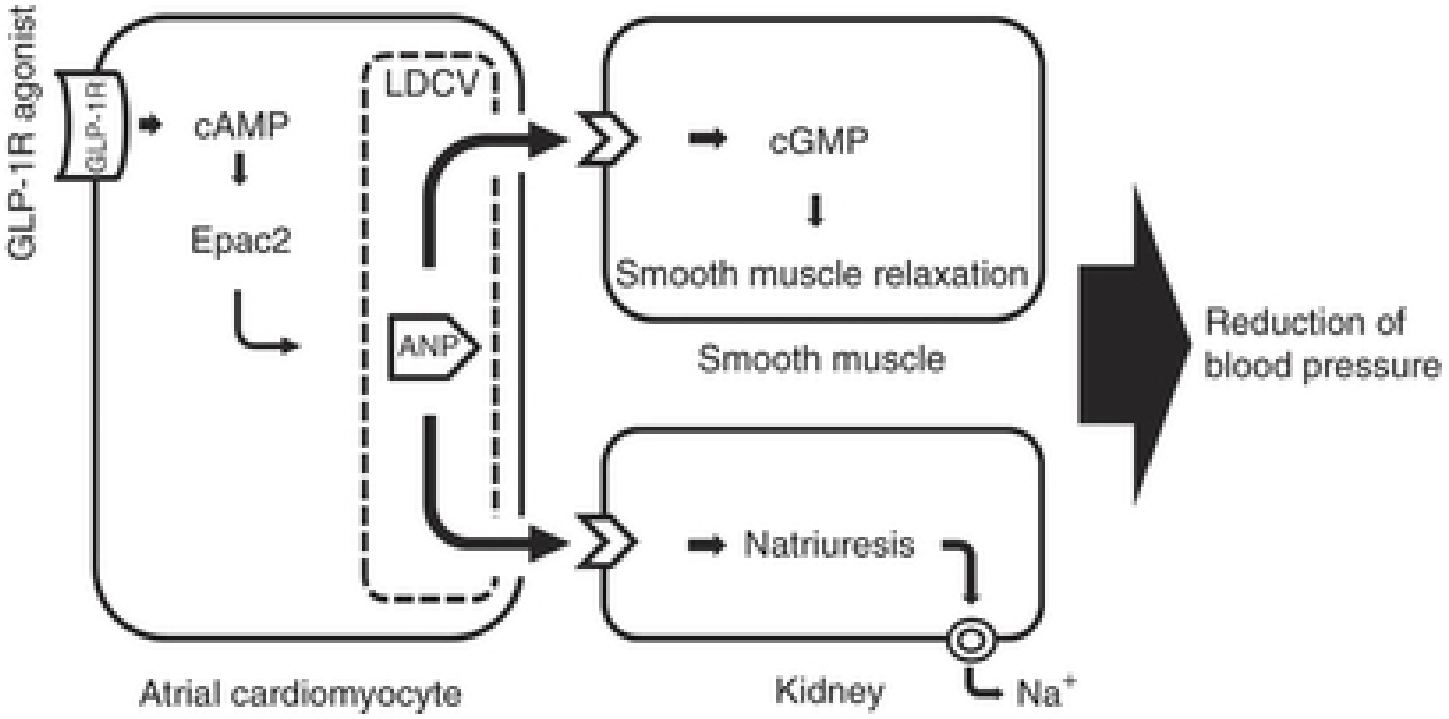
F. Sun et al. Clinical Therapeutics

Meta-analysis of change in systolic blood pressure (mm Hg) in RCTs after at least 12 weeks of treatment with GLP-1 RA



Katout M al. Am J Hypertens 27: 130-139 , 2014

GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure



Minsuk Kim et al. 2013


Does it really work????

Punti di forza

Popolazione ben definita
Disegno dello studio
Trattamento somministrato in condizioni strettamente controllate
Massima complia

"Ideal" world evidence

Efficacy

Limiti

Esclusione di molti pazienti
Difficoltà a generalizzare i risultati
Centri specializzati
Durata e dimensioni campione limitate, no info su lungo termine
Trial effect"

Punti di Forza

Più ampio spettro di popolazioni e di setting assistenziali (esclusi nei trials)
Effetti lungo periodo
Effetti su outcomes che non erano stati considerati nei trials
Eventi avversi rari /tossicità in sottogruppi
Valutare la persistenza in terapia e la compliance
Analisi farmaco-economiche

"Real" world evidence

Effectiveness

Limiti

Rischio di selection bias
Limitato numero di informazioni
Dati mancanti o eterogeneità nella definizione dei dati

Adv Ther (2015) 32:838–853
DOI 10.1007/s12325-015-0245-x

ORIGINAL RESEARCH

Effectiveness and Persistence with Liraglutide Among Patients with Type 2 Diabetes in Routine Clinical Practice—EVIDENCE: A Prospective, 2-Year Follow-Up, Observational, Post-Marketing Study

Jean-Francois Gautier · Luc Martinez · Alfred Penfornis · Eveline Eschwège · Guillaume Charpentier · Benoît Huret · Suliya Madani · Pierre Gourdy

N= 3152

Drop-out = 31.8%

% pts HbA1c <=7.0% = 29.5%

End-point	Baseline	24 months
HbA1c	8.46	7.44
FPG	180	146
Weight	95.2	91.1
BMI	34.0	32.5

Table 2 Motivations that influenced the decision of physicians to prescribe liraglutide—FAS

Motivation	*n*/total analyzed (%)
Improvement of glycemic control	2552/3145 (81.1)
Reduction of hypoglycemic episodes	290/3144 (9.2)
Improvement of weight control	2113/3145 (67.2)
Potential beneficial effect on beta-cell function	915/3145 (29.1)
Improvement of blood pressure	284/3143 (9.0)
Adverse effect of current treatment	324/3145 (10.3)
Patient dissatisfaction with current treatment	578/3144 (18.4)
Trying a new treatment	578/3144 (18.4)
Potential beneficial effect of other properties of GLP-1	956/3144 (30.4)

Due to missing data, the % value relates to the number of patients analyzed within the FAS population for that particular motivation and not the total FAS population. Physicians may have had more than one motivation for prescribing liraglutide

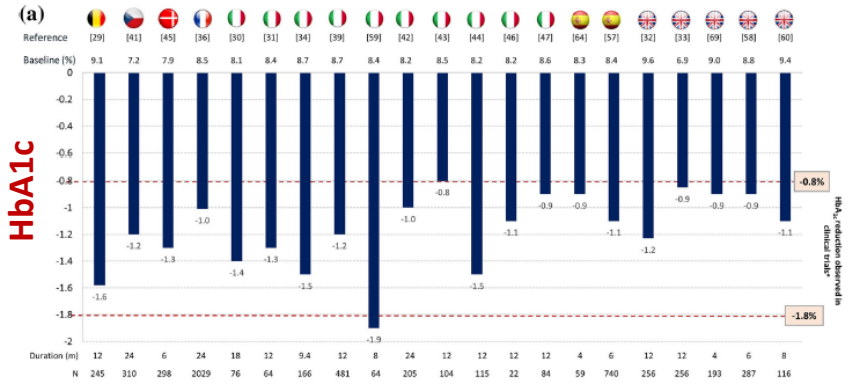
FAS full analysis set, *GLP-1* glucagon-like peptide-1, *n* number for subset

Diabetes Ther
DOI 10.1007/s13300-016-0180-0

REVIEW

Clinical Effectiveness of Liraglutide in Type 2 Diabetes Treatment in the Real-World Setting: A Systematic Literature Review

Amrita Ostawal · Emina Mocevic · Nana Kragh · Weiwei Xu



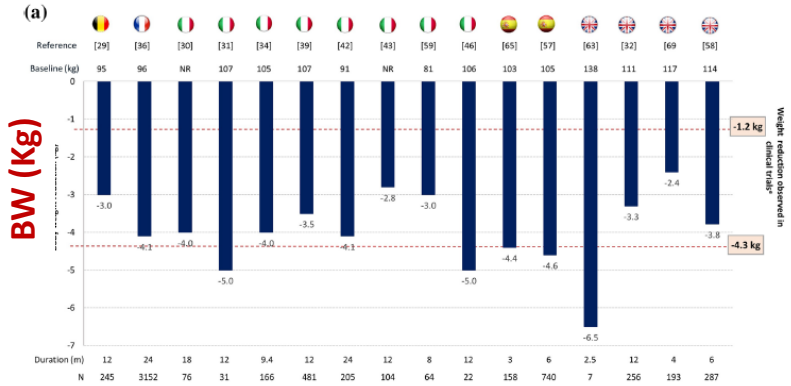


Table 2 Overview of studies reporting NICE Composite endpoint in real-world evidence studies

Code	Intervention	Mean baseline HbA1c (SD), %	*N*	Follow-up duration (months)	NICE composite endpoint[b] achieved
Full-text publications					
Nyeland et al. 2015 [58]	Liraglutide	8.8 (1.9)	287	6	25.10%
	Sitagliptin	8.6 (1.5)	2781		10.4%[a]
Heymann et al. 2014 [51]	Liraglutide	9.7 (NA)	1101	6	20.10%
Russo et al. 2015 [44]	Liraglutide	8.2 (1.3)	115	12	47%
Evans et al. 2014 [33]	Liraglutide	9.6 (0.5)	229	12	32%
	Exenatide	9.8 (0.8)	148		24%
	DPP-4i	8.1 (0.4)	710		64%
Evans et al. 2013 [32]	Exenatide BID	9.6 (0.5)	148	12	3 months: 27% 6 months: 24% 9 months: 26% 12 months: 25% Audit end: 21%
	Liraglutide	9.8 (0.8)	256		3 months: 35% 6 months: 32% 9 months: 31% 12 months: 29% Audit end: 28%
	DPP-4i (sitagliptin, saxagliptin, or vildagliptin)	8.1(0.4)	710		3 months: 59% 6 months: 61% 9 months: 52% 12 months: 54% Audit end: 57%
Conference abstracts					
Heymann et al. 2013 [80]	Liraglutide	8.7 (1.3)	453	6	20.10%
Karasik et al. 2013 [81]	Liraglutide	8.57 (1.20)	614	6	16.90%
Fatima et al. 2014 [82]	Liraglutide	8.7 (NA)	43	6	42%

Table 2 continued

Code	Intervention	Mean baseline HbA1c (SD), %	*N*	Follow-up duration (months)	NICE composite endpoint[b] achieved
Mattson et al. 2015 [79]	Liraglutide	7.69 (1.43)	180	6	27%
	Sitagliptin	7.53 (1.50)	208		10%

Effectiveness of liraglutide on CVD risk factors

Extraglycemic effects

Country	First author	Journal	Year	N centers	N	FUP (months)	Drop-out (%)	HbA1c (%)	FBG	BMI	Weight	Waist	Total	HDL	LDL	Trigly	SBP	DBP	MAU
Spain	Mezquita Raya P	Diabetes Ther	2015	7	753	6	-	1.1		-1.7	-4.6	-	-	-	-0.2	-0.09	-5.9	-3.2	-
Italy	Lapolla	Clinical Therapeutics	2015	7	481	12	5.0	-1.2	-28	-1.3	-3.5	-2.6	-	-	-	-	-	-	-
Belgium	Buysschaert	Diabet Metab Syndr	2015	1	245	12	31.8	-1.6	-	-1.1	-	-	-	-	-	-	-	-	-
Italy	Ponzani P	Minerva endocrinologica	2013	1	205	24	16.1	-1	-45	-1.8	-4.9	-4	-3.5	0.5	-2	-21	-4.4	-0.6	-
Italy	Ponzani P	Minerva endocrinologica	2016	1	255	36	28.2	-1	-46	-	-3.9	-	-3.5	6.9	-3	-30	-3.9	0.9	-
Italy	Rondinelli M	Submitted	2015	2	261	36	37.9	-1	-27	-1.1	-2.9	-	-	-	-25	-	0	0	-16.6

Effetti extraglicemici dei GLP1-RAs

J Endocrinol Invest
DOI 10.1007/s40618-014-0163-9

ORIGINAL ARTICLE

Twelve-month treatment with Liraglutide ameliorates Visceral Adiposity Index and common cardiovascular risk factors in type 2 diabetes outpatients

G. T. Russo · A. M. Labate · A. Giandalia · E. L. Romeo · P. Villari · A. Alibrandi · G. Perdichizzi · D. Cucinotta

Received: 4 April 2014 / Accepted: 12 August 2014

Abstract
Aim In addition to the effects on glycemic c body weight, GLP-1 receptor agonists may favo other major cardiovascular disease (CVD) ri although currently available data are still spa retrospective study, we evaluated the effects o treatment with liraglutide on major CVD risk fa type 2 diabetes outpatients (60 men and 55 w stable hypoglycemic, anti-hypertensive and/or ering therapy.
Methods Clinical and anthropometric data, me lipid profile, as well as the Visceral Adiposity In an obesity-related CVD risk factor, were meas participants at baseline and after 12-month trea
Results Treatment with liraglutide was asso a significant reduction from baseline values blood glucose (−42.1 mg/dl, $P < 0.05$), HbA_1 −17 mmol/mol, $P < 0.05$), body weight ($P < 0.05$), waist circumference (-6.8 cm, $P < 0.001$), total-cholesterol (−27.4 mg/dl, $P < 0.05$), LDL-

G. T. Russo and A. M. Labate contributed equally to the manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s40618-014-0163-9) contains supplementary material, which is available to authorized users.

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A. Alibrandi
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Published online: 31 August 2014

J Endocrinol Invest

Table 2 Effects of 12-month treatment with liraglutide on major cardiovascular risk factors

	Baseline values	Follow-up values	Variation from baseline
Waist circumference (cm)	117.8 ± 12.6	110.9 ± 12.8	−6.8 ± 13.5#
BMI (kg/m^2)	37.2 ± 6.3	34.6 ± 6.2	−2.6 ± 6.2*
HbA_{1c} (%)	8.2 ± 1.3	6.8 ± 0.7	−1.5 ± 1.3*
HbA_{1c} (mmol/mol)	66 ± 16	49 ± 8	−17 ± 16*
FBG (mg/dl)	172.7 ± 40.5	130.6 ± 27.1	−42.1 ± 43.4*
Total-cholesterol (mg/dl)	182.2 ± 40.6	154.8 ± 30.0	−27.4 ± 42.4*
LDL-cholesterol (mg/dl)	102.8 ± 36.6	77.4 ± 26.7	−25.4 ± 39.3*
HDL-cholesterol (mg/dl)	42.5 ± 11.1	51.8 ± 12.38	+9.3 ± 11.4#
Triglycerides (mg/dl)	184.6 ± 88.6	128.58 ± 56.8	−56.1 ± 68.3*
Non-HDL-cholesterol (mg/dl)	139.7 ± 40.2	103.1 ± 27.4	−36.6 ± 40.2*
SBP (mmHg)	138.9 ± 13.3	124.2 ± 11.3	−14.7 ± 12.3#
DBP (mmHg)	84.8 ± 7.3	75.8 ± 7.3	−9.0 ± 8.5*

Data are *n*, mean ± SD; mean variation from baseline values ± SD

FBG fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

* $P < 0.05$, # $P < 0.001$

CVD	Cardiovascular disease
T2D	Type 2 diabetes
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
VAI	Visceral Adiposity Index

Introduction

Cardiovascular disease (CVD) is still the leading cause of morbidity and mortality in type 2 diabetic (T2D) patients [1]. To reduce this burden, the current management of T2D aims to correct hyperglycemia, while taking into account all the other major CVD risk factors [2], i.e., dyslipidemia, hypertension and obesity.

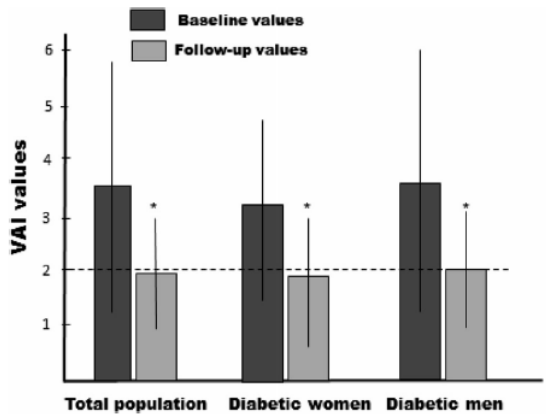
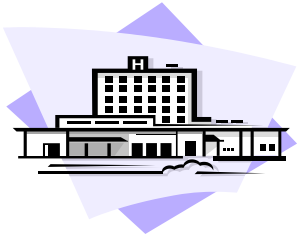


Fig. 1 Effects of 12-month treatment with liraglutide on VAI values. *All comparisons were significant ($P < 0.001$). Mean VAI value <2 is refereed as the cut-off point for adipose dysfunction associated with CVD risk [17, 31]

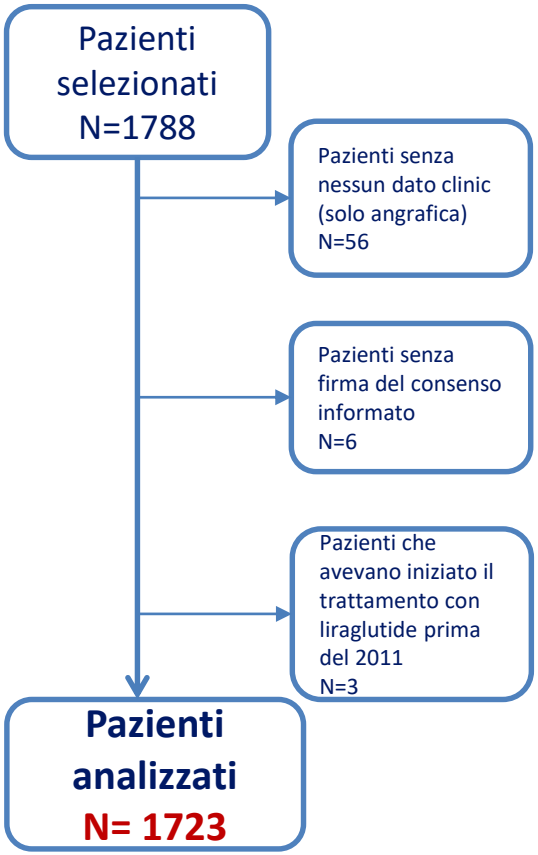
Studio REAL

DISEGNO STUDIO

National, observational, longitudinal, retrospective,multicenter study

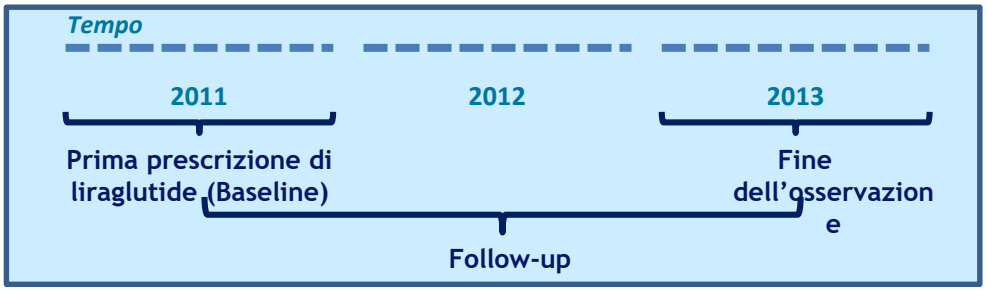


45 **Diabetes Outpatient Clinics**



Criteri d'inclusione

- **Soggetti di età > 18 anni che hanno ricevuto una prescrizione di liraglutide nel corso del 2011.**
- **I pazienti sono stati selezionati utilizzando le cartelle cliniche elettroniche.**
- **Una query ad hoc è stata sviluppata per estrarre l'elenco dei pazienti che avevano iniziato liraglutide durante l' anno 2011 .**
- **Ogni centro ha fornito i dati relativi a tutti i pazienti eleggibili per evitare qualsiasi *bias* di selezione.**



Follow-up medio di 24 mesi

Long-term effectiveness of liraglutide for treatment of type 2 diabetes in a real life setting: a 24-month non-interventional, retrospective, multicentre study in Italy

A. Lapolla[1] , C. Berra[2], M. Boemi[3], A.C. Bossi[4], R. Candido[5], G. Di Cianni[6], S. Frontoni[7], S. Genovese[8], P. Ponzani[9], V. Provenzano[10], G. Russo[11], L. Sciangula[12], N. Simioni[13], C. Bette[14], A. Nicolucci[15] on behalf of the NN2211-4118 Study Group.

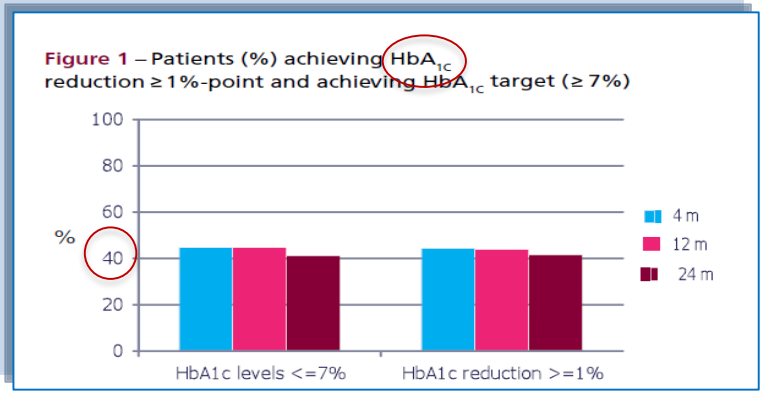
[1]University of Padua, Italy , [2]Istituto Clinico Humanitas, Milan, [3]Ospedale INRCA, Ancona, [4]Ospedale Treviglio Caravaggio, Treviglio [5]Ass 1 Triestina, Trieste, [6]Ospedale di Livorno, Livorno, [7]Ospedale S.G Calibita Fatebenefratelli, Rome, [8]Ospedale Multimedica, Sesto San Giovanni, Milan, [9]Ospedale La Colletta, Arenzano, [10]Ospedale Civile di Partinico, Palermo, [11]Policlinico G Martino, Messina, [12]Ospedale Felice Villa, Mariano Comense, [13]Presidio Ospedaliero di Cittadella, Padua, [14]Novo Nordisk, Rome, Italy, [15]COREsearch, Pescara.

