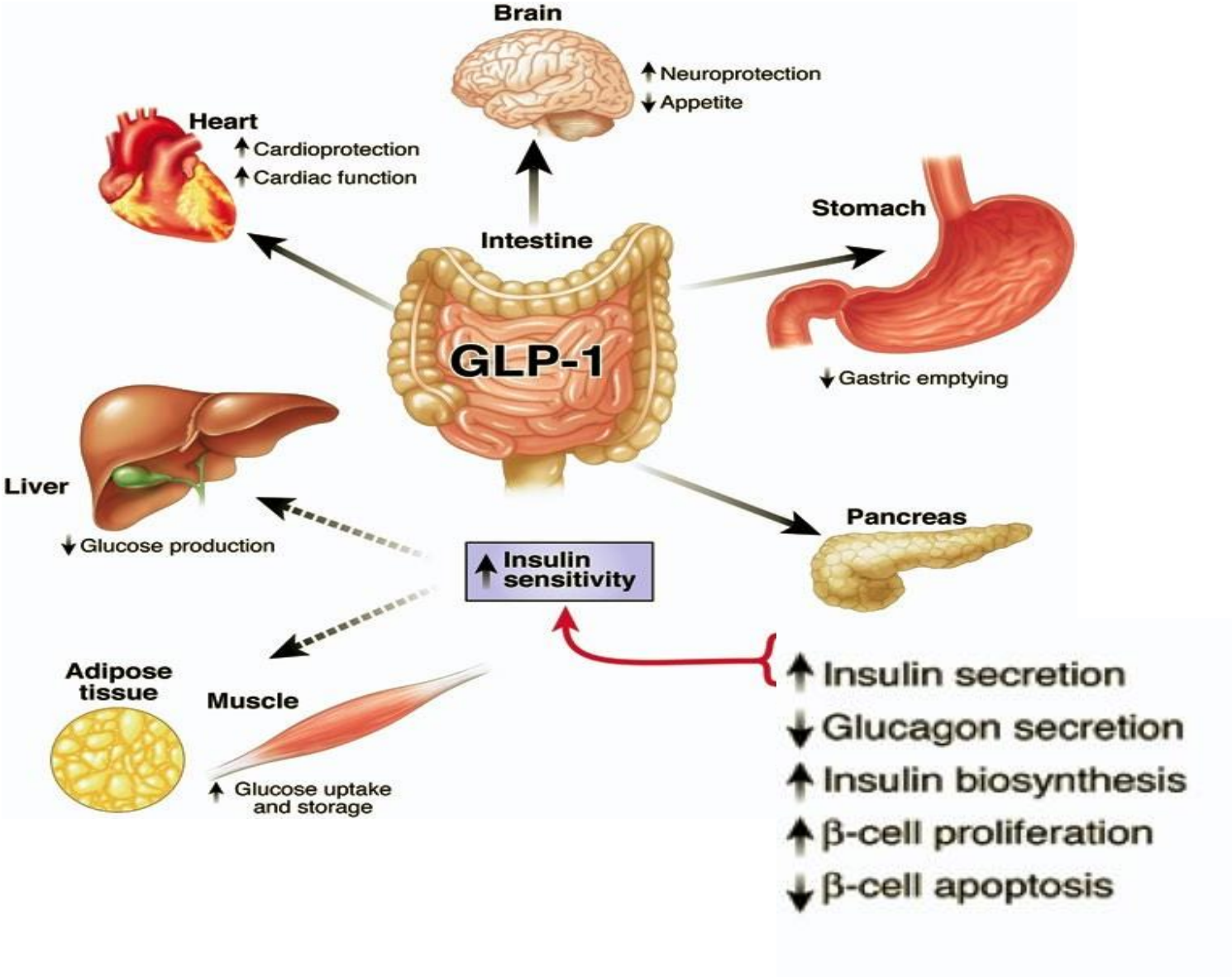
ACCADEMIA di
ALTA FORMAZIONE CLINICA
per MEDICI del TERRITORIO

MILANO | 2023

20 maggio

aGlp1

Gli ormoni gastrointestinali hanno cambiato il punto di vista del diabete



INCRETIN

Mucosa intestinale conteneva ormoni

Ormoni intestinali=incretine

Incretine come cura per il Diabete

1902 — 1932 — 1935 — 1960 — 1986 — 1992

Bayliss & Starling

La Barre

Heller H

Possibilita' di dosare Insulina nel sangue

EFFETTO INCRETINICO

Nauck MA et al. (1986): JCEM; 63: 492-498.