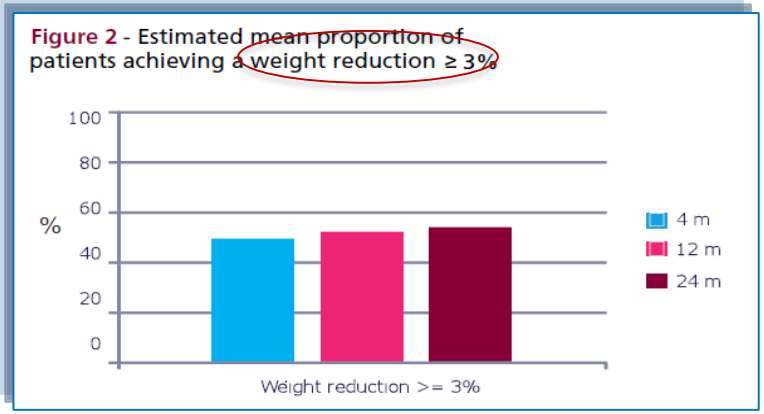
NAPOLI, 17-20 maggio 2017
XXI CONGRESSO NAZIONALE AMD

A 24 mesi After 24 months, 78.5% of patients were still on treatment; 48.7% were treated with maximum dose (1.8 mg); only in 63.2% liraglutide was an add-on to the previous therapy

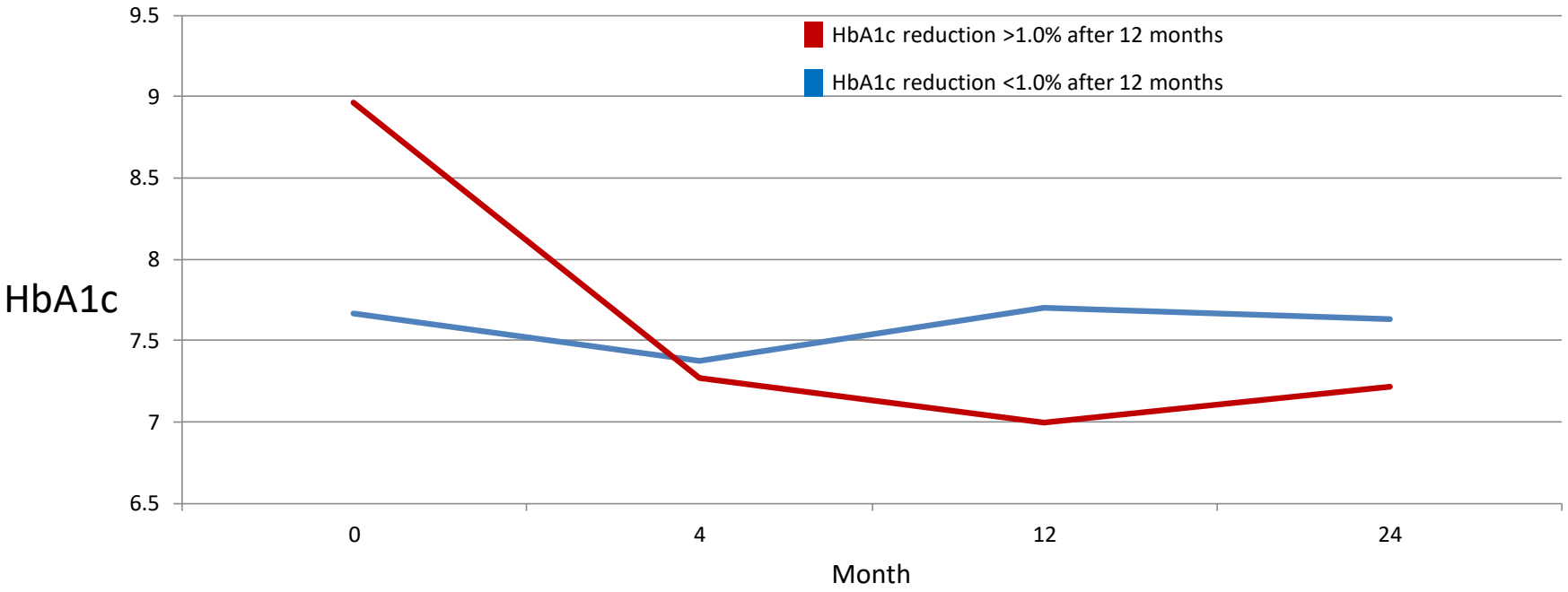
Table 1 – Baseline patients characteristics

Variable		Mean±SD or %
Population (N)		1723
Age (years)		58.9±9.5
Gender (%)	Females	45.1
	Males	54.9
Diabetes duration (years)		9.6±7.1
Diabetes duration in classes (%)	≤1	8.0
	2-4	24.2
	5 - 10	30.7
	11-15	18.8
	16 – 20	9.3
	>20	9.0
HbA_{1C} (%)		8.3±1.4
HbA_{1C} in classes (%)	≤7.0	14.7
	7.1 - 7.5	15.3
	7.6 - 8.0	20.6
	8.1 – 8.9	25.9
	>9.0	23.4
Fasting blood glucose (mg/dL)		171.8±52.2
Body weight (kg)		99.6±18.9
BMI (kg/m²)		35.6±5.9
Systolic blood pressure (mmHg)		139.3±18.1
Diastolic blood pressure (mmHg)		81.3±10.0



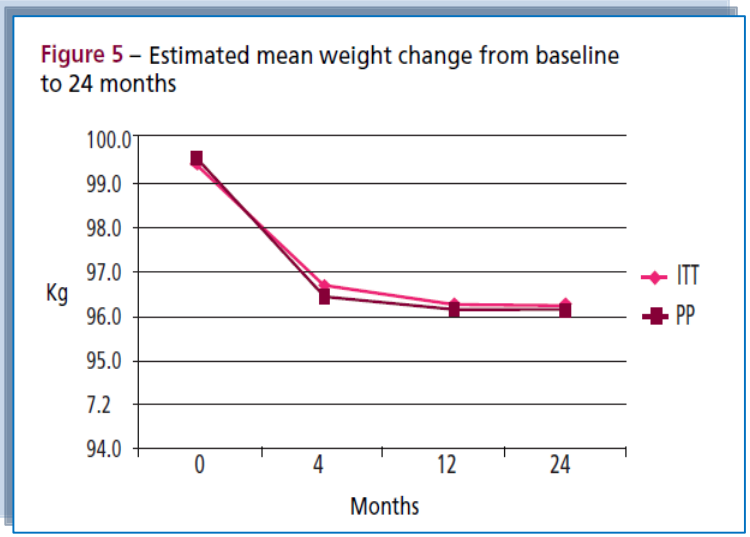


Changes from baseline to 24 months in HbA1c by primary endpoint (i.e. HbA1c reduction >=1.0% after 12 months).

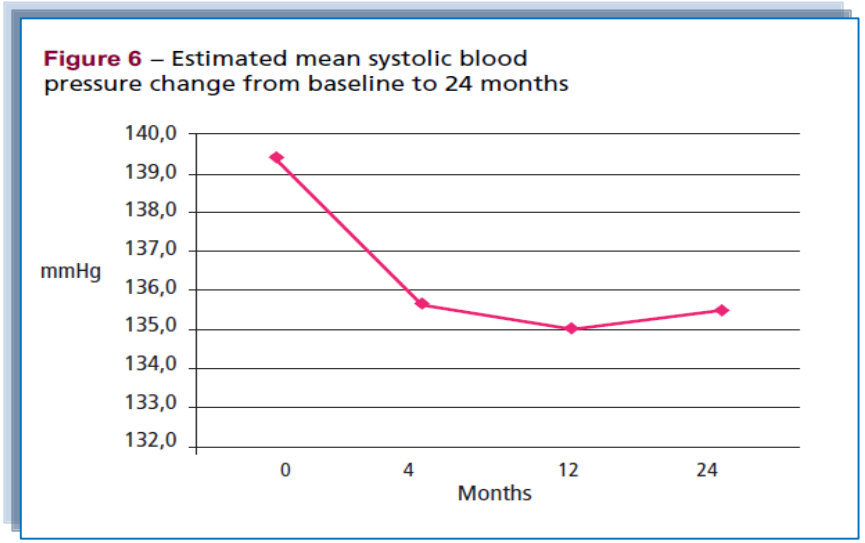


Real Study : Effectiveness on CVD risk factors

Body weight



SBP

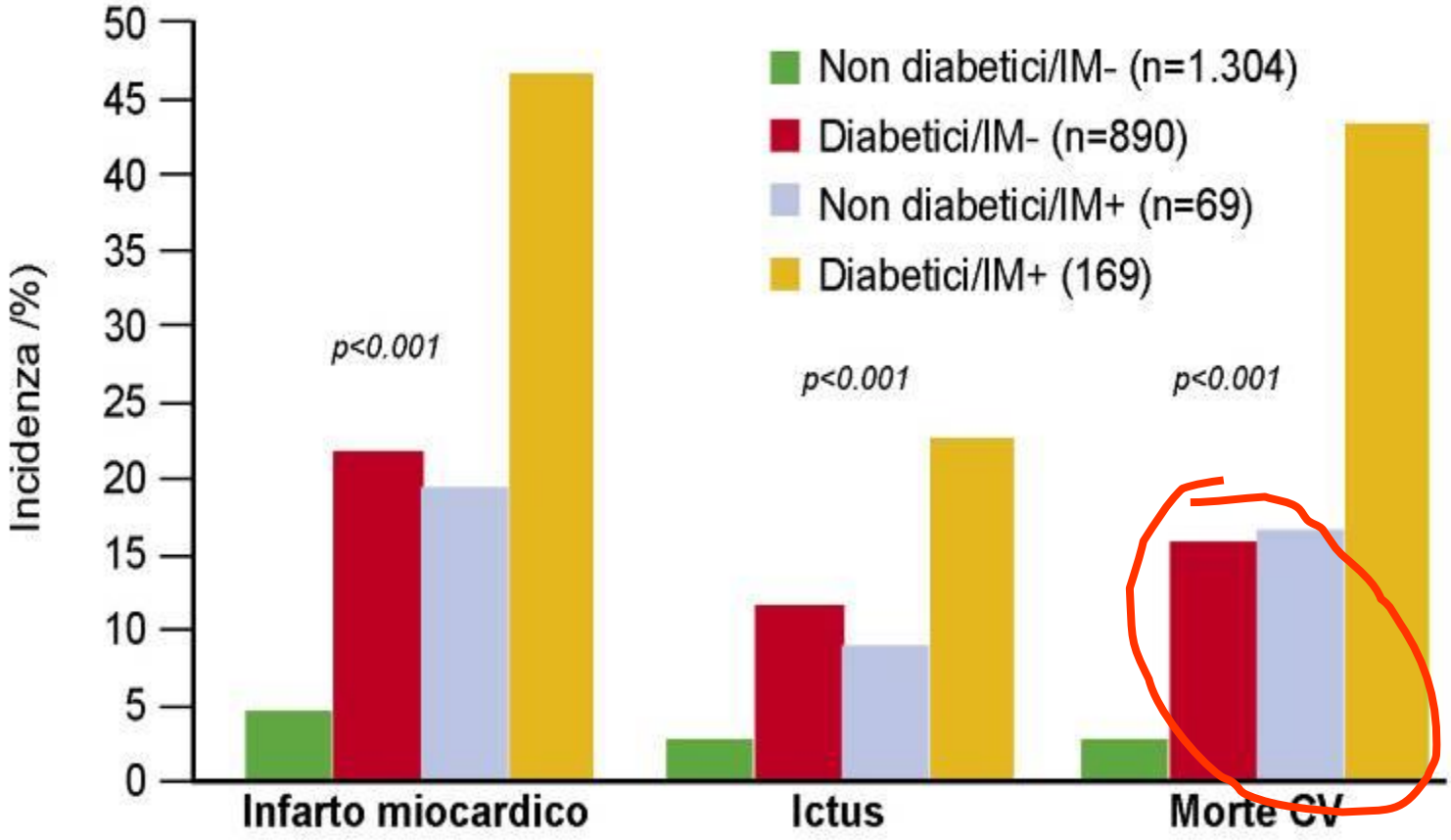


Endpoint	Baseline HbA1c (estimated mean level and 95%CI)	Change after 4 months (estimated mean change from baseline and 95%CI)	Change after 12 months (estimated mean change from baseline and 95%CI)	Change after 24 months (estimated mean change from baseline and 95%CI)
T-C	180.5 (178.2;182.8)	-12.01 (-15.2;-8.8)	-11.03 (-13.9;-8.2)	-11.11 (-13.5;-8.8)
HDL	44.8 (44.2;45.4)	-0.58 (-1.26;-0.09)	0.82 (0.23;1.40)	1.34 (0.85;1.82)
LDL	103.5 (101.5;105.6)	-8.96 (-11.81;-6.11)	-9.03 (-11.64;-6.41)	-11.16 (-13.49;-8.82)
Tryglycerides	172.3 (167.5;177.2)	-6.04 (-12.34;0.27)	-12.67 (-18.35;-7.00)	-9.35 (-14.21;-4.49)
Albuminuria	54.0 (41.5;66.5)	-5.10 (-21.34;11.14)	-8.91 (-23.76;5.94)	2.50 (-10.96;15.95)

Appropriate hypoglycaemic treatment according to patient clinical characteristic and lifestyle

Glucose Control	Lifestyle/Frailty/ Hypoglycaemia	BMI / Waist	Co-morbidities	Long-term complications
HbA1c ✓ FBG ✓ PPG ✓ Durability ✓ Hypoglycaemia ✓	Age Sex Ethnic group Diabetes duration ✓ Others	Normal ✓ Obesity ✓ Sarcopeny	Hypertension ✓ Dyslipidemia ✓ Osteoporosis Cancer NAFLD/ Liver Respiratory Neurological disorders Others	CVD? DKD? Neuropathy Retinopathy

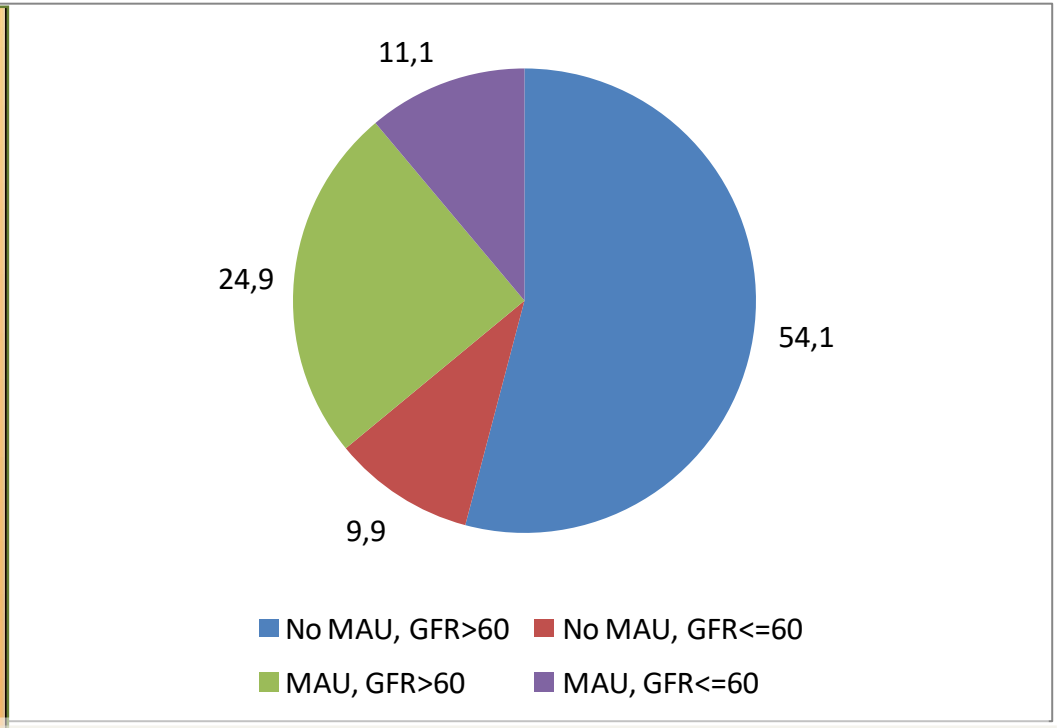
Elevato rischio di eventi CV nei pazienti con diabete tipo 2



IM-=senza precedente infarto miocardico;
IM+=con precedente infarto miocardico;
CV=cardiovascolari

Haffner SM, N Engl J Med 1998; 339:229-234

GFR and Micro/macroalbuminuria in T2DM subjects in the Annali AMD Initiative



I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.

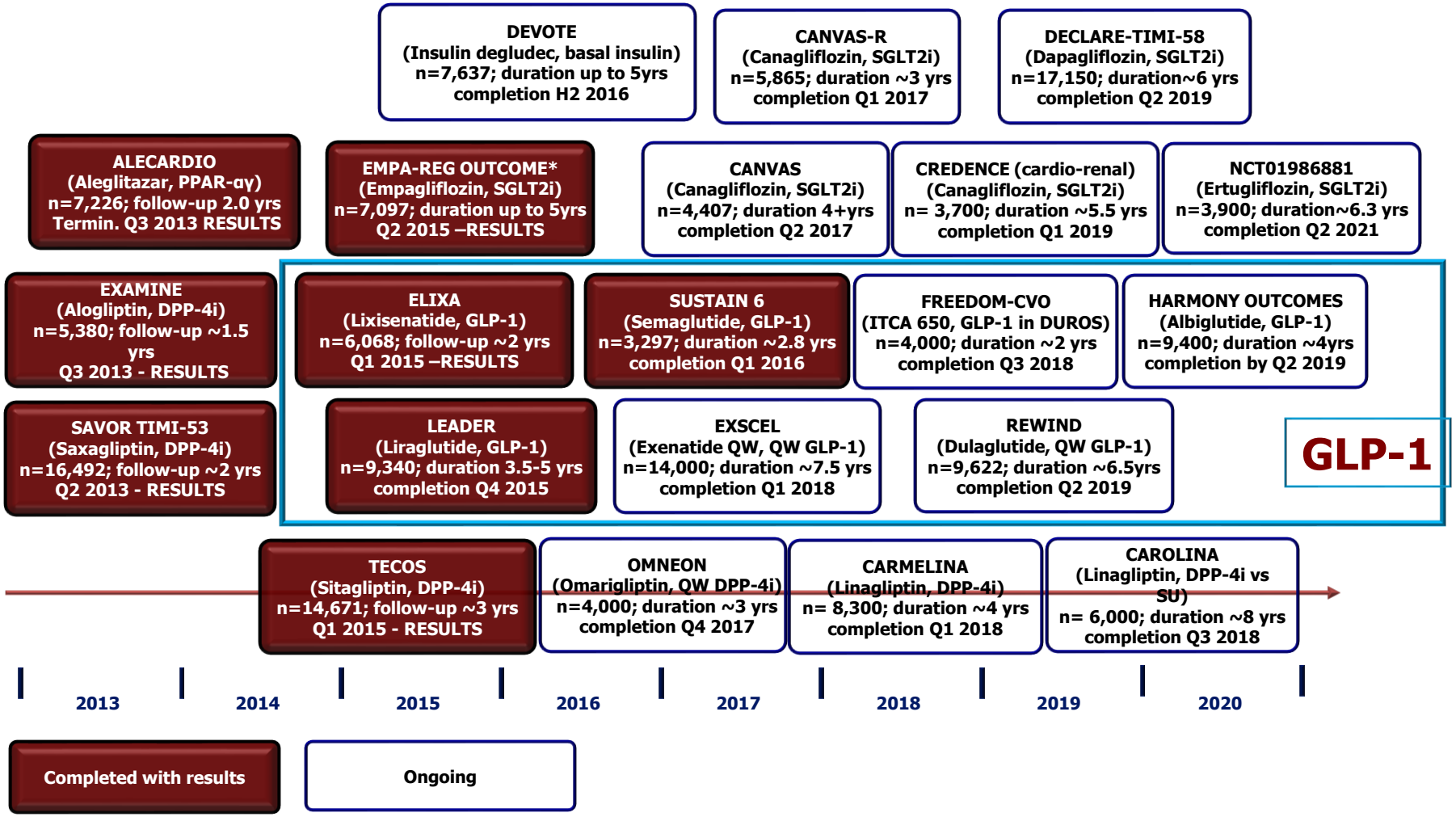
De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, Russo G, Rossi MC, Nicolucci A, Guida P,Di Bartolo P,Pontremoli R and the AMD-Annals Study Group. Nephrol Dial Transplant (2015) 0: 1–8; doi: 10.1093/ndt/gfv101

Tabella 16. Terapia non insulinica nel diabete tipo 2 con insufficienza renale cronica

Stadio IRC	LIEVE	MODERATA	GRAVE	DIALISI
eGFR	>60 ml/min	30-60 ml/min	15-30 ml/min	<15 ml/min
Metformina	≥2 g/die	Non indicato (utilizzabile)	NO	NO
Acarbosio	Da titolare	Da titolare	NO	NO
Gliptine				
Sitagliptin	100 mg/die	50 mg/die	25 mg/die	25 mg/die
Vildagliptin	100 mg/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2,5 mg/die	2,5 mg/die	NO
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12,5 mg/die[a]	6,25 mg/die	6,25 mg/die
GLP-1 agonisti				
Exenatide	20 µg/die	Cautela[b]	NO	NO
Exenatide LAR	2 mg/die	NO[c]	NO	NO
Liraglutide	Dosi usuali	Dosi usuali	NO	NO
Lixisenatide	Dosi usuali	Cautela[b]	NO	NO
Sulfoniluree	Da titolare	Da titolare[d]	NO	NO
Repaglinide	Da titolare	Non indicato (utilizzato)	NO	NO
Pioglitazone	Dosi usuali	Dosi usuali	Dosi usuali	NO[e]
Gliflozine				
Dapagliflozin	Dosi usuali	NO	NO	NO
Empagliflozin	Dosi usuali	NO	NO	NO
Canagliflozin	Dosi usuali	NO	NO	NO

[a] La riduzione della dose da 25 a 12,5 mg/die è prevista quando eGFR scende sotto 50 ml/min.
[b] Cautela necessaria quando eGFR è inferiore a 50 ml/min
[c] Farmaco non indicato quando eGFR è inferiore a 50 ml/min
[d] Alcune sulfoniluree (gliquidione, glimepiride) hanno metabolismo prevalentemente epatico, ma non sono state comunque studiate in modo esteso in pazienti con insufficienza renale; una accurata titolazione della dose è comunque raccomandabile, almeno per eGFR inferiore a 60 ml/min.
[e] Il pioglitazone è controindicato per eGFR inferiore a 5 ml/min.

Ongoing and recently completed cardiovascular outcomes trials within diabetes enrolling >130,000 patients



Source: ClinicalTrials.gov (30 June 2015). 'Completion date' is the estimated completion date for the primary outcomes measure. *Also known as C-SCADE-8.

European Heart Journal (2015) **36**, 2288–2296
doi:10.1093/eurheartj/ehv239

REVIEW

Clinical update

Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes

Ele Ferrannini[1]* and Ralph A. DeFronzo[2]

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Received 7 April 2015; revised 5 May 2015; accepted 16 May 2015; online publish-ahead-of-print 10 June 2015

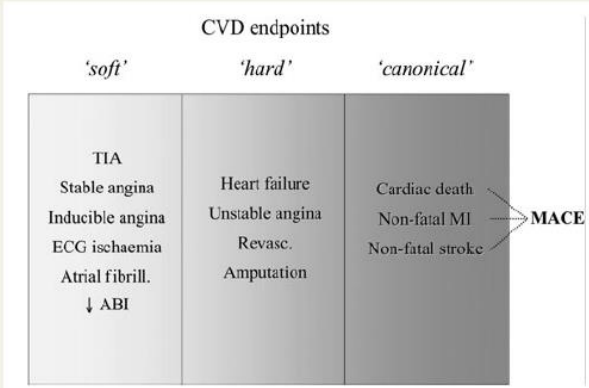
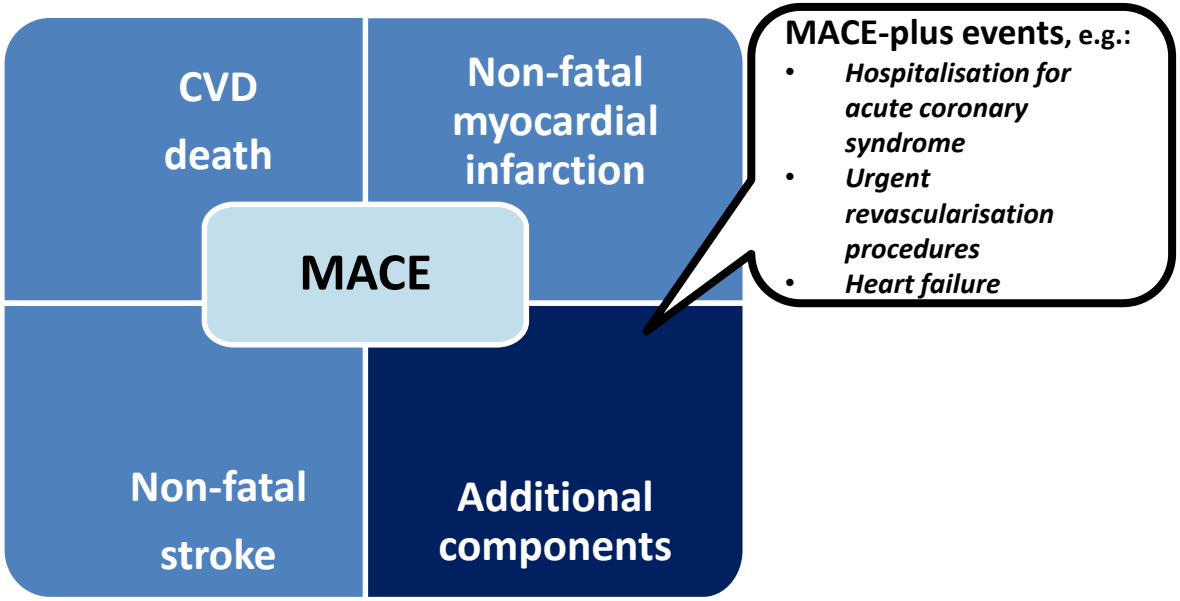


Figure 2 Major adverse cardiac events and other major adverse cardiovascular events are the tip of the iceberg of atherosclerotic cardiovascular disease. ABI, ankle-brachial index.



ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=3034)	Lixisenatide (N=3034)
Age — yr	60.6±9.6	59.9±9.7
Age ≥65 yr — no. (%)	1040 (34.3)	1003 (33.1)
Female sex — no. (%)	938 (30.9)	923 (30.4)
Duration of diabetes — yr	9.4±8.3	9.2±8.2
Glycated hemoglobin — %	7.6±1.3	7.7±1.3
Retinopathy — no. (%)	331 (10.9)	320 (10.5)
Neuropathy — no. (%)	498 (16.4)	512 (16.9)
Body weight — kg	85.1±19.6	84.6±19.2
Body-mass index†	30.2±5.8	30.1±5.6
Qualifying ACS event — no. (%)		
NSTEMI	1183 (39.0)	1165 (38.4)
STEMI	1317 (43.4)	1349 (44.5)
Unstable angina	528 (17.4)	514 (16.9)
Unclassified	6 (0.2)	6 (0.2)

Table 1. (Continued.)

Characteristic	Placebo (N=3034)	Lixisenatide (N=3034)
Days from ACS to randomization	72.2±43.9	71.8±43.4
Urinary albumin:creatinine ratio¶		
Median	10.5	10.2
Interquartile range	6.0–33.6	6.0–29.6

ELIXA Methods

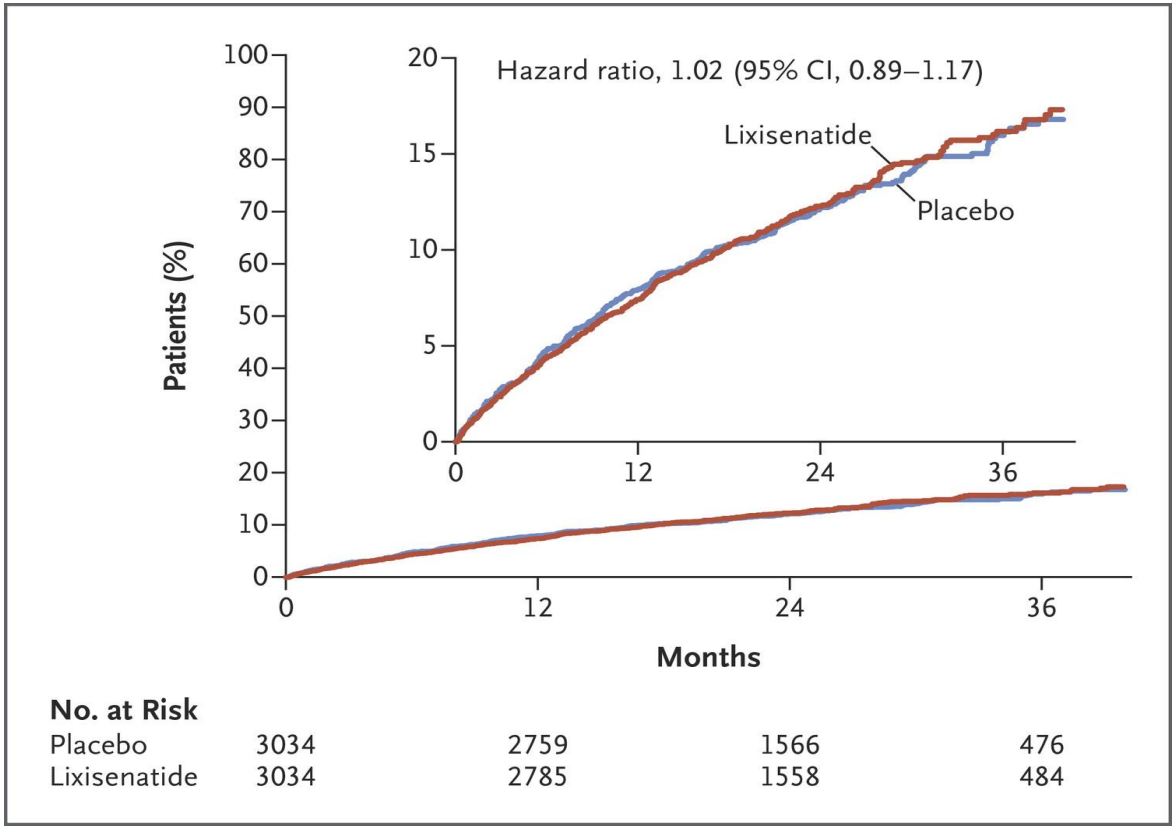
METHODS

We randomly assigned patients with type 2 diabetes who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days to receive lixisenatide or placebo in addition to locally determined standards of care. The trial was designed with adequate statistical power to assess whether lixisenatide was noninferior as well as superior to placebo, as defined by an upper boundary of the 95% confidence interval for the hazard ratio of less than 1.3 and 1.0, respectively, for the primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.

STUDIO ELIXA: Lixisenatide e MACE

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



No. at Risk

Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

Pfeffer MA et al. N Engl J Med 2015;373:2247-2257.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Table S2. Baseline characteristics.

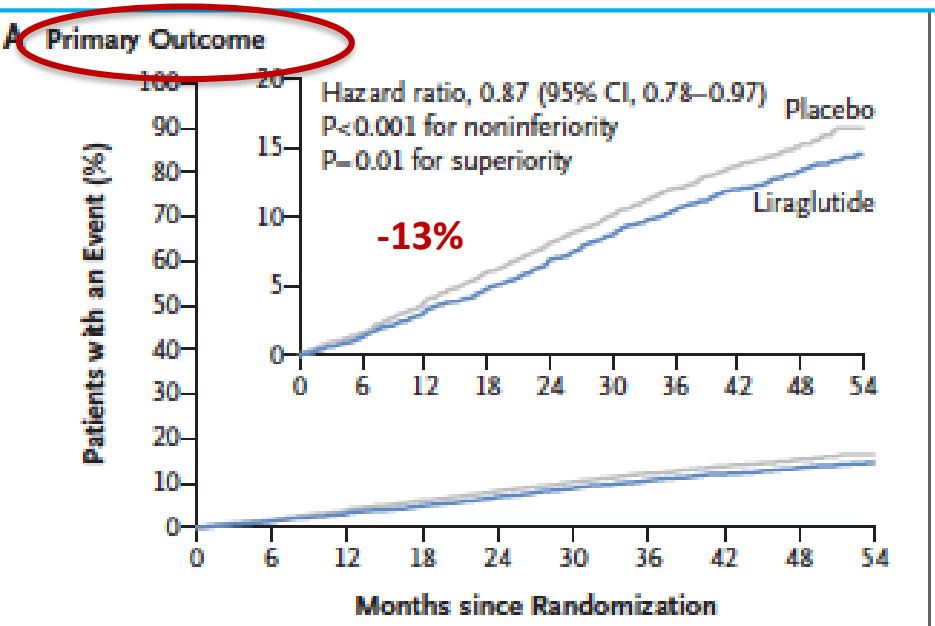
	Liraglutide (N=4,668)	Placebo (N=4,672)
Male sex	3011 (64.5)	2992 (64.0)
Age, years	64.2 ±7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
Glycated hemoglobin, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mm Hg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mm Hg	77.2 ± 10.3	77.0 ± 10.1
Heart failure[a]	835 (17.9)	832 (17.8)
Established CVD (age ≥50)	3831 (82.1)	3767 (80.6)
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or transient ischemic attack	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD[b]	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia[c]	1241 (26.6)	1231 (26.3)
Heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease[d]	1185 (25.4)	1122 (24.0)
CVD risk factors (age ≥60)	837 (17.9)	905 (19.4)
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle-brachial index <0.9	110 (2.4)	116 (2.5)
Renal function		
Normal (eGFR ≥90)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30)	117 (2.5)	107 (2.3)

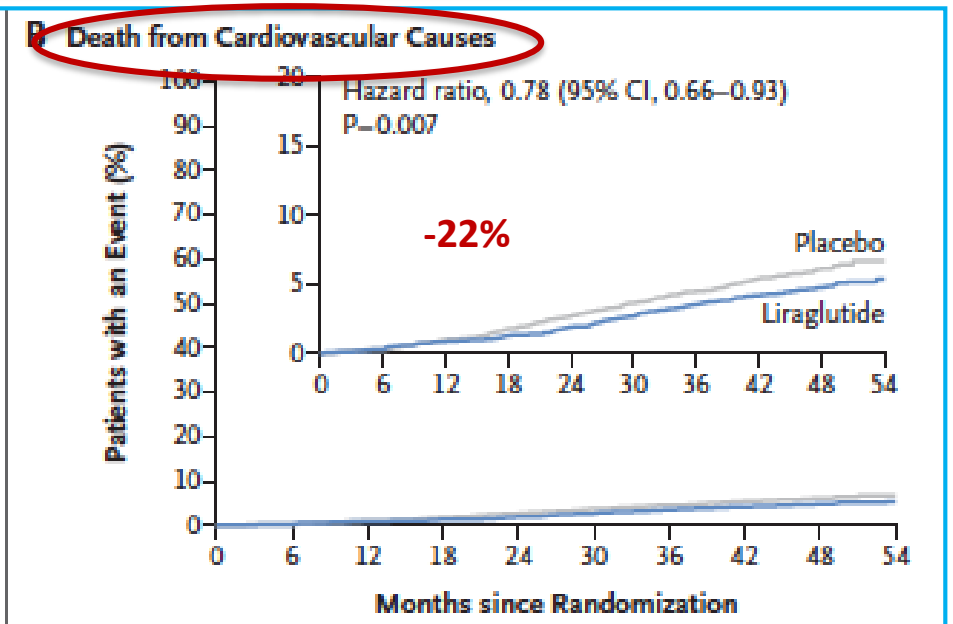
STUDIO LEADER: Liraglutide , MACE e Mortalità

The NEW ENGLAND JOURNAL of MEDICINE

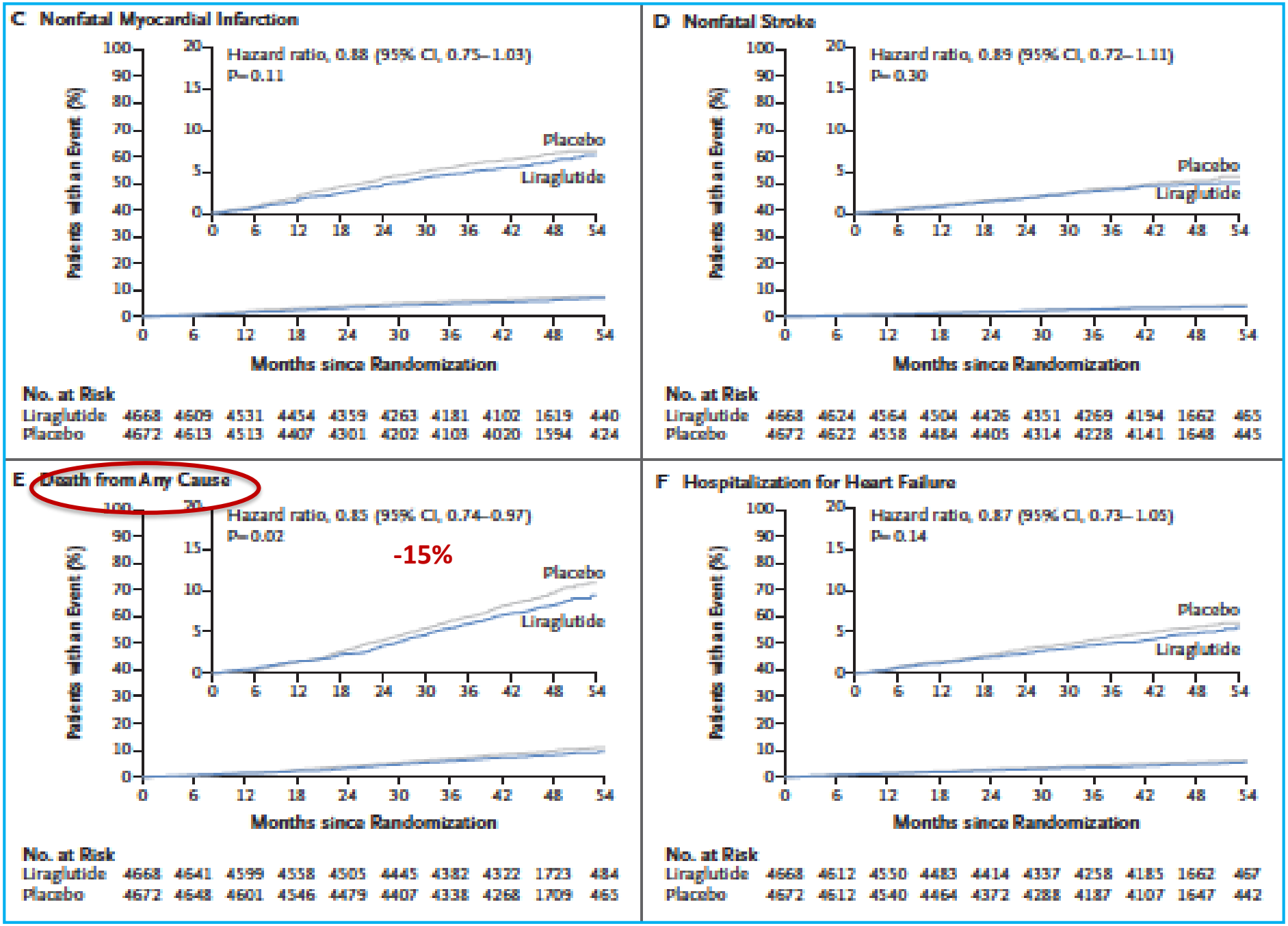
ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes





Marso SP, et al. *N Engl J Med*. 2016; 375:311-22,



Marso SP, et al. *N Engl J Med*. 2016; 375:311-22,

STUDIO SUSTAIN 6 : Semaglutide e MACE

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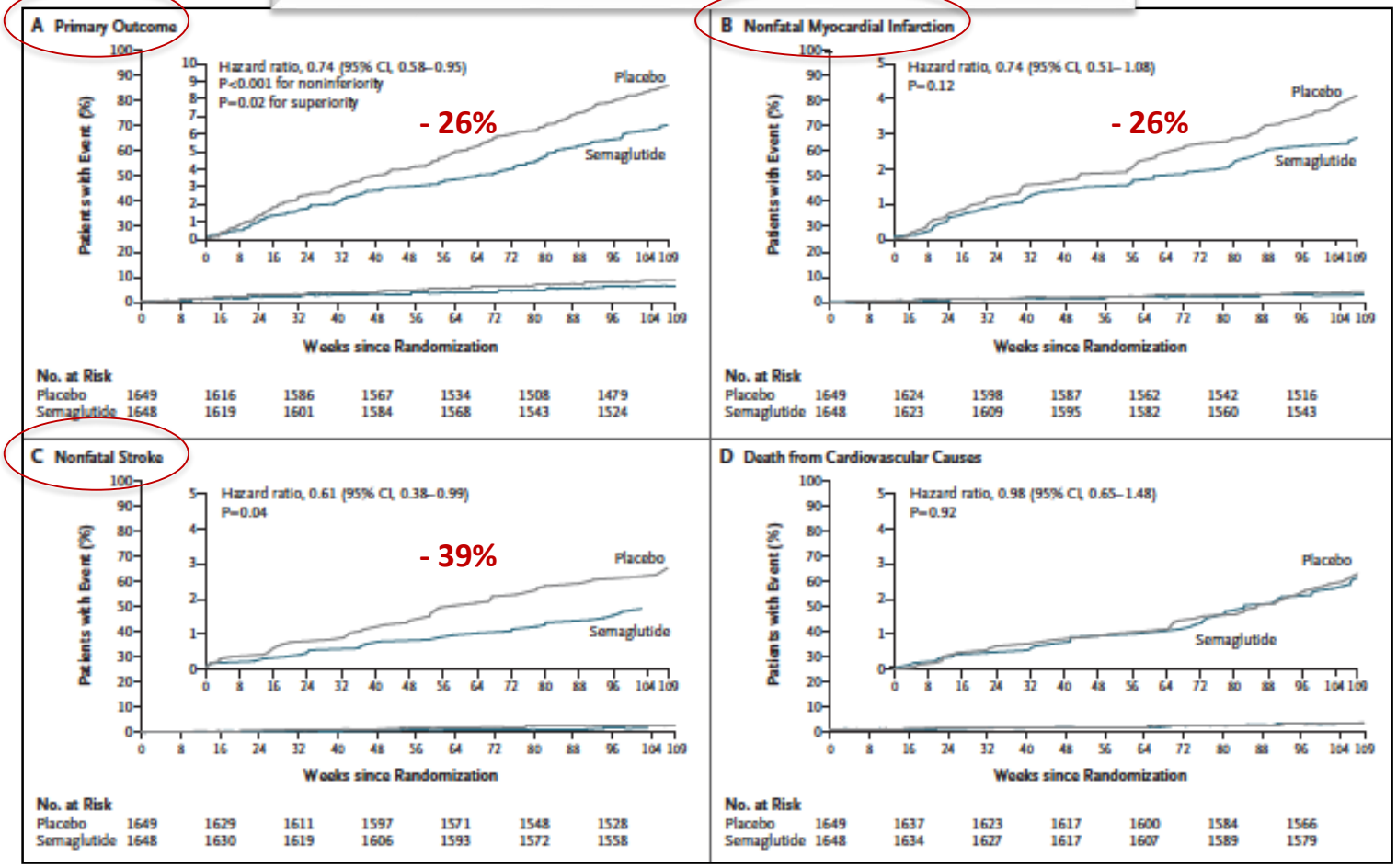
ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