INCRETIN

INTESTINE

SECRETION

INSULIN

Dr. Jean La Barre (1932): Bull. Acad. R. Belg. 12: 620-634

INCRETIN

IN

CRET

IN

Dr. Jean La Barre (1932): Bull. Acad. R. Belg. 12: 620-634

INCRETINE

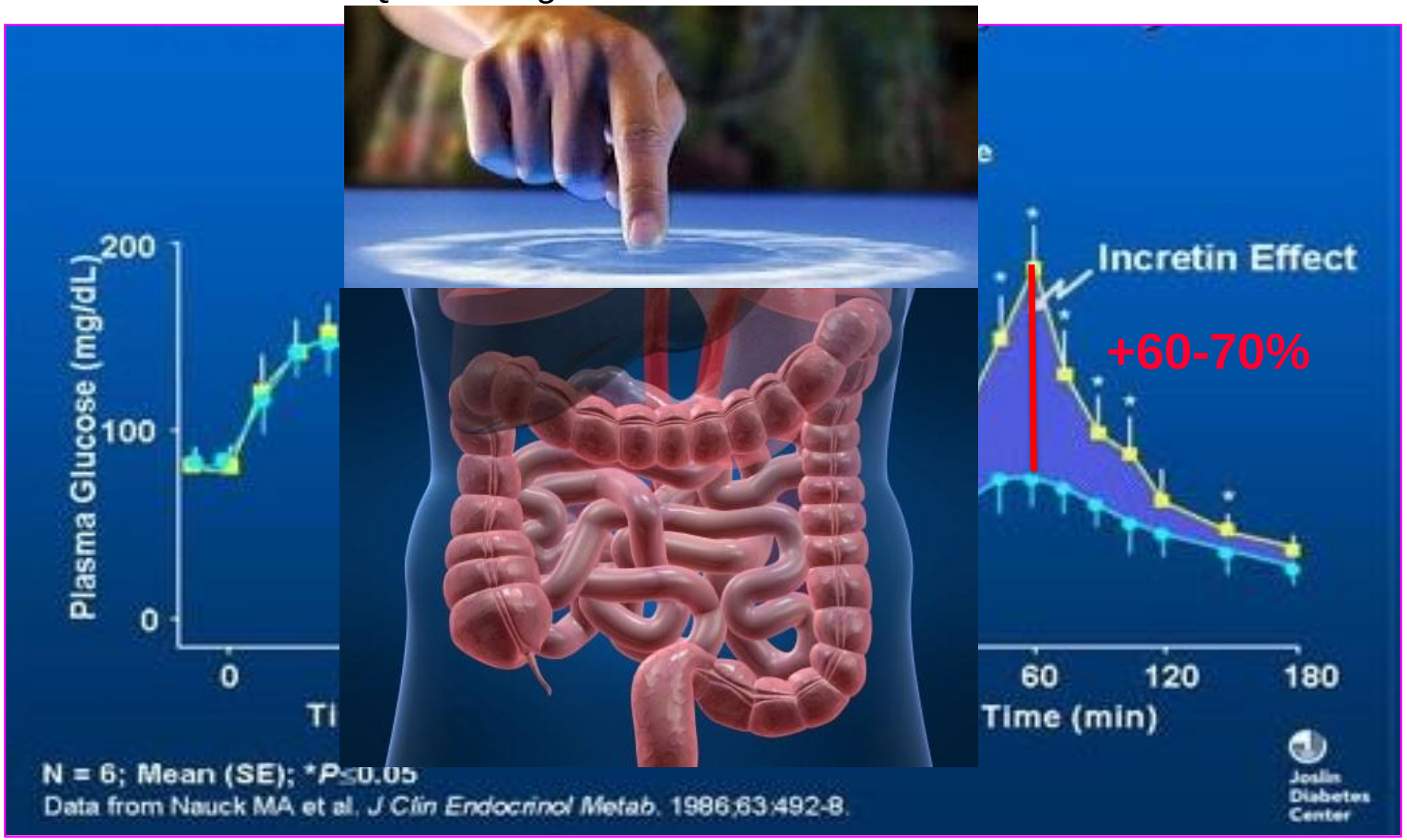
GIP: secreto dalle cellule K dell'intestino prossimale. I diabetici sono resistenti alla sua azione (alti livelli plasmatici). Opzione terapeutica poco attraente