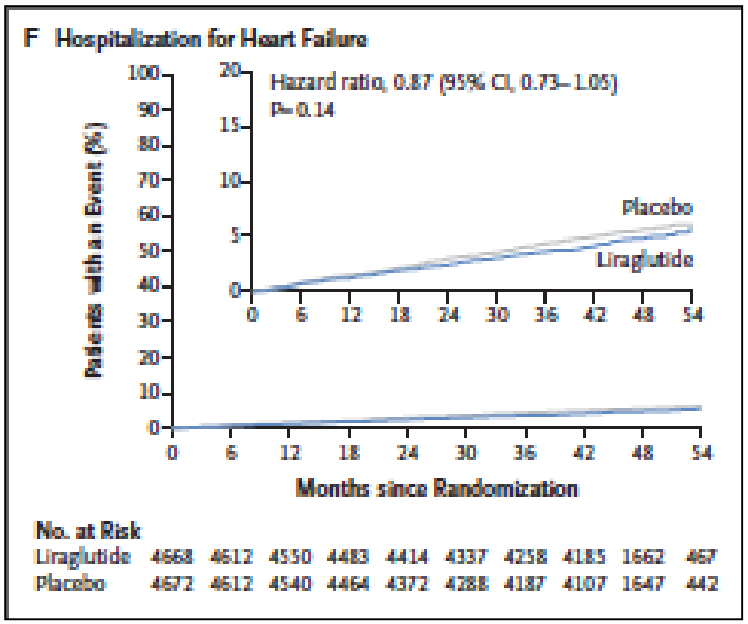
Marso SP, et al. *N Engl J Med*. 2016,

GLP1RAs CVOTs trials : Hospitalization for Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Additional end points — no. (%)						
Hospitalization for heart failure	127 (4.2)	1.9	122 (4.0)	1.8	0.96 (0.75–1.23)	0.75

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ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57

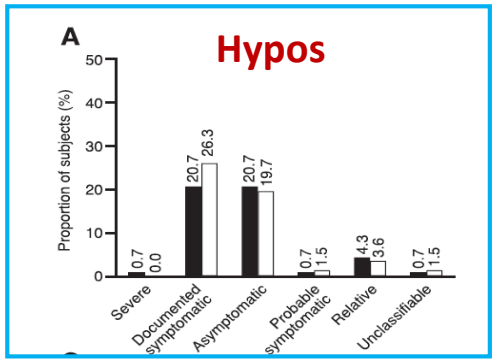
Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial

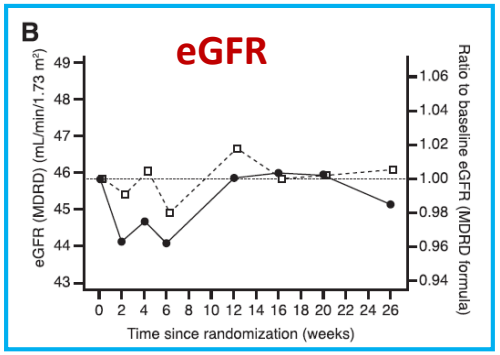
Melanie J. Davies,[1] Stephen C. Bain,[2] Stephen L. Atkin,[3] Peter Rossing,[4] David Scott,[5] Minara S. Shamkhalova,[6] Heidrun Bosch-Traberg,[7] Annika Syrén,[7] and Guillermo E. Umpierrez[8]

Diabetes Care 2016;39:222–230 | DOI: 10.2337/dc14-2883

Efficacy

Safety





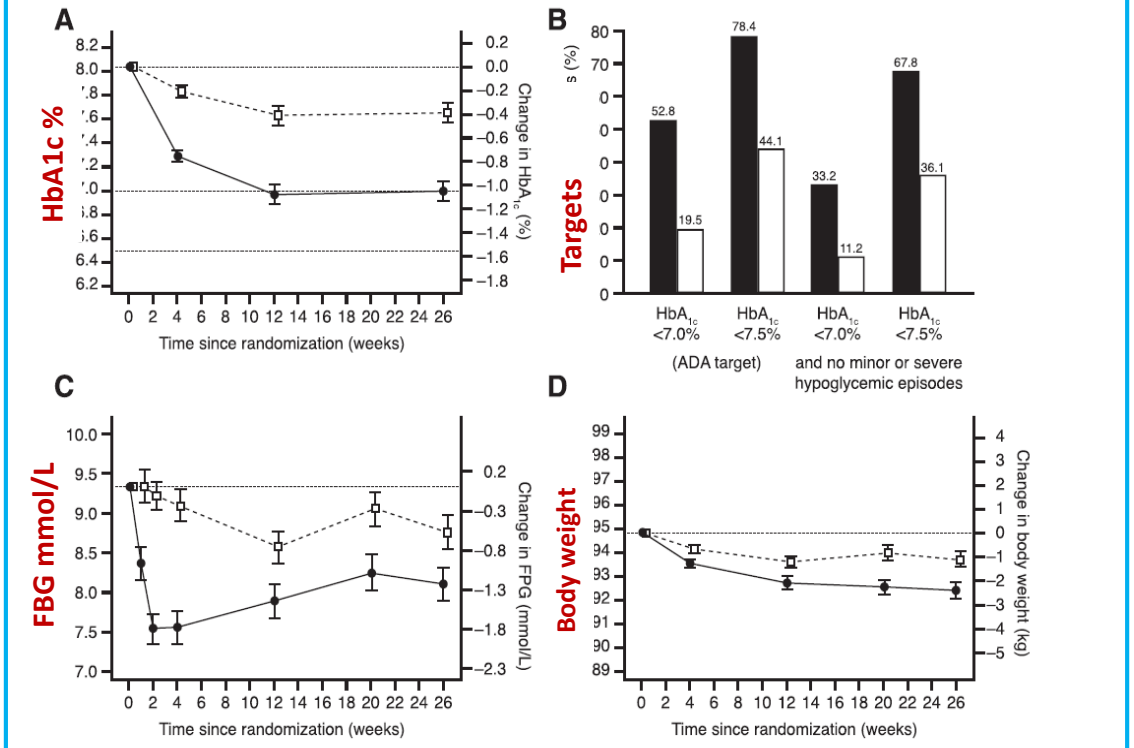


Figure 1—*A*: Estimated means plot (±SE) of HbA_{1c} (%) by treatment week and change from baseline to week 26. *B*: Responder end points for HbA_{1c} <7.0%, HbA_{1c} <7.5%, HbA_{1c} <7.0% and no minor or severe hypoglycemic episodes, and HbA_{1c} <7.5% and no minor or severe hypoglycemic episodes at week 26. *C*: Estimated means plot (±SE) of FPG (mmol/L) by treatment week and change from baseline to week 26. *D*: Estimated means plot (±SE) of body weight (kg) by treatment week and change from baseline to week 26. Black circle/black bar, liraglutide 1.8 mg; white square/white bar, placebo.

LEADER

Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Microvascular Outcomes

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for the LEADER investigators

Johannes Mann, MD, Friedrich Alexander University of Erlangen, Germany

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Microvascular event definitions

Event type		Event definition – one or more of the below
Microvascular events	**Renal**	• New onset of persistent macroalbuminuria • Persistent doubling of serum creatinine* • Need for continuous renal replacement therapy • Death due to renal disease
	Eye	• Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous haemorrhage • Diabetes-related blindness

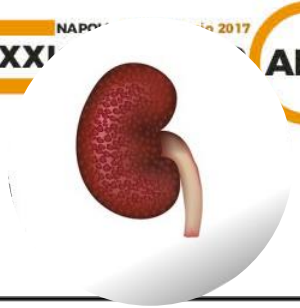
Adjudication of microvascular endpoints

Renal events	Laboratory measurements and events prospectively collected and adjudicated
Eye events	Collected as adverse events and adjudicated (eyes not systematically assessed at baseline or during the trial)

*and eGFR ≤45 mL/min/1.73 m^2 per MDRD

eGFR: estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany



Baseline renal function

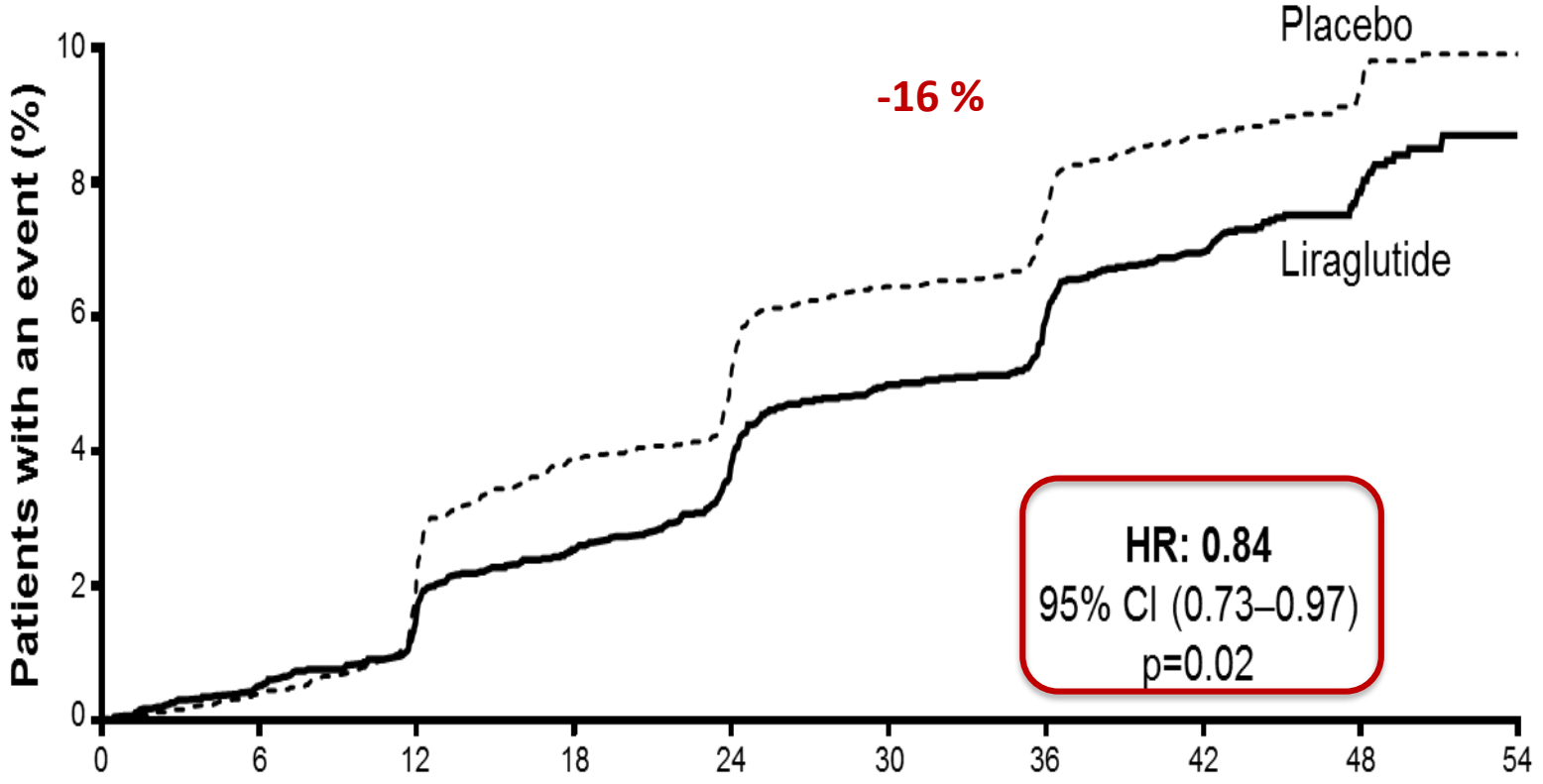
Renal function	Liraglutide (N=4668)	Placebo (N=4672)
Normal renal function (eGFR ≥90 mL/min/1.73m^2)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60 to <90 mL/min/1.73m^2)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30 to <60 mL/min/1.73m^2)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30 mL/min/1.73m^2)	117 (2.5)	107 (2.3)

Proteinuria	Liraglutide (N=4668)	Placebo (N=4672)
Microalbuminuria	915 (19.6)	1007 (21.6)
Macroalbuminuria	257 (5.5)	264 (5.7)

Full analysis set. Data are means ± standard deviations or number of patients (percentage of either liraglutide-treated or placebo-treated group).
Albuminuria is based on medical history as reported by investigator.
Percentage data refer to proportion of patients.
eGFR: estimated glomerular filtration rate.

1. Marso SP et al *N Engl J Med* 2016;375:311–322.; 2. Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Time to first microvascular event



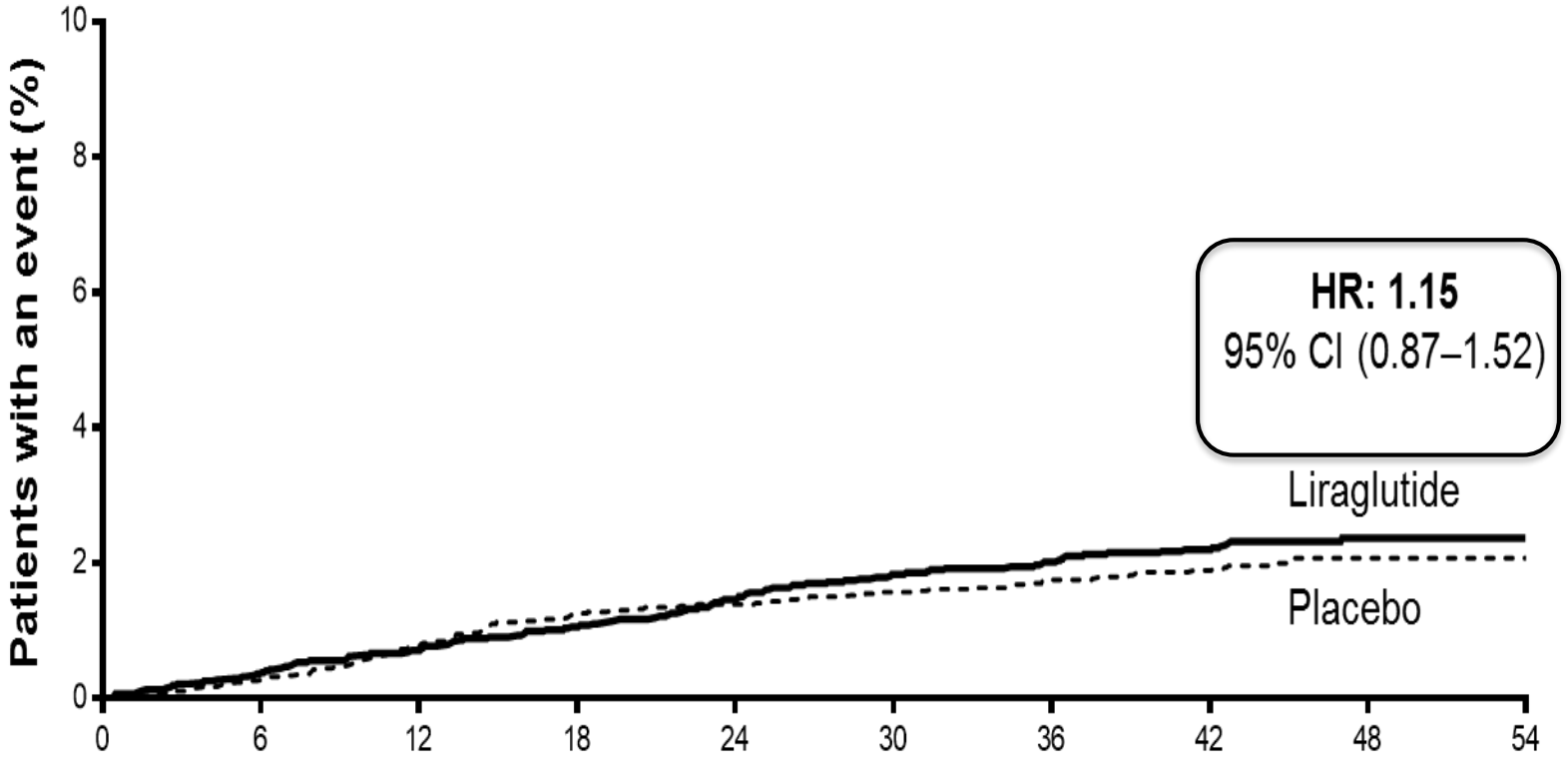
Patients at risk										
Liraglutide	4668	4618	4530	4446	4344	4234	4137	4038	1603	444
Placebo	4672	4631	4504	4373	4260	4134	4030	3921	1589	422

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs 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; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Time to first eye event

Photocoagulation or treatment with intravitreal agents, vitreous haemorrhage, or blindness



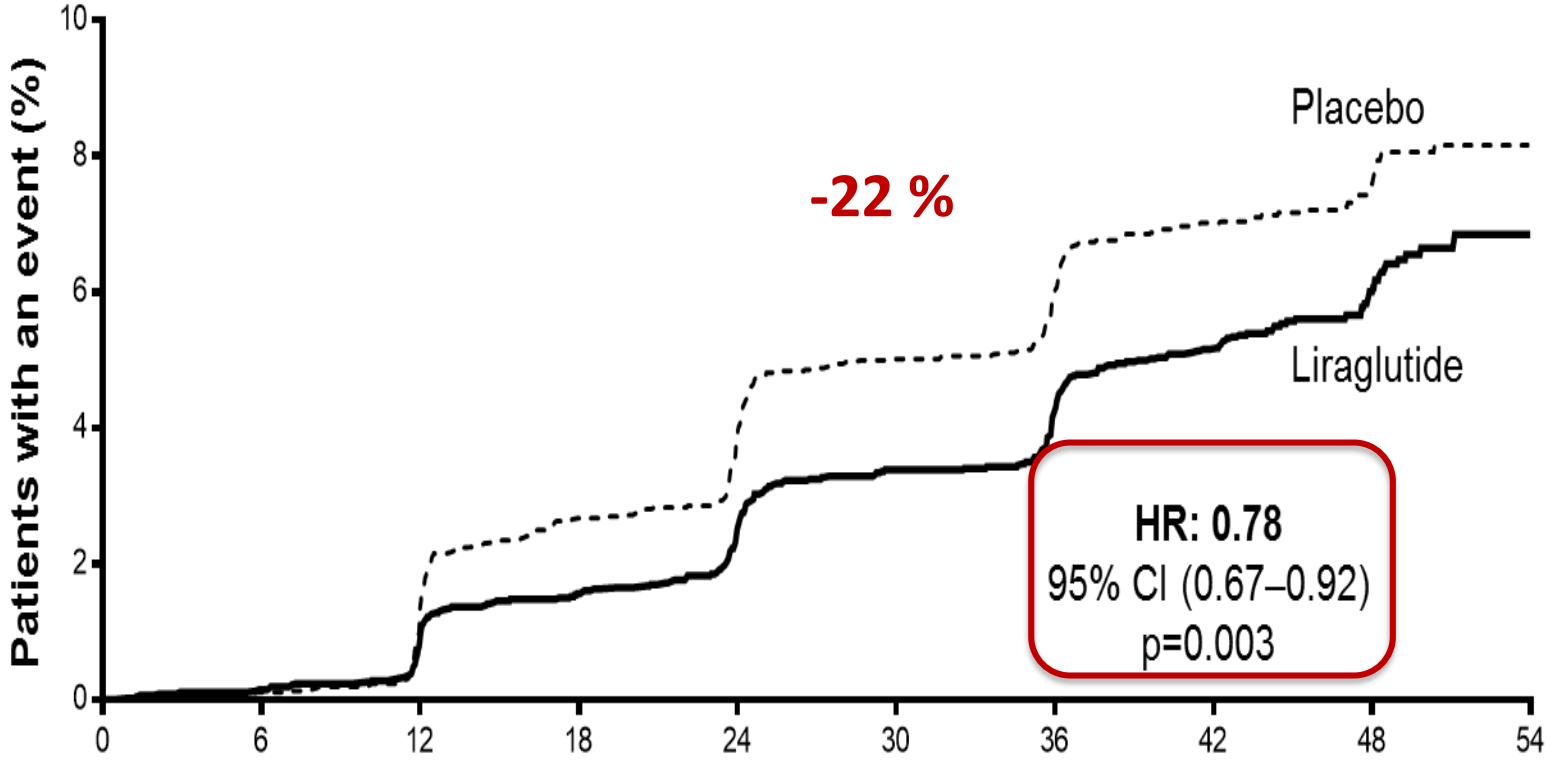
Patients at risk										
Liraglutide	4668	4624	4566	4509	4442	4366	4297	4231	1689	473
Placebo	4672	4636	4565	4489	4417	4339	4264	4188	1681	454