GLP1: peptide di 30 aa secreto dalle cellule L intestinali (ileo e colon)

GLP1R presenti nelle isole pancreatiche, nel SNC e in altri organi

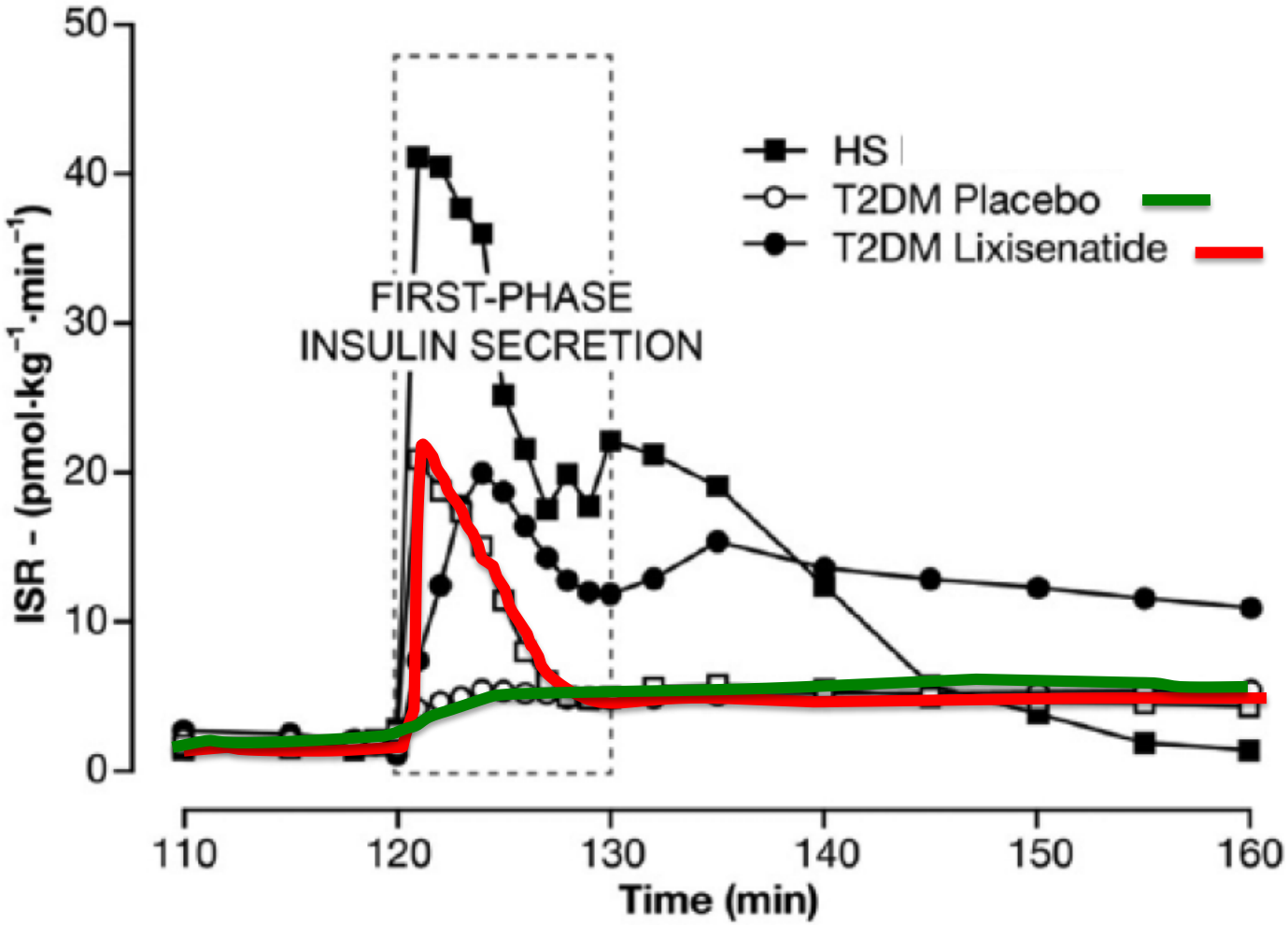
Effetto incretinico

Quando il glucosio tocca l'intestino



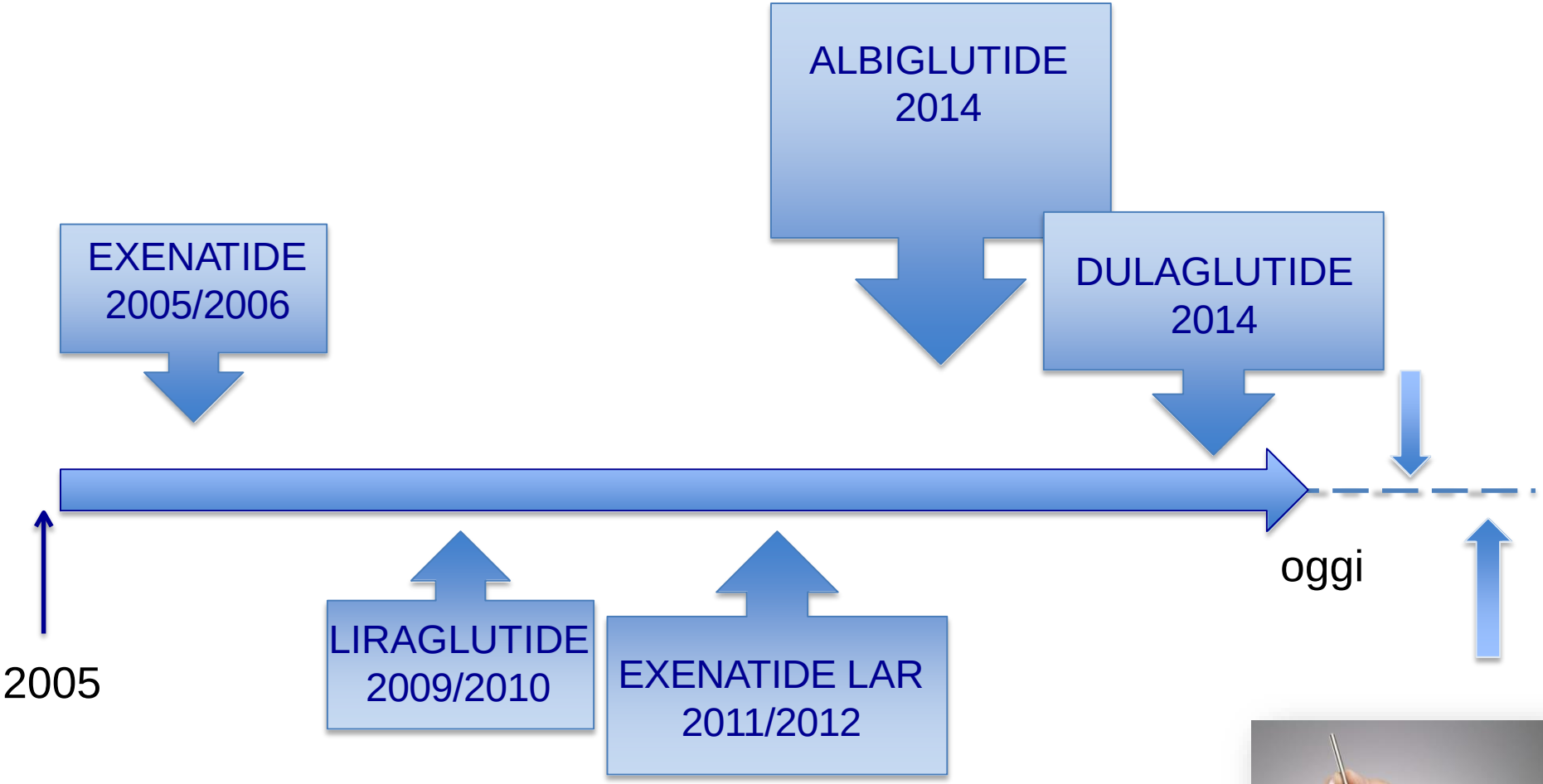
Nauck et al. 1986

I GLP-1 Ra ripristinano la prima fase della secrezione insulinica