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs 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; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Time to first renal event

Macroalbuminuria, doubling of serum creatinine,* ESRD, renal death



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

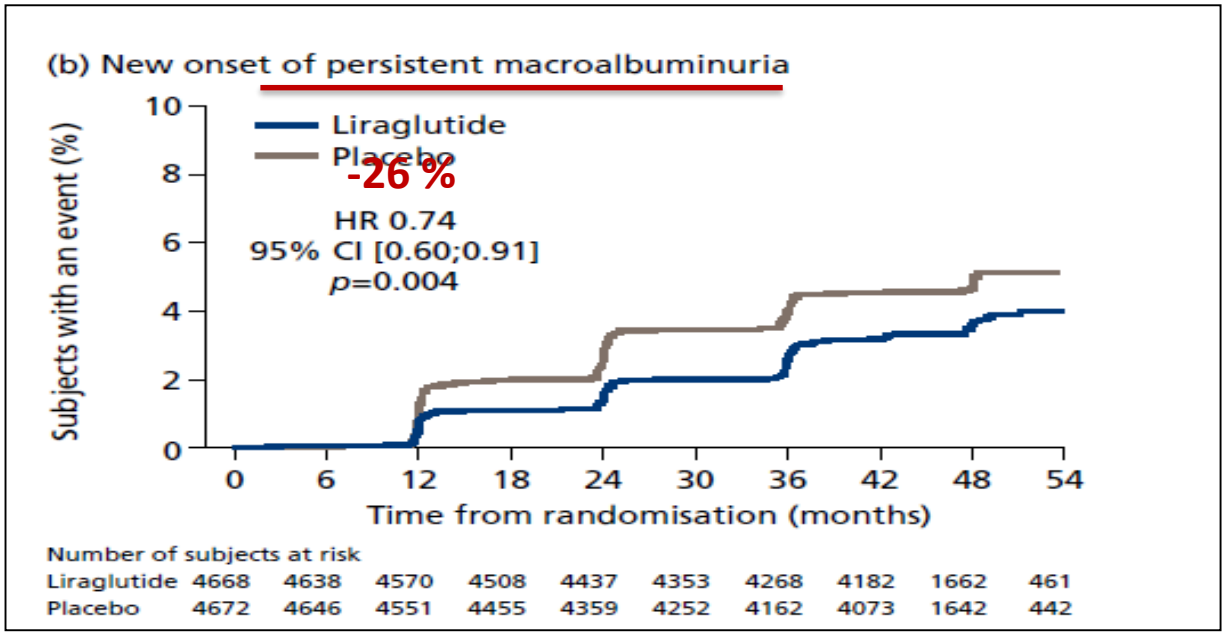
*and eGFR ≤45 mL/min/1.73 m^2 per MDRD

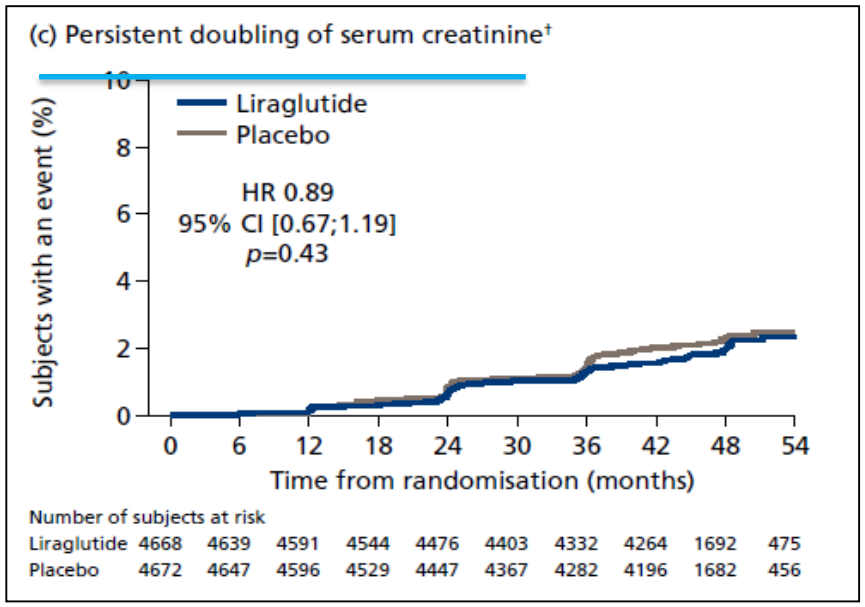
The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months.

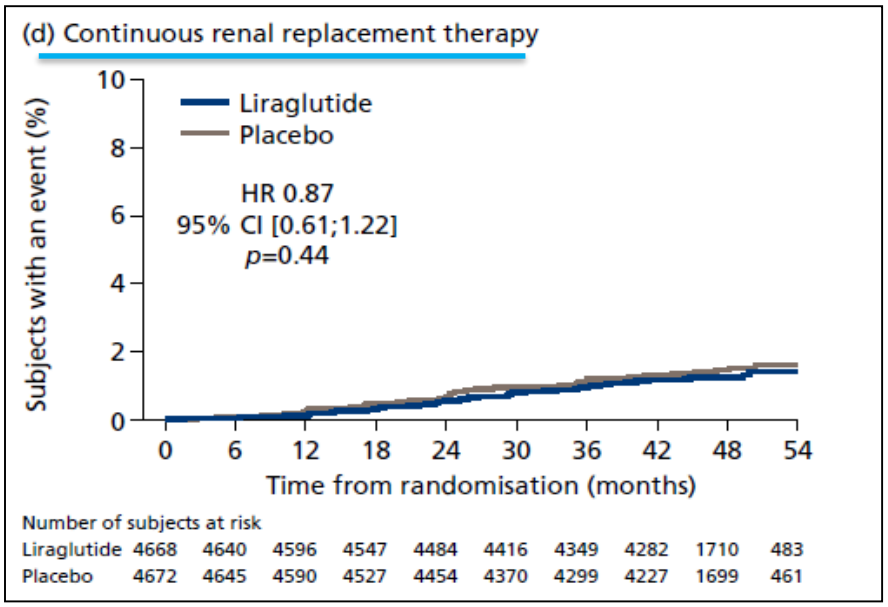
CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

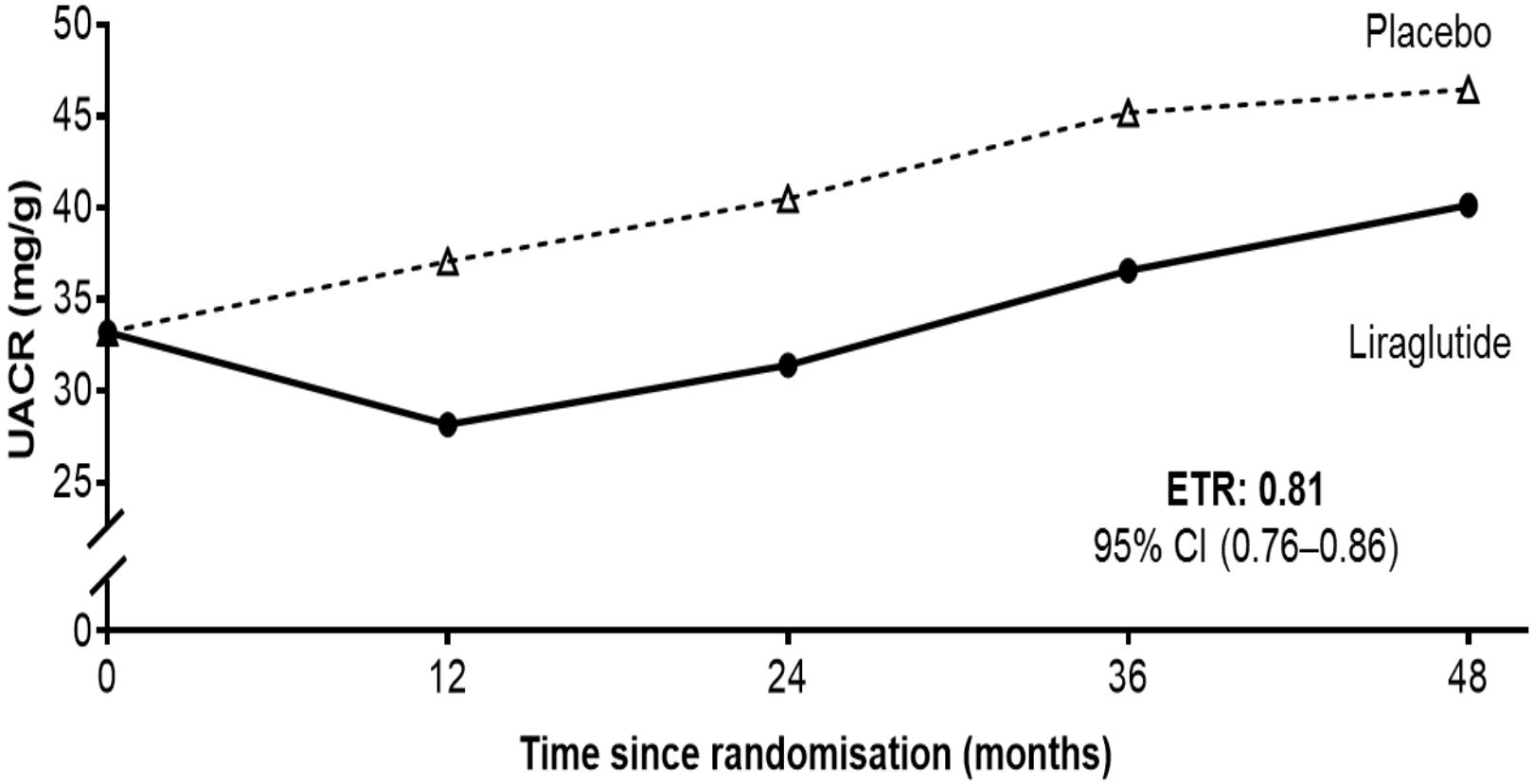
Studio LEADER : *Renal Outcomes*







Urinary albumin–creatinine ratio over time



Values below LLOQ not included (app. 20% of total)

Full analysis set. Estimated geometric means.

ETR: estimated treatment ratio; LLOQ: lower limit of quantification; UACR: urinary albumin-creatinine ratio

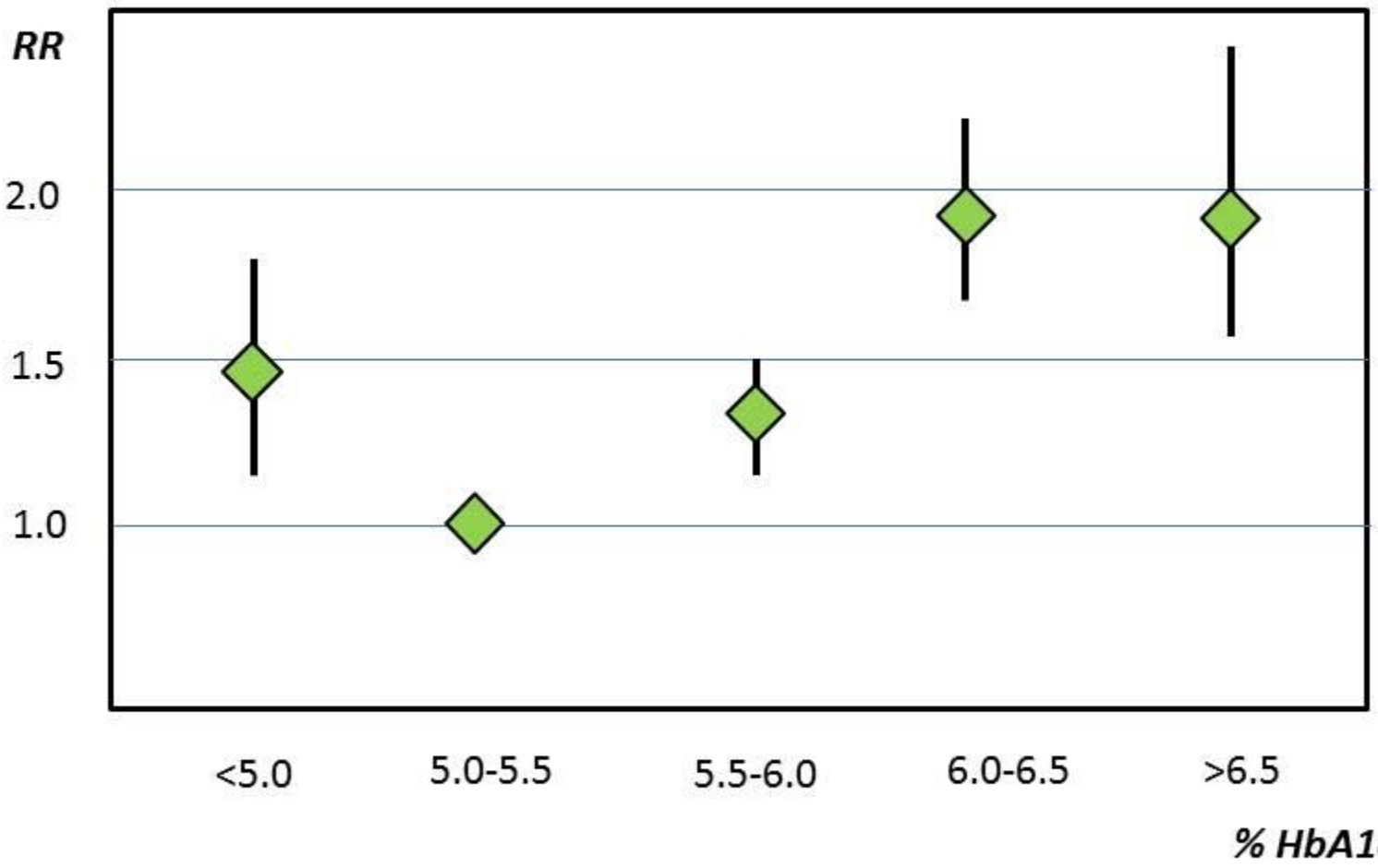
Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Potenziali meccanismi alla base del beneficio CVD e renale

- ✓ Effetto sulla glicemia
- ✓ Effetto sui fattori di rischio CVD
- ✓ Effetti pleiotropici GLP1RAs mediati da (diversi) recettori

All-cause mortality in population

Relationship with HbA1c



Selvin E et al. *N Engl J Med* 362:800-11, 2012

Comparisons of CVOTs: CVD Risk Factors:

	ELIXA	LEADER	SUSTAIN
	Lixisenatide	Liraglutide	Semaglutide
HbA1c (vs pbo, %)	-0.6	-0.4	-0.8
SBP (vs pbo, mmHg)	-0.8	-1.2	-1.9
BW (vs pbo, Kg)	-0.6	-2.3	-3.5
HR (vs pbo, bpm)	+0.4	+3.0	+2.2
MACE	---	-13%	-26%

Zinman B, et al. *N Engl J Med*. 2015; 373:2117-28.
Marso SP, et al. *N Engl J Med*. 2016; 375:311-22.
Marso SP, Consoli A, et al. *N Engl J Med*. 2016 [Epub ahead of print]

Metabolic and CVD risk factors: Change at 3 years

Outcome	Change from baseline to 36 months		ETD (95% CI)	p-value
	Liraglutide	Placebo		
HbA_{1c}, %	-1.2	-0.8	-0.4 (-0.5 – -0.3)	<0.001
Body weight, kg	-2.7	-0.5	-2.3 (-2.5 – -2.0)	<0.001
Systolic blood pressure, mmHg	-1.5	-0.2	-1.2 (-1.9 – -0.5)	<0.001
Diastolic blood pressure, mmHg	-0.8	-1.4	0.6 (0.2 – 1.0)	0.004
Heart rate, bpm	2.8	-0.2	3.0 (2.5 – 3.4)	<0.001
LDL-cholesterol, mmol/L	-0.039	-0.002	-0.041 (-0.077 – -0.006)	0.02
HDL-cholesterol, mmol/L	0.040	0.031	0.009 (-0.001 – 0.018)	0.07

*Hazard ratios and p-values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate. The p-value is for superiority.
bpm: beats per minute; CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}, glycated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Incidence of Coronary Heart Disease in Type 2 Diabetic Men and Women

Impact of microvascular complications, treatment, and geographic location

ANGELO AVOGARO, MD[1]
CARLO GIORDA, MD[2]
MARINA MAGGINI, PHD[3]
EDOARDO MANNUCCI, MD[4]
ROBERTO RASCHETTI, PHD[3]
FLAVIA LOMBARDO, PHD[3]
STEFANIA SPILA-ALEGIANI, PHD[3]
SALVATORE TURCO, MD[5]
MARIO VELUSSI, MD[6]
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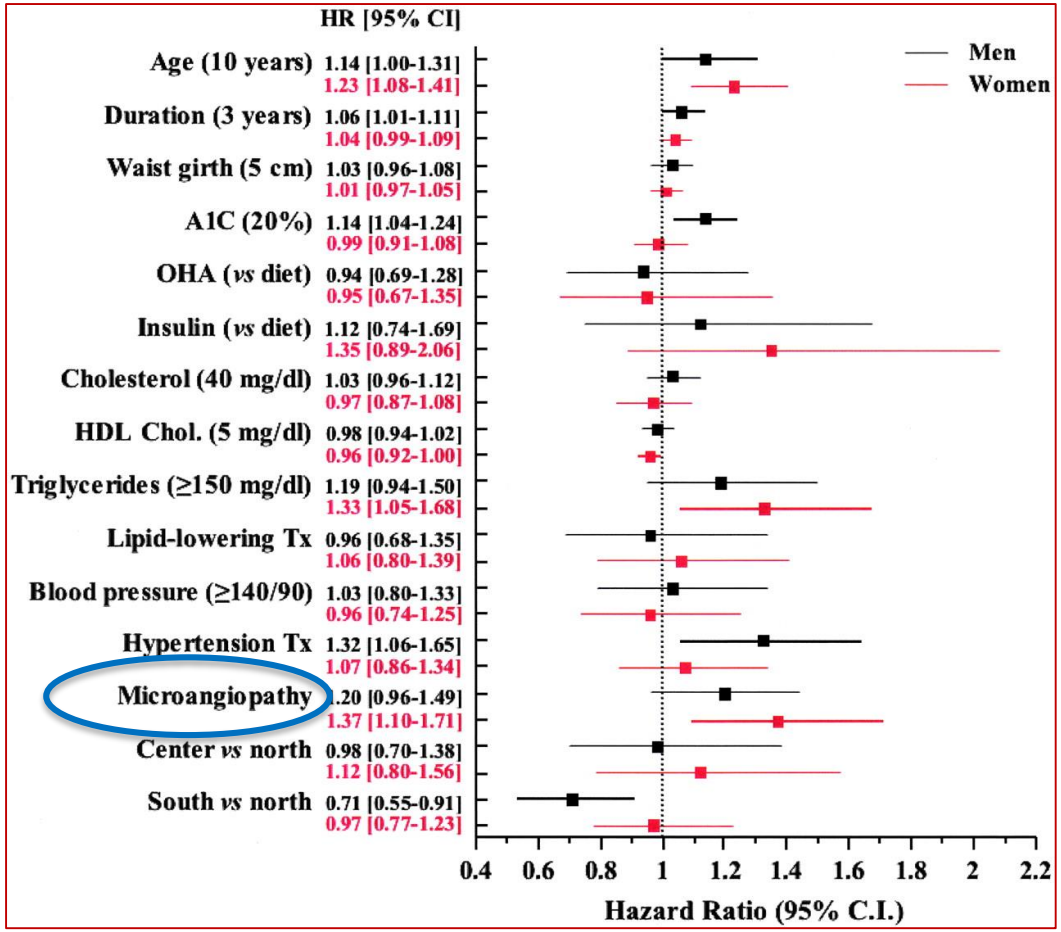
FOR THE DIABETES AND INFORMATICS STUDY GROUP, ASSOCIATION OF CLINICAL DIABETOLOGISTS, ISTITUTO SUPERIORE DI SANITÀ

Diabetes is estimated to be responsible for 5.2% of all deaths (1). Since the Framingham Study (2), epidemiology has consistently shown that diabetes confers an increased risk for coronary heart disease (CHD) and cardiac mortality (3–6). Salient features of this association are the following: *1*) relative



Independent predictors of incident CHD in diabetic men (black) and women (red).

American Diabetes Association.

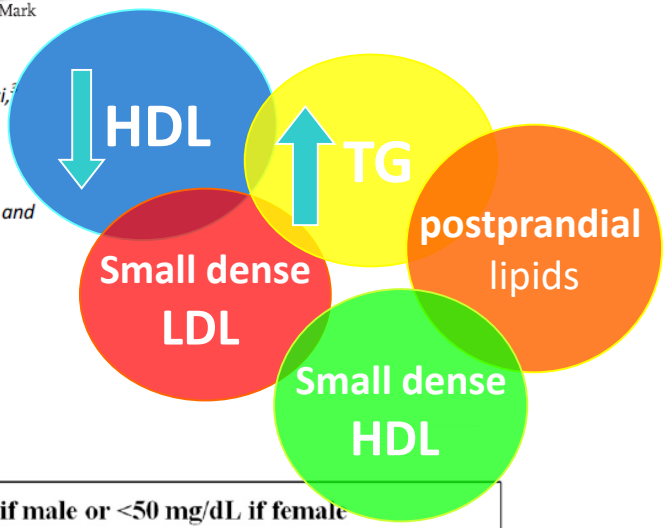
Diabetes Care 30:1241–1247, 2007

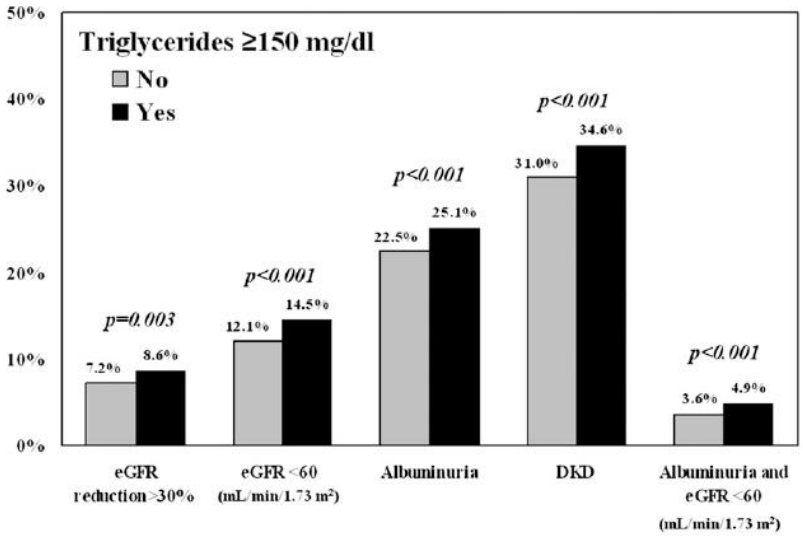
Diabetes Care Volume 39, December 2016

Plasma Triglycerides and HDL-C Levels Predict the Development of Diabetic Kidney Disease in Subjects With Type 2 Diabetes: The AMD Annals Initiative

Giuseppina T. Russo,[1] Salvatore De Cosmo,[2] Francesca Viazzi,[3] Antonio Pacilli,[2] Antonio Ceriello,[4,5] Stefano Genovese,[5] Pietro Guida,[6] Carlo Giorda,[7] Domenico Cucinotta,[1] Roberto Pontremoli,[3] Paola Fioretto,[8] and the AMD-Annals Study Group

Diabetes Care 2016;39:1–10 | DOI: 10.2337/dc16-1246





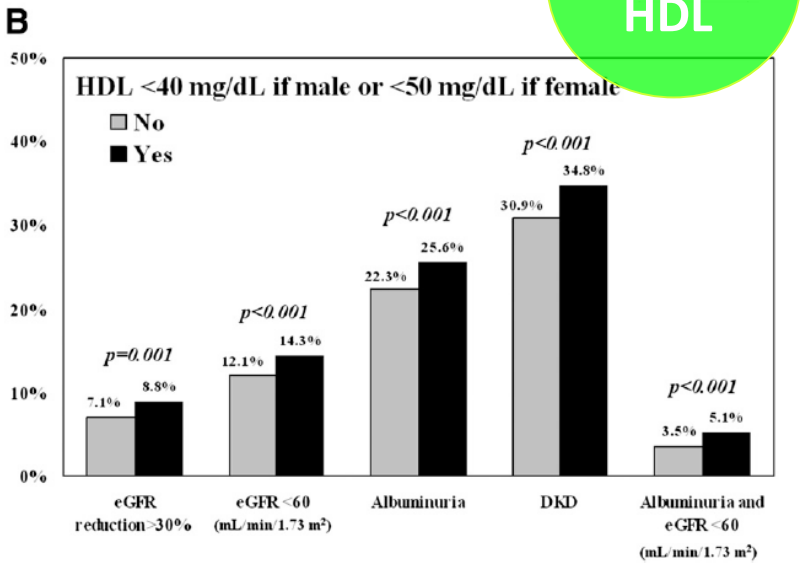
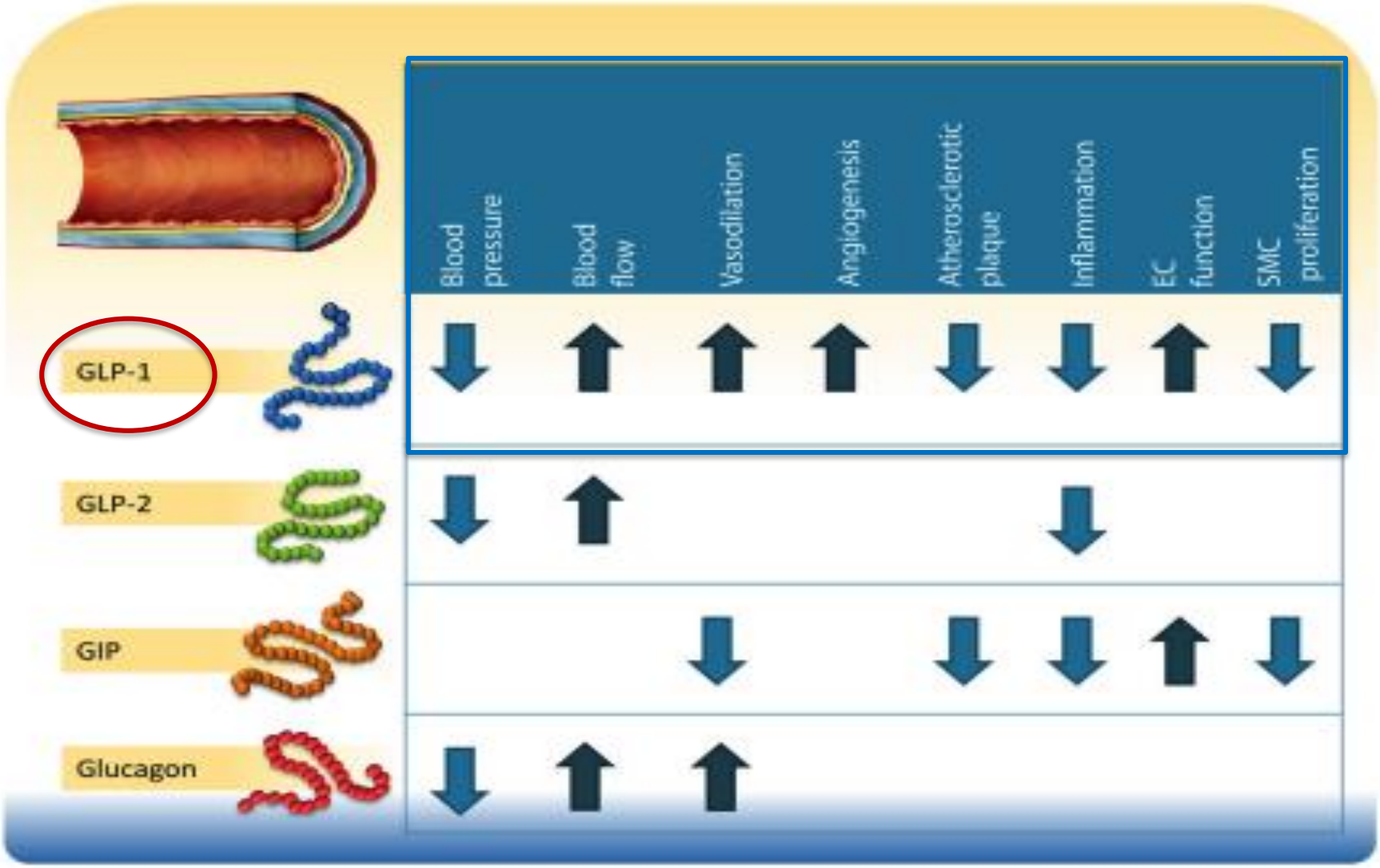


Figure 1—*A*: DKD incidence according to baseline TG ≥150 mg/dL. *B*: DKD incidence according to baseline HDL-C (<40 mg/dL in men; <50 mg/dL in women).

Potenziali meccanismi alla base della protezione cardio-renale con GLP1Ras



Pujadas et al. End Rev 2016

Rizzo et al. Cardiovasc Diabetol (2016) 15:162
DOI 10.1186/s12933-016-0480-8

Cardiovascular Diabetology

NAPOLI, 17-20 maggio 2017
XXI CONGRESSO NAZIONALE AMD

ORIGINAL INVESTIGATION Open Access

Liraglutide improves metabolic parameters and carotid intima-media thickness in diabetic patients with the metabolic syndrome: an 18-month prospective study

Manfredi Rizzo[1,2], Ali A. Rizvi[2†], Angelo Maria Patti[1], Dragana Nikolic[1*†], Rosaria Vincenza Giglio[1], Giuseppa Castellino[1], Giovanni Li Volti[3], Massimiliano Caprio[4,5], Giuseppe Montalto[1,6], Vincenzo Provenzano[7], Stefano Genovese[8] and Antonio Ceriello[8,9]

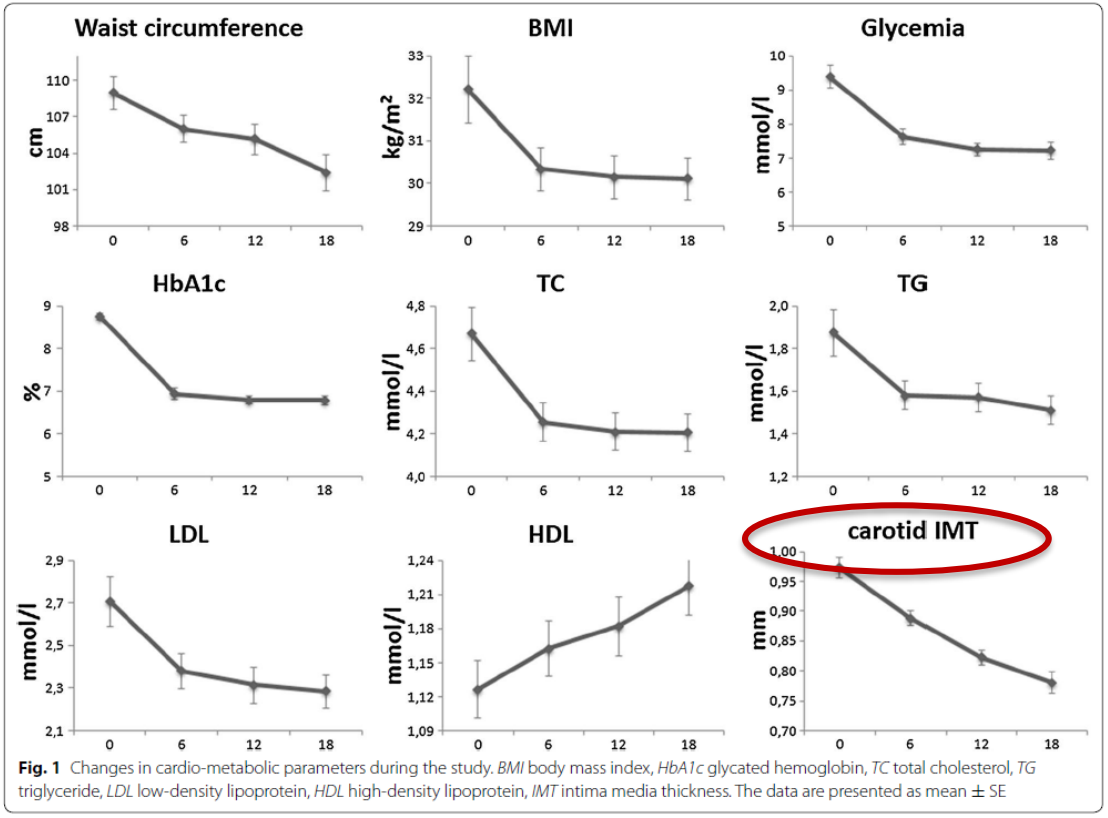


Fig. 1 Changes in cardio-metabolic parameters during the study. *BMI* body mass index, *HbA1c* glycated hemoglobin, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *IMT* intima media thickness. The data are presented as mean ± SE

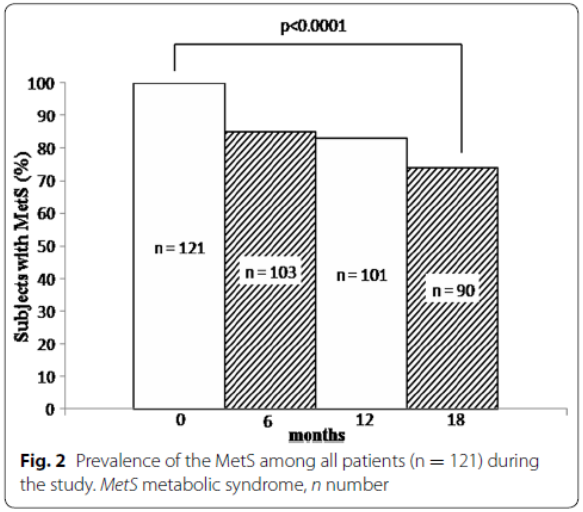


Fig. 2 Prevalence of the MetS among all patients (n = 121) during the study. *MetS* metabolic syndrome, *n* number

MOLECULAR MEDICINE REPORTS 10: 2587-2594, 2014

Liraglutide ameliorates renal injury in streptozotocin-induced diabetic rats by activating endothelial nitric oxide synthase activity via the downregulation of the nuclear factor-κB pathway

SAI-JUN ZHOU[1*], LIAN BAI[1,2*], LIN LV[1], RUI CHEN[1], CHUN-JUN LI[1], XIANG-YANG LIU[1], DE-MIN YU[1] and PEI YU[1]

[1]Department of Diabetic Nephropathy Hemodialysis, 2011 Collaborative Innovation Center of Tianjin for Medical Epigenetics, Key Laboratory of Hormones and Development (Ministry of Health), Metabolic Diseases Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin 300070; [2]Department of Endocrinology, Dongying Municipal Authorities Hospital, Dongying, Shandong 257091, P.R. China

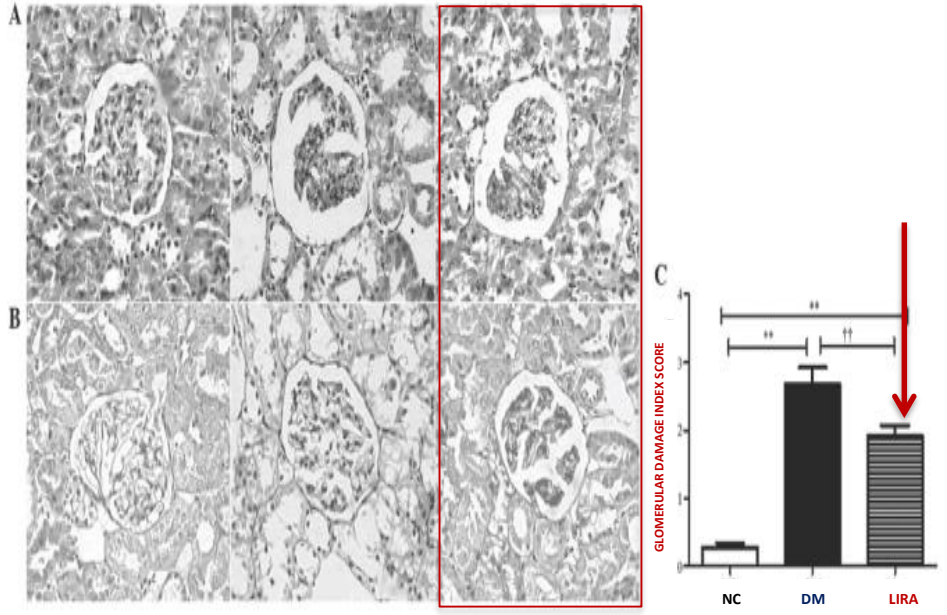


Figure 1. Liragrutide ameliorates histological damage of kidneys in diabetic rats. Representative (A) hematoxylin and eosin staining and (B) PAS staining for histopathological observations of the kidney sections from each group of rats. To semiquantify the damage of kidneys, the GDI was determined. (C) The GDI was calculated for the PAS-stained sections at a magnification of x400 with a score system of 0 to 4: 0 represents no lesion; 1+ represents sclerosis <25%; 2+ represents sclerosis of 25-50% of the glomerus; 3+ represents sclerosis of 50-75% of the glomerus; 4+ represents sclerosis >75%. Values are presented as the mean ± standard deviation (n=6). **P<0.01 vs. the control; ††P<0.01 vs. the DM group. NC, normal control; DM, diabetes mellitus rats induced by injection of streptozotocin; Lira, diabetic rats treated by injection of liragrutide; GDI, glomerular damage index; PAS, periodic acid Schiff base.

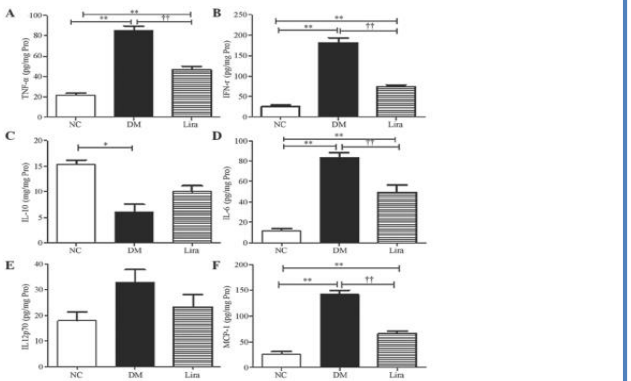
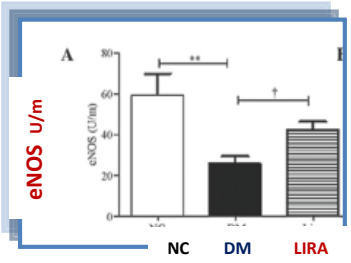


Figure 4. Liragluide downregulated inflammation in diabetic kidney. The protein expression levels of (A) TNF-α, (B) IFN-γ, (C) IL-10, (D) IL-6, (E) IL-12p70 and (F) MCP-1 in diabetic kidneys. Renal tissue was homogenized and the concentrations of inflammatory cytokines were evaluated by an cytometric bead array kit. Values are expressed as the mean ± standard deviation of the data. *P<0.05 and **P<0.01 vs. the control; †P<0.05 and ††P<0.01 vs. DM. DM, diabetes mellitus rats induced by injection of streptozotocin; Lira, diabetic rats treated by injection liragrutide; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; IL, interleukin.



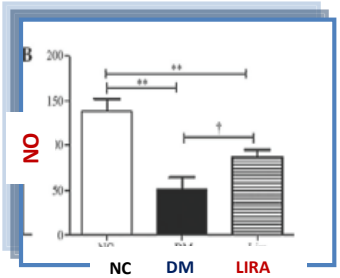
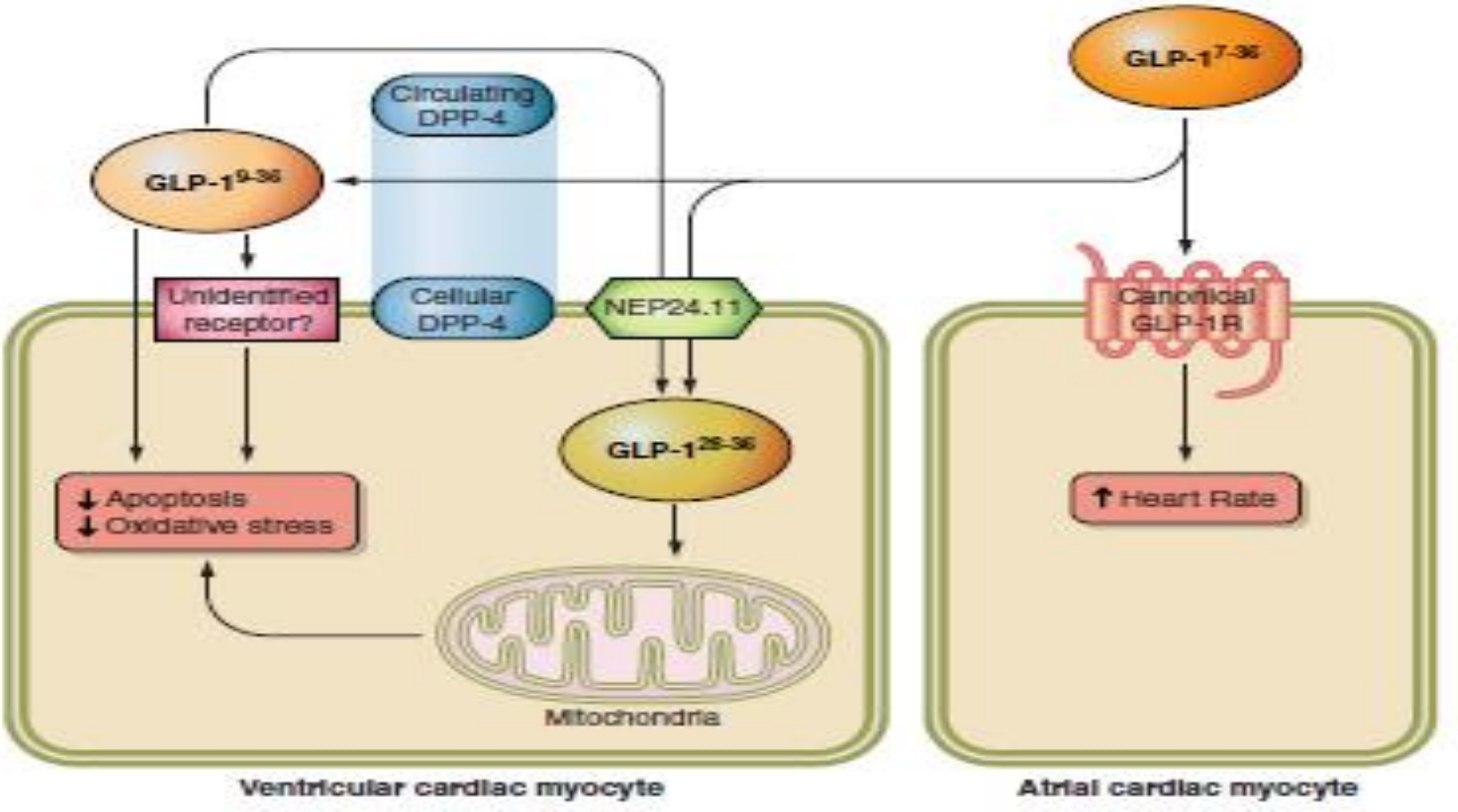