Becker et al. 2014

I GLP-1 R agonisti



GLP-1 R analoghi/agonisti

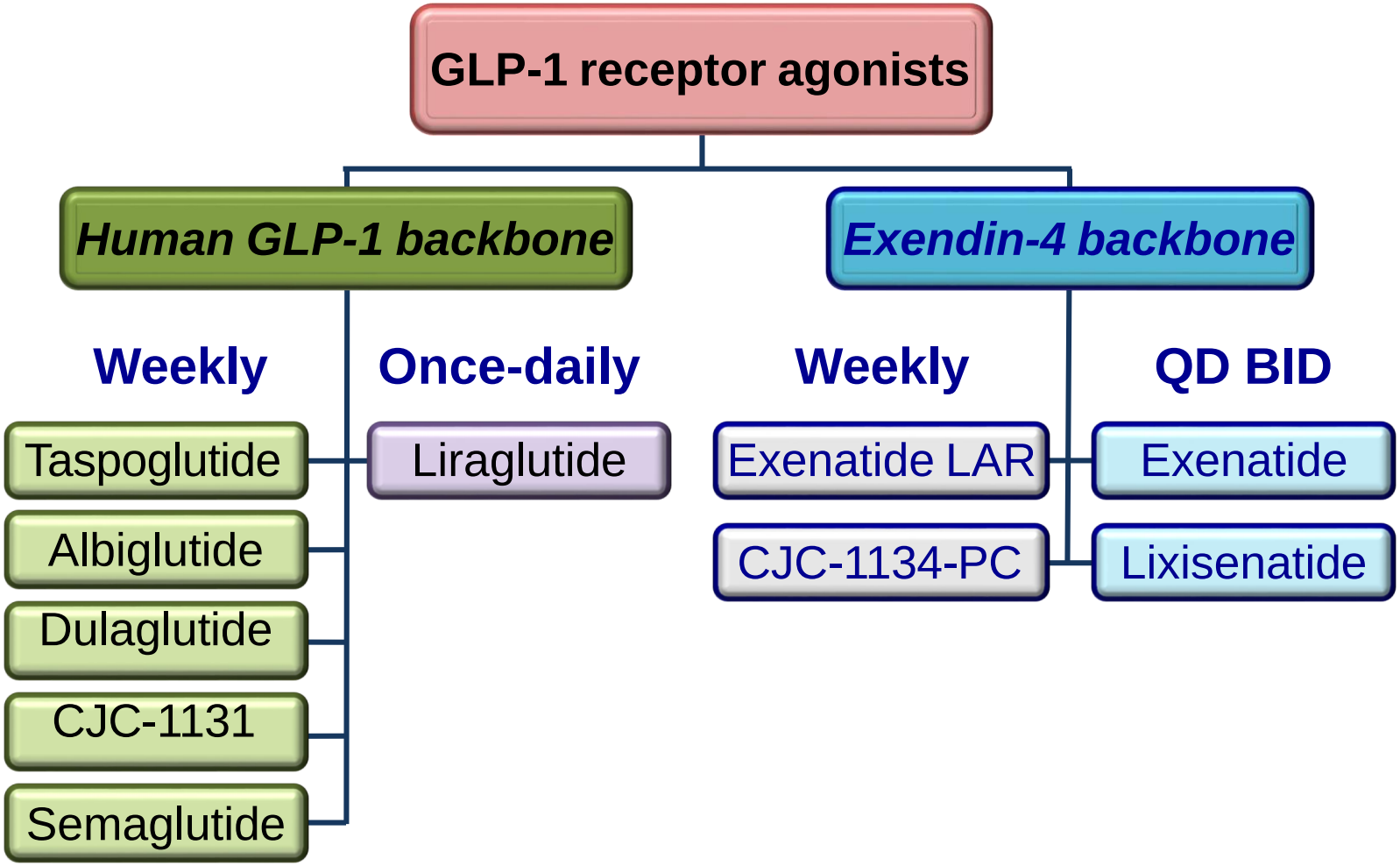
OMOLOGIA CON GLP-1 UMANO → STRUTTURA → DURATA → MECCANISMO D'AZIONE → TEMPO DI AZIONE →