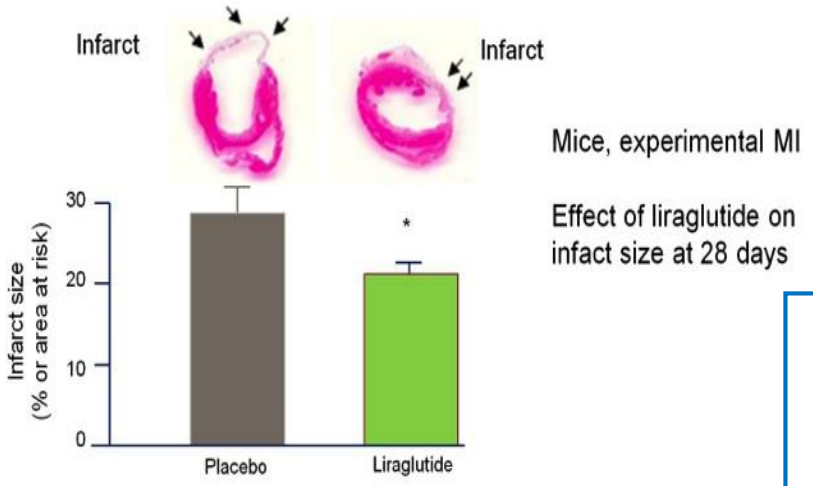
Figure 5. Liraglutide restored the activity of eNOS and the production of NO. (A) the activity of eNOS in kidneys; (B) the production of NO by the kidneys. eNOS activity classifying kit and NO test kit were used to detect the eNOS levels and NO in the glomerular, respectively. Values are expressed as the mean ± standard deviation of the data and demonstrate reduced NO production and decreased eNOS activity in the diabetic rat kidneys, and that Liragrutide restored eNOS activity and NO production. *P<0.01 vs. the control; †P<0.05, P<0.01 vs. DM. DM, diabetes mellitus rats induced by injection of streptozotocin; Lira, diabetic rats treated by injection liragrutide; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

Potential GLP-1-mediated actions in atrial and ventricular cardiac myocytes



Ussher JR, Am J Physiol Heart Circ Physiol. 2014

Effetti del GLP-1 sull'ischemia miocardicardica: *Studi Animali*

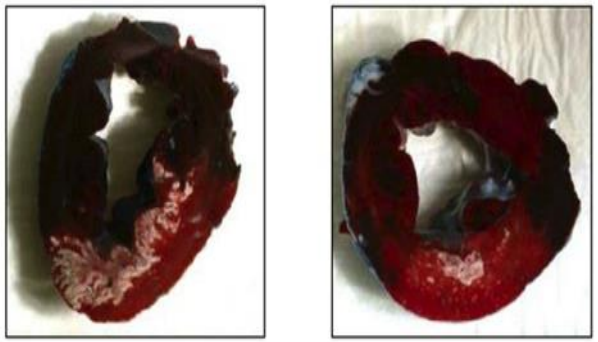


Mice, experimental MI

Effect of liraglutide on infact size at 28 days

Noyan-Ashraf et al. Diabetes 2009;58:975–83

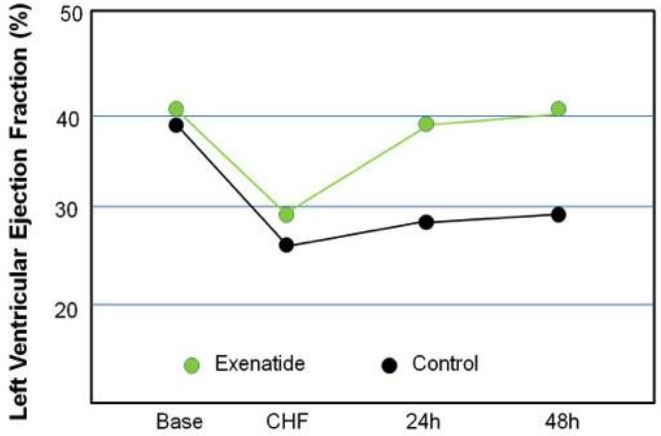
- Porcine model of ischaemia-reperfusion injury; effect of exenatide



PBS Exenatide

Timmers L, *et al. J Am Coll Cardiol* 2009;53;501–10.

Effect of exenatide on cardiac function in dogs with pacing-induced dilated cardiomyopathy

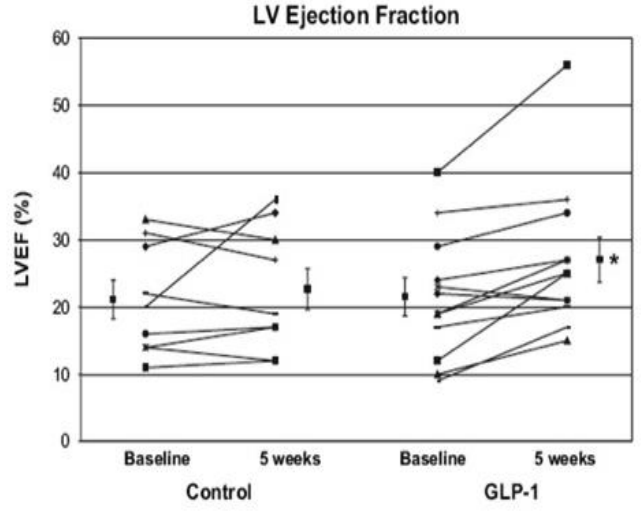


Nikolaidis LA et al. *Circulation* 2004; 110:955-961.

GLP1 e cuore: studi pilota sull'uomo

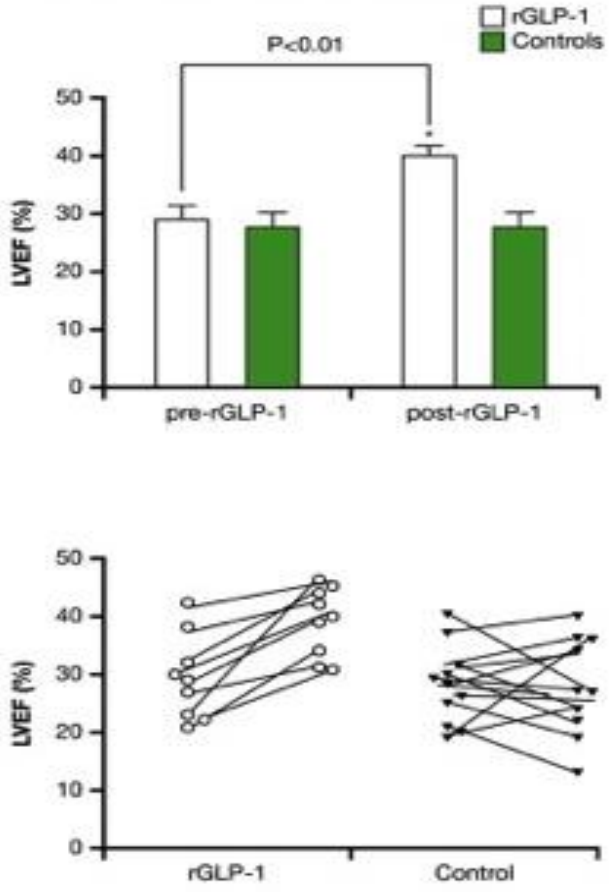
Pazienti non DM2 con scompenso cardiaco: effetti della infusione continua di GLP1

Non-diabetic patients with chronic heart failure
Effects of continuous subcutaneous GLP1 infusion



Sokos GG et al. *J Cardiac Failure* 2006

Pazienti con IMA sottoppsti a PTCA, effetti di 72h di infusione di GLP-1



Nikolaidis LA, *et al. Circulation* 2004;109:962–5.

MEDIA
MeDia 2014;14:62-66
62
SEZIONE DI FORMAZIONE PER L'AUTOVALUTAZIONE
AGGIORNAMENTO

Analoghi del *glucagon-like peptide-1*: cosa ci riserva il futuro

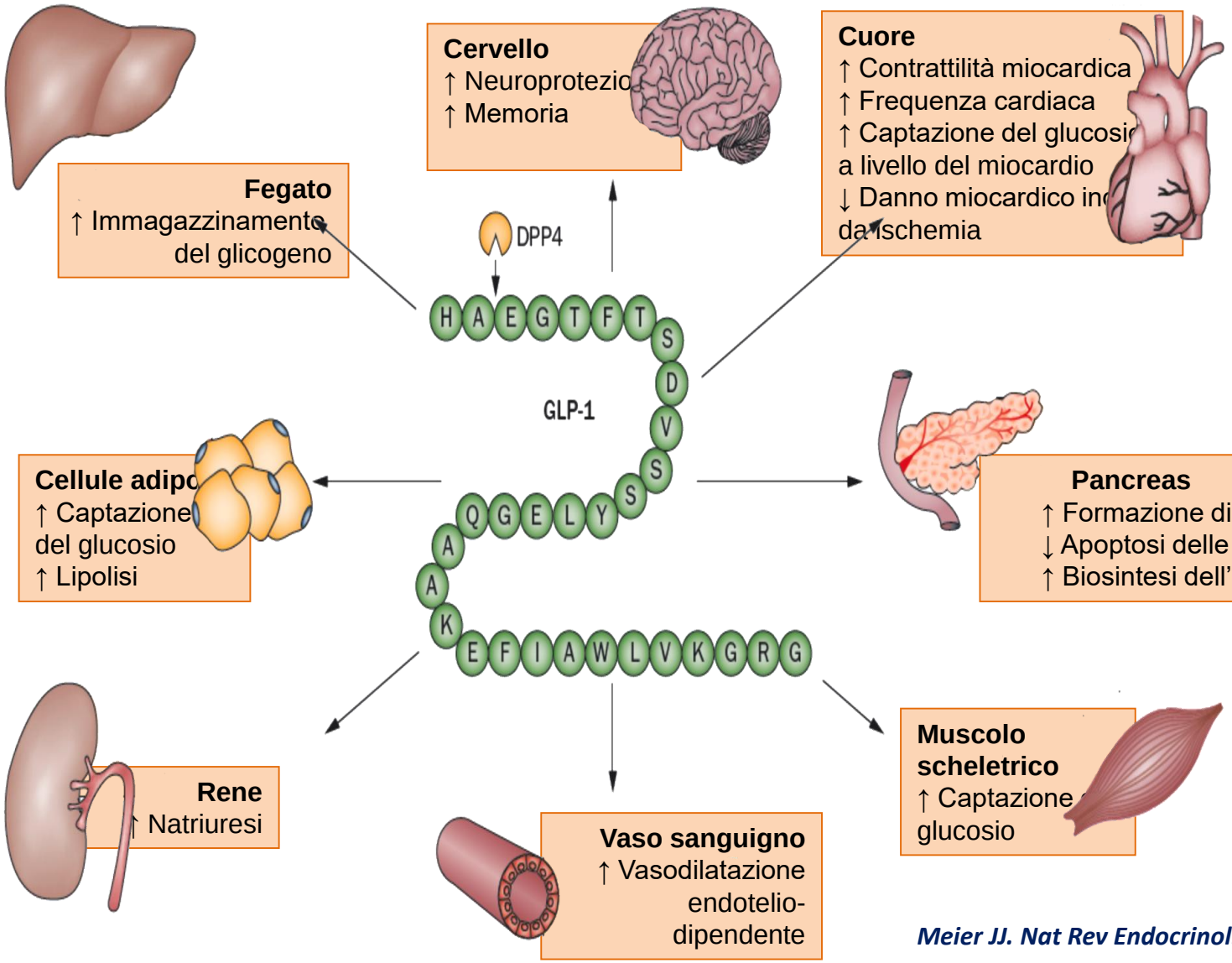
Riassunto

Gli analoghi del GLP-1 rappresentano una valida opzione terapeutica per il trattamento dei pazienti con diabete mellito tipo 2, soprattutto per i vantaggi in termini di efficacia sul controllo glicemico, ridotto rischio di ipoglicemia e per gli effetti sul peso corporeo.
Questa classe di farmaci si sta arricchendo di un numero sempre maggiore di molecole, alcune in fase di prossima introduzione sul mercato e altre in corso di sperimentazione clinica. Il vantaggio di alcune delle nuove formulazioni risiede soprattutto nella lunga emivita rispetto ai primi analoghi introdotti in commercio, caratteristica che rende questa classe di farmaci ancora più flessibile grazie alla possibilità di una somministrazione settimanale.
Oltre agli evidenti benefici sul controllo metabolico e sul raggiungimento dei target glicemici senza aumentare il rischio di ipoglicemia, di notevole interesse sarà inoltre lo studio dei potenziali effetti protettivi di questa classe di farmaci sull'apparato cardiovascolare e sulla funzione beta-cellulare.

Elisabetta L. Romeo
Umberto Alecci
Annalisa Giandalia
Rosalia Zingale
Giuseppa Perdichizzi
Giuseppina T. Russo

Dipartimento di Medicina Clinica e Sperimentale, Università di Messina

GLP-1: Un ampio spettro di azioni biologiche



Meier JJ. Nat Rev Endocrinol. 2012;8:728-42

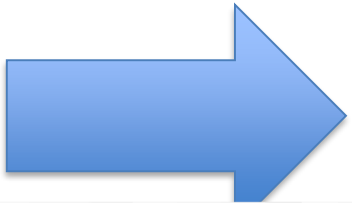
GILA MONSTER

Sino ad oggi i GLP1RAs non hanno deluso le aspettative……

GILA MONSTER

PRINCIPE AZZURRO

Sino ad oggi i GLP1RAs non hanno deluso le aspettative……



GILA M

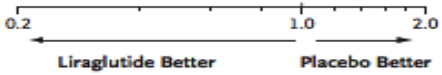
Grazie per l'attenzione

PRINCIPE AZZURRO

Sino ad oggi i GLP1RAs non hanno deluso le aspettative……

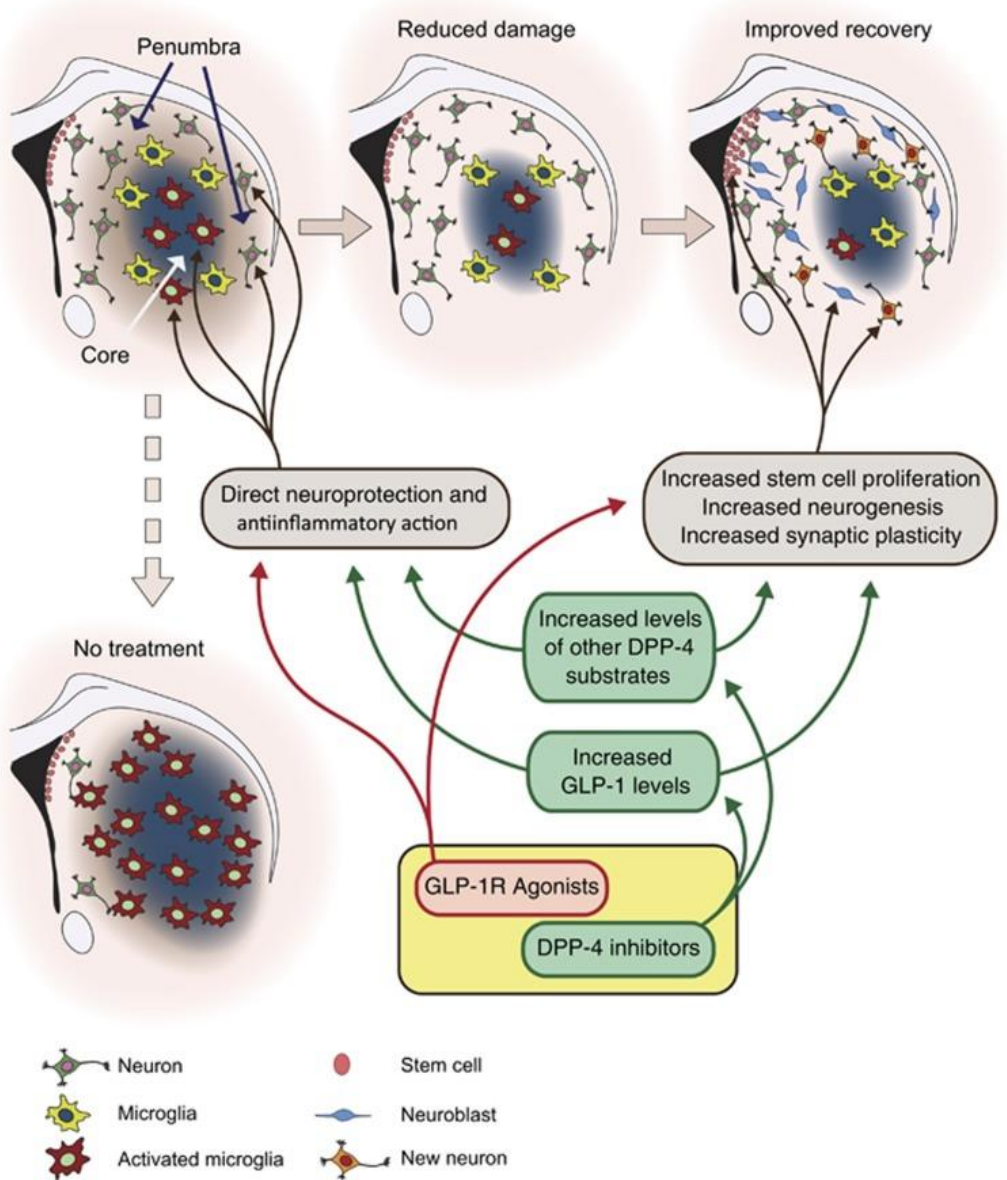
STUDIO LEADER: subgroup analysis

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)	
Sex					0.84
Female	3337	183/1657 (11.0)	209/1680 (12.4)	0.88 (0.72–1.08)	
Male	6003	425/3011 (14.1)	485/2992 (16.2)	0.86 (0.75–0.98)	
Age					0.27
<60 yr	2321	140/1197 (11.7)	166/1124 (14.8)	0.78 (0.62–0.97)	
≥60 yr	7019	468/3471 (13.5)	528/3548 (14.9)	0.90 (0.79–1.02)	
Geographic region					0.20
Europe	3296	207/1639 (12.6)	252/1657 (15.2)	0.82 (0.68–0.98)	
North America	2847	212/1401 (15.1)	216/1446 (14.9)	1.01 (0.84–1.22)	
Asia	711	24/360 (6.7)	37/351 (10.5)	0.62 (0.37–1.04)	
Rest of the world	2486	165/1268 (13.0)	189/1218 (15.5)	0.83 (0.68–1.03)	
Race					0.32
White	7238	494/3616 (13.7)	543/3622 (15.0)	0.90 (0.80–1.02)	
Black	777	47/370 (12.7)	59/407 (14.5)	0.87 (0.59–1.27)	
Asian	936	40/471 (8.5)	56/465 (12.0)	0.70 (0.46–1.04)	
Other	389	27/211 (12.8)	36/178 (20.2)	0.61 (0.37–1.00)	
Ethnic group					0.30
Hispanic	1134	68/580 (11.7)	86/554 (15.5)	0.74 (0.54–1.02)	
Non-Hispanic	8206	540/4088 (13.2)	608/4118 (14.8)	0.89 (0.79–1.00)	
Body-mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	
Duration of diabetes					0.42
≤11 yr	4429	265/2216 (12.0)	316/2213 (14.3)	0.82 (0.70–0.97)	
>11 yr	4892	340/2441 (13.9)	376/2451 (15.3)	0.90 (0.78–1.04)	
Risk of CVD					0.04
≥50 yr of age and established CVD	7598	536/3831 (14.0)	629/3767 (16.7)	0.83 (0.74–0.93)	
≥60 yr of age and risk factors for CVD	1742	72/837 (8.6)	65/905 (7.2)	1.20 (0.86–1.67)	
Chronic heart failure					0.53
Yes	1305	112/653 (17.2)	119/652 (18.3)	0.94 (0.72–1.21)	
No	8035	496/4015 (12.4)	575/4020 (14.3)	0.85 (0.76–0.96)	
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	



Marso et al. 2016

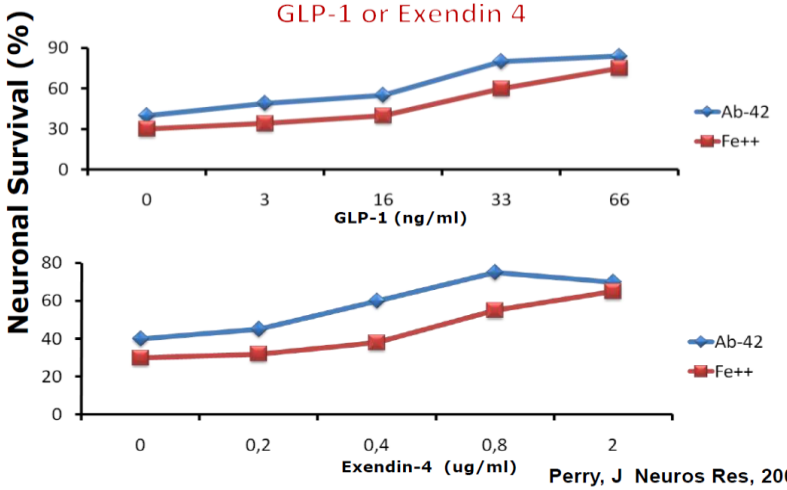
Neuroprotective mechanisms against stroke induced by GLP-1R and DPP-4 inhibitors