METABOLISMO → ELIMINAZIONE → N. SOMM. → DOSAGGI → DEVICES →

Livelli di evidenza

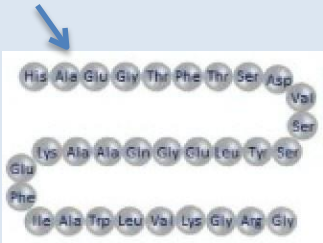
Cosa abbiamo a disposizione*?

*Disponibili o in fase avanzata di studio



modified from: Madsbad S. et al. DOM 2011

I GLP-1 R agonisti

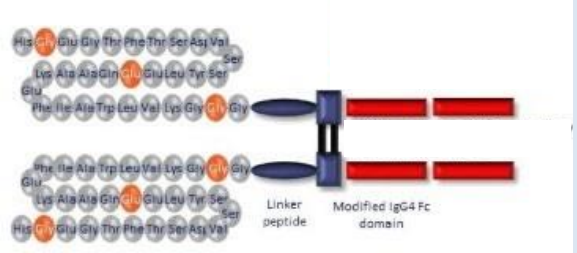


hGLP-1

EXENATIDE
(53% omologia)

LISIXENATIDE
(53% omologia)

LIRAGLUTIDE
(97% omologia)



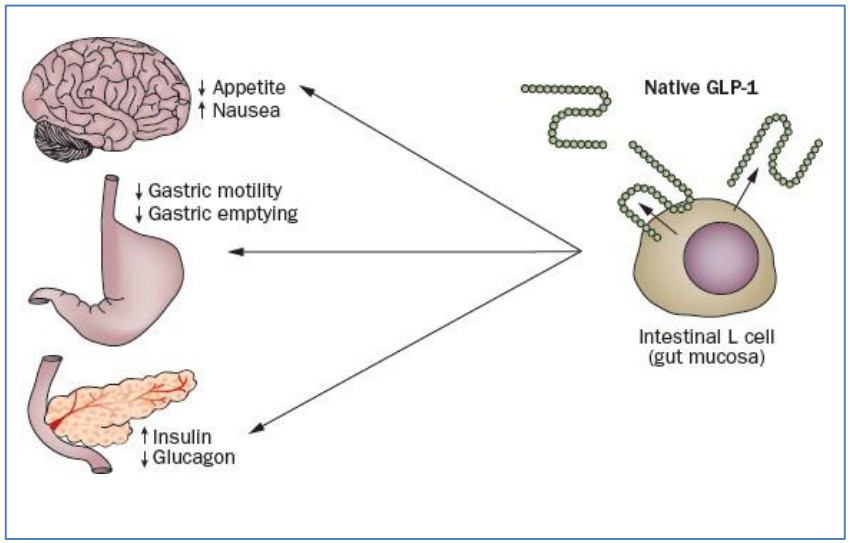
DULAGLUTIDE
(90% omologia)

ALBIGLUTIDE
(95% omologia)