Darsalia et al. 2015

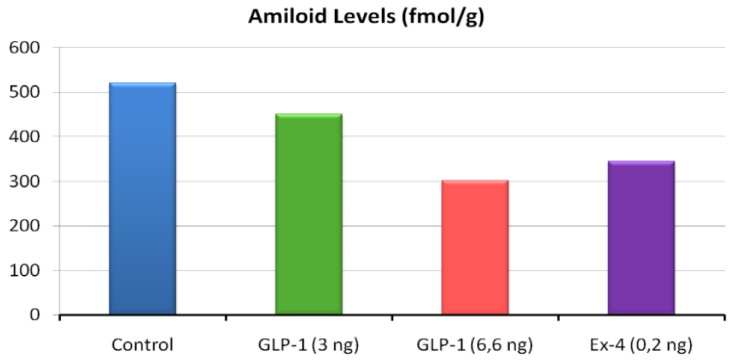
Effetti neuroprotettivi dei GLP1RAs (modelli animali)

Survival of rat hippocampal neurons exposed to β-Amiloid or Fe^{++} in culture when treated with GLP-1 or Exendin 4



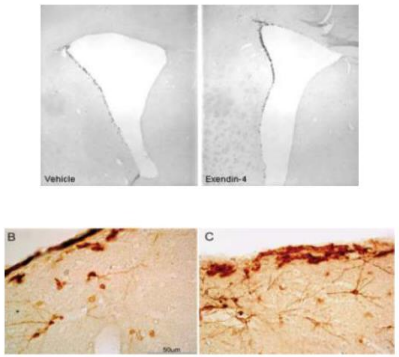
Perry, J Neuros Res, 2003

Effect of ICV infusion of GLP-1 or Exendin-4 on Whole-Brain levels of β-Amiloid in the rat



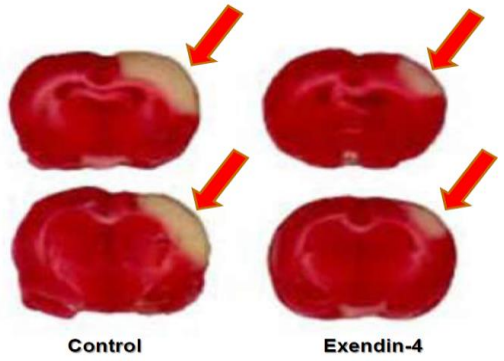
Perry, J Neuros Res, 2003

Exendin-4 Stimulates Subventricular Zone Neurogenesis in an Animal Model of Parkinson's Disease



Bertilsson G, J Neurosc Res 2008, 86:326

Exendin-4 reduces cortical infarction area in an animal model of stroke



Li Y, PNAS 2009, 106:1285

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
REVIEW ARTICLE

Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus

Onno N Groeneveld, L Jaap Kappelle, Geert Jan Biessels*
University Medical Center Utrecht, Brain Center Rudolf Magnus, Department of Neurology, Utrecht, the Netherlands

Studi pilota sull'uomo

Table 3 | Randomized controlled trials on the effect of incretin-based agents on mild cognitive impairment and Alzheimer's disease

Study	Agent	Study population	Endpoint
A pilot study of Exendin-4 in Alzheimer's disease (NCT01255163)	Agent: exendin-4 Comparator: placebo	Phase 2 study Period: 2010–2016 Patients aged ≥60 years (without diabetes), with MCI or early AD	Primary end-point: Safety and tolerability of exendin-4 Secondary end-point: Behavorial and cognitive performance measures Changes on structural and functional MRI and MRS Hormonal and metabolic changes and changes in CSF and plasma AD biomarkers Clinical Dementia Rating ADAS – cognitive subscale
ELAD study (NCT01843075)	Agent: liraglutide Comparator: placebo	Phase 2 study Period: 2014–2017 Patients aged 50–85 years (without diabetes), with AD	Primary end-point: FDG-PET imaging: change in cerebral glucose metabolic rate FDG-PET imaging: change in cerebral glucose metabolic rate from baseline to follow up in the treatment group compared with the placebo group Secondary end-point: Change in *z*-scores for the ADAS Executive, MRI changes, CSF markers, and microglial activation

AD, Alzheimer's disease; ADAS, Alzheimer's Disease Assessment scale; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose-positron emission tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

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NAFLD

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ORIGINAL ARTICLE

Exenatide improves hepatic steatosis by enhancing lipid use in adipose tissue in nondiabetic rats

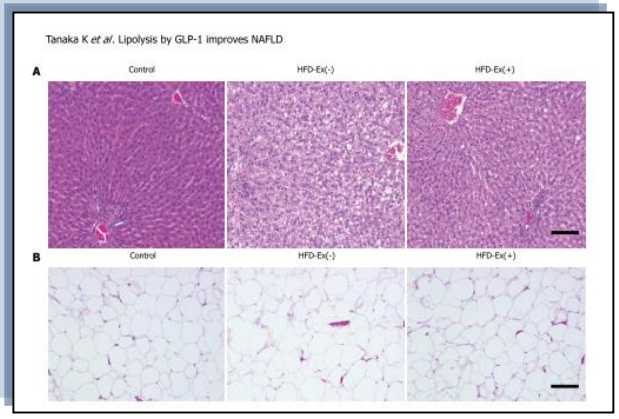

Figure 3 Histological evaluation of lipid accumulation in the liver and adipose tissue. A: Numerous hepatocytes containing lipid droplets were observed in the high-fat diet (HFD)-Ex(-) group, whereas scant lipid-containing hepatocytes were found in the HFD-Ex(+) group; B: In epididymal white adipose tissue, there were abundant enlarged adipocytes in the HFD-Ex(-) group but not in the HFD-Ex(+) group; C: The number of hepatic lipid droplets was significantly decreased in the HFD-Ex(+) group compared with the HFD-Ex(-) group; D: The mean diameter of adipocytes in the HFD-Ex(+) group was significantly smaller than that in the HFD-Ex(-) group and was similar to that in the control group. The fold changes were calculated as the ratio of the average size of adipocytes in the HFD-Ex(+) or HFD-Ex(-) group to that in the control group. $n = 5$, $^aP < 0.05$ between groups. Scale bar = 100 μm. ND: Not detected.

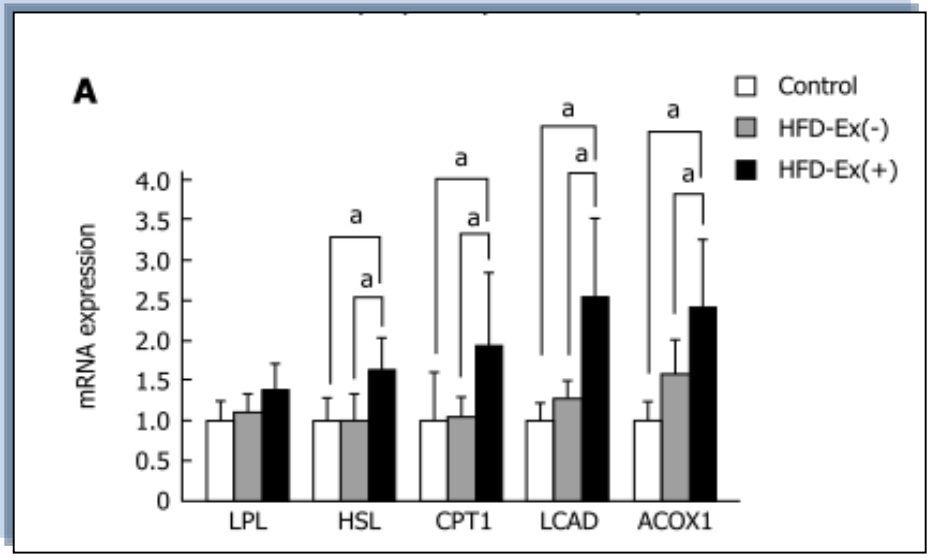

Figure 5 Effects of exenatide on the expression levels of genes associated with lipid metabolism, reactive oxygen species elimination, and macrophage activation in adipose tissue. A: The expression levels of hormone-sensitive lipase (HSL), carnitine palmitoyltransferase-1 (CPT1), long-chain acyl-CoA dehydrogenase (LCAD), and acyl-CoA oxidase 1 (ACOX1) were significantly greater in the high-fat diet (HFD)-Ex(+) group than in the control and HFD-Ex(-) groups; B: The expression levels of catalase and superoxide dismutase (SOD)2 were significantly greater in the HFD-Ex(+) group than in the control and HFD-Ex(-) groups. There were no significant differences in tumor necrosis factor (TNF) or monocyte chemotactic protein 1 (MCP1) expression levels among the three groups. The fold changes were calculated as the ratio of the expression level in the HFD-Ex(+) or HFD-Ex(-) group to that in the control group. $n = 8$, $^aP < 0.05$ between groups.

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DOI: 10.3748/wjg.v20.i23.7356

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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Incretin based therapies: A novel treatment approach for non-alcoholic fatty liver disease

Blaslov K *et al*. Incretins and NAFLD: What do we (not) know?

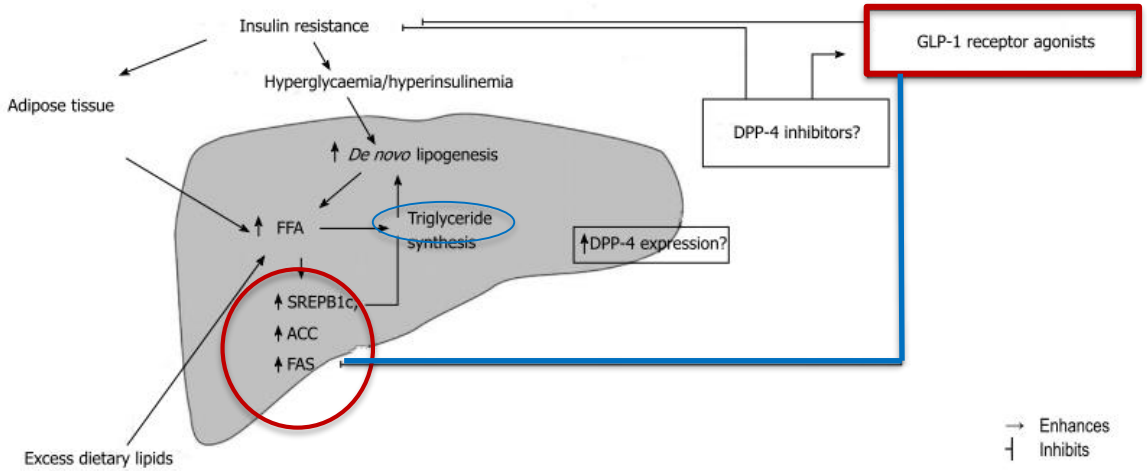

Figure 1 The pathogenesis of non-alcoholic fatty liver disease and the possible effect of incretin system components in treatment. Modified according to Dowman *et al*[63]. ACC: Acetyl-CoA carboxylase; DPP-4: Dipeptydil peptidase-4; GLP-1: Glucagon-like peptide-1; FFA: Free fatty acid; FAS: Fatty acid synthetase; SREPB1c: Sterol regulatory element-binding protein.

ARTICLES
INTEGRATIVE PHYSIOLOGY
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Effects of Combined Exenatide and Pioglitazone Therapy on Hepatic Fat Content in Type 2 Diabetes

Padma Sathyanarayana[1], Medhavi Jogi[1], Raja Muthupillai[2], Ramkumar Krish[illegible]urthy[2], Susan L. Samson[1] and Mandeep Bajaj[1]

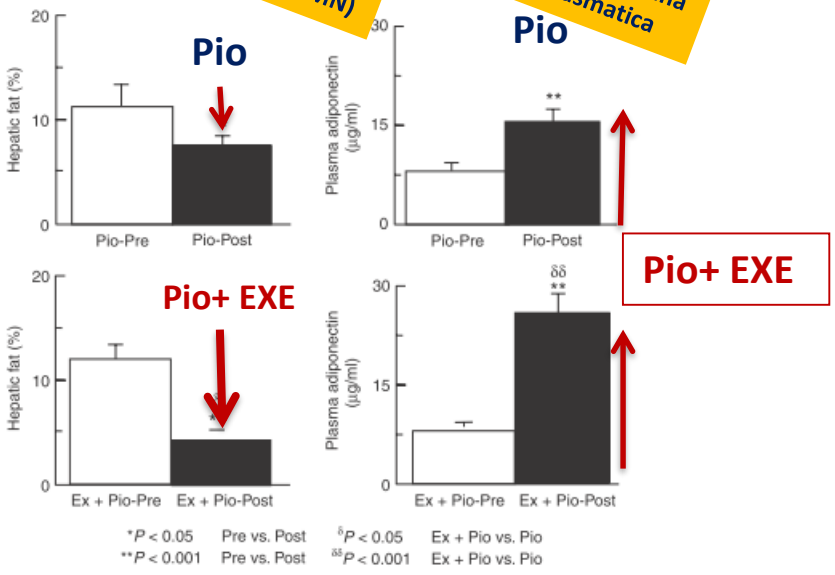
Table 1 Anthropometric and metabolic parameters in 21 T2DM patients at baseline, after 12 months of pioglitazone (*N* = 10) therapy (PIO-POST), and after 12 months of exenatide plus pioglitazone (*N* = 11) combination therapy (PIO + EX-POST)

	PIO-PRE	PIO-POST	PIO + EX-PRE	PIO + EX-POST
Body weight (kg)	93.1 ± 7.5	96.8 ± 7.3*	95.5 ± 5.0	95.7 ± 5.1***
BMI	29.7 ± 1.9	30.9 ± 2.1*	34.1 ± 1.3	34.3 ± 1.5
HbA_{1c} (%)	8.3 ± 0.4	7.3 ± 0.3**	8.1 ± 0.5	6.8 ± 0.4**
Fasting plasma glucose (mg/dl)	197 ± 21	155 ± 17*	167 ± 18	119 ± 11**
Fasting plasma insulin (μU/ml)	13 ± 1	11 ± 1*	15 ± 1	13 ± 1*
Fasting plasma FFA (μmol/l)	487 ± 46	331 ± 30*	603 ± 58	369 ± 42**
Total cholesterol (mg/dl)	176 ± 9	181 ± 11	189 ± 14	175 ± 11
LDL cholesterol (mg/dl)	96 ± 7	101 ± 10	118 ± 10	111 ± 9
HDL cholesterol (mg/dl)	44 ± 2	48 ± 3	48 ± 3	54 ± 4*
Triglycerides (mg/dl)	192 ± 25	165 ± 19*	136 ± 13	85 ± 7**,†
ALT (U/l)	25 ± 2	19 ± 2*	35 ± 6	18 ± 2**,***
AST (U/l)	20 ± 2	16 ± 2*	25 ± 5	16 ± 1*

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFA, free fatty acid; HDL, high-density lipoprotein; HbA_{1c}, hemoglobin A_{1c}; LDL, low-density lipoprotein; T2DM, type 2 diabetes.
*$P < 0.05$ vs. PRE. **$P < 0.01$ vs. PRE. ***$P < 0.05$ vs. PIO, change from baseline. †$P < 0.01$ vs. PIO, change from baseline.

Hepatic fat content (RMN)

Adiponectina plasmatica



Pio+ EXE

British Journal of Clinical Pharmacology
DOI:10.1111/bcp.12777

Glucagon-like peptide-1 (GLP-1) receptor agonists: potential to reduce fracture risk in diabetic patients?

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Keywords
bone mineral density, bone quality

Potenziali effetti sull'osso

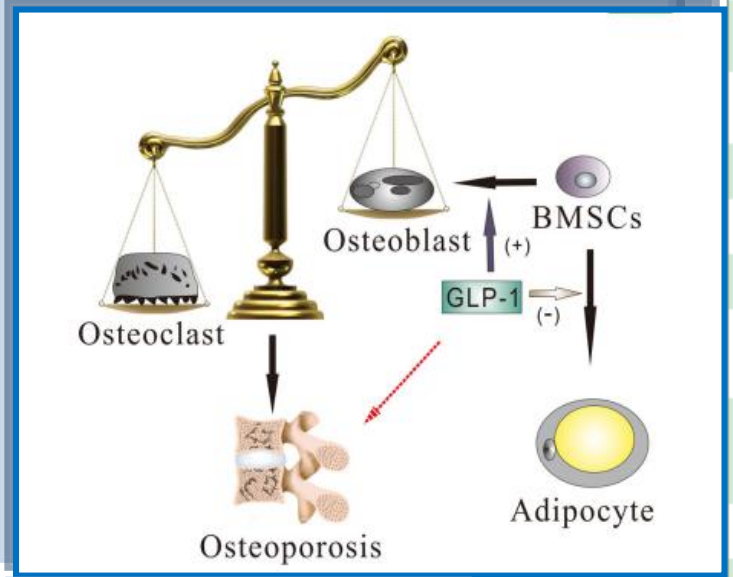

Figure 1
Model for the influence of GLP-1 on osteogenesis. Bone homeostasis is regulated by the balance between osteoblastic bone formation and osteoclastic bone resorption. An imbalance between these two factors will lead to osteoporosis. GLP-1 not only inhibits adipocyte differentiation from BMSCs, but also inhibits osteoblast differentiation, and thus improves bone metabolism. GLP-1 glucagon-like peptide-1; BMSCs bone mesenchymal precursor cells

Table 1
Published molecular and pre-clinical studies on the association between GLP-1 and bone metabolism

Author *et al.*	Study subject	Study method	Main result
Yamada [49]	GLP-1R knockout mice, bone marrow cells and osteoblasts	Exendin-4 and calcitonin treatment	GLP-1R knockout mice have cortical osteopenia and bone fragility as well as increased osteoclastic numbers and bone resorption activity and reduced levels of calcitonin mRNA transcripts in the thyroid. Exendin-4 increased calcitonin gene expression in the thyroid of mice
Mabilleau [50]	Male GLP-1R knockout mice	Analyze the presentation of GLP-1R knockout mice	GLP-1R knockout mice presented with a significant reduction in ultimate load, yield load, stiffness, cortical thickness, bone outer diameter and the maturity of the collagen matrix. But the mineral quantity and quality did not change significantly
Ma [51]	Old ovariectomy rats	Exendin-4 administration lasted for 16 weeks	Exendin-4 not only inhibited bone resorption by increasing the OPG : RANKL ratio, but also promoted bone formation by increasing the expression of OC and Runx2 in old ovariectomy rats
Nuche-Berenguer [52]	Streptozotocin-induced type 2 diabetic rats, fructose-induced insulin-resistant rats	Continuous infusion of GLP-1 for 3 days	GLP-1 increased OC and OPG in type 2 diabetic, insulin-resistant rats and RANKL in type 2 diabetic rats. GLP-1 induced an insulin- and PTH- independent bone anabolic action in insulin-resistant and type 2 diabetic rats
Nuche-Berenguer [53]	Hyperlipidic rats	Continuous infusion of GLP-1 and exendin-4 for 3 days	GLP-1 and exendin-4 similarly reversed the decreased femoral and vertebral bone mass by increasing OC gene expression and the OPG : RANKL ratio in hyperlipidic rats
Sanz [57]	hMSCs	Intervention with GLP-1 in cell proliferation and cell differentiation	GLP-1 significantly reduced the expression of PPARγ, C/EBPα, and LPL and prevented cell differentiation into adipocytes in hMSCs
Nuche-Berenguer [66]	Osteoblastic MC3T3-E1 cells	Analysis of GLP-1 binding and cross-linking studies	GLP-1 can directly and functionally interact with osteoblastic cells independent of the cAMP-linked GLP-1 receptor, possibly through a GPMPG-coupled receptor
Kim [78]	Type 2 diabetic OLETF rats, osteocyte-like MLO-Y4 cells and osteocytes of rat femurs	Investigated the presence of GLP-1 receptors and the effect of exendin-4 treatment through RT-PCR, Western blot and confocal microscopy	GLP-1 receptor was present on MLO-Y4 cells and osteocytes of rat femurs. Exendin-4 reduced the levels of SOST/sclerost in MLO-Y4 cells. Besides, exendin-4 reduced serum levels of SOST, increased serum levels of osteocalcin and femoral BMD in type 2 diabetic OLETF rats
Gier [88]	Thyroid tissue samples with medullary thyroid carcinoma, C cell hyperplasia, papillary thyroid carcinoma, and normal human thyroid	Immunofluorescence for expression of calcitonin and GLP-1 receptors	The neoplastic and hyperplastic lesions of thyroid C cells express the GLP-1 receptor and GLP-1 receptor expression is also detected in 18% of papillary thyroid carcinomas and in C cells in 33% of control thyroid lobes in humans
Hegedus [89]	T2DM or non-diabetic obese patients receiving liraglutide treatment	CT concentrations were measured at 3-month intervals for no more than 2 years	No significant change.
Bjerre [90]	The thyroid of mice, rats, cynomolgus monkeys and humans	The activation of the thyroid GLP-1 receptor with GLP-1 RA	GLP-1 RA stimulated calcitonin release, up-regulation of calcitonin gene expression and subsequently C-cell hyperplasia in rats. In contrast, humans and/or cynomolgus monkeys had low GLP-1 receptor expression in thyroid C-cells and GLP-1 RA did not activate adenylate cyclase or generate calcitonin release in primates

Appropriate hypoglycaemic treatment according to patient clinical characteristic and lifestyle

Glucose Control	Lifestyle/Frailty/ Hypoglycaemia	BMI / Waist	Co-morbidities	Long-term complications
HbA1c ✓ FBG ✓ PPG ✓ Durability ✓ Hypoglycaemia ✓	Age Sex Ethnic group Diabetes duration ✓ Others	Normal ✓ Obesity ✓ Sarcopeny	Hypertension ✓ Dyslipidemia ✓ Osteoporosis ✓ Cancer NAFLD/ Liver ✓ Respiratory Neurological ✓ disorders Others	CVD ✓ DKD ✓ Neuropathy Retinopathy