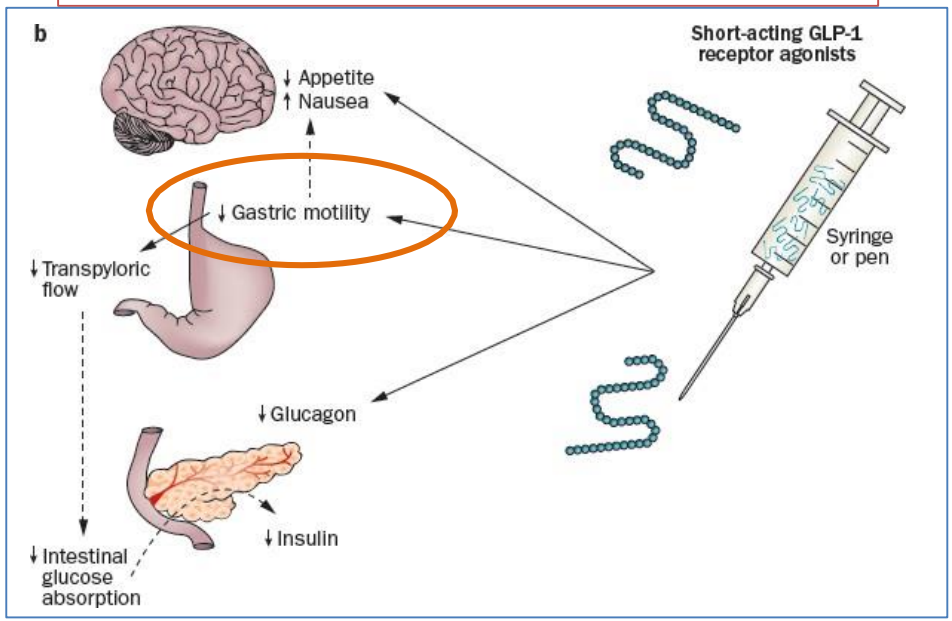
Agonisti del Recettore del GLP-1 & 3E: Efficacia, Efficienza, Eccellenza

Efficacia: *Capacità di raggiungere l'obiettivo prefissato*

Efficienza: *Capacità costante di rendimento impiegando le risorse minime indispensabili*

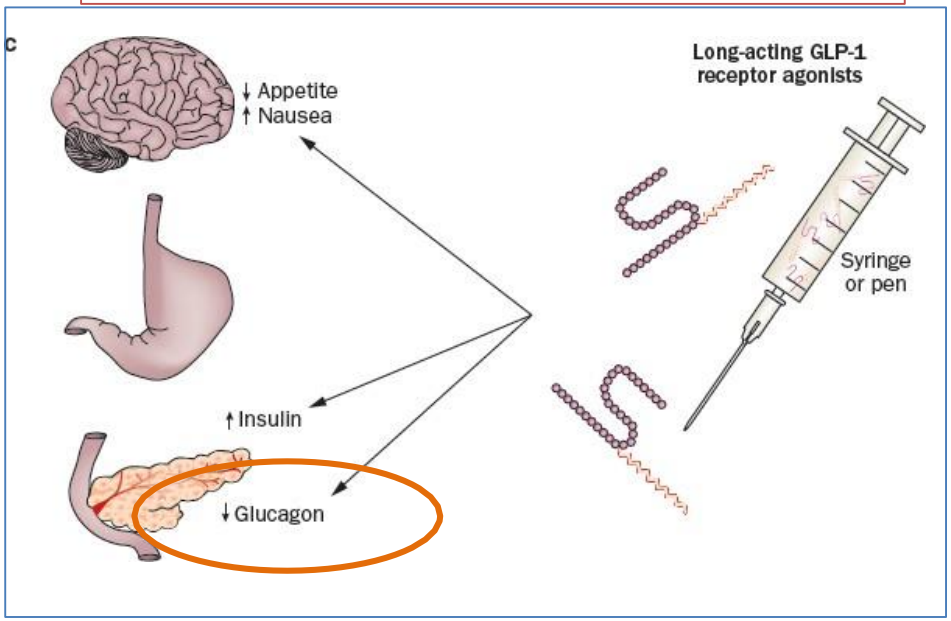


ANALOGHI A **BREVE** DURATA D'AZIONE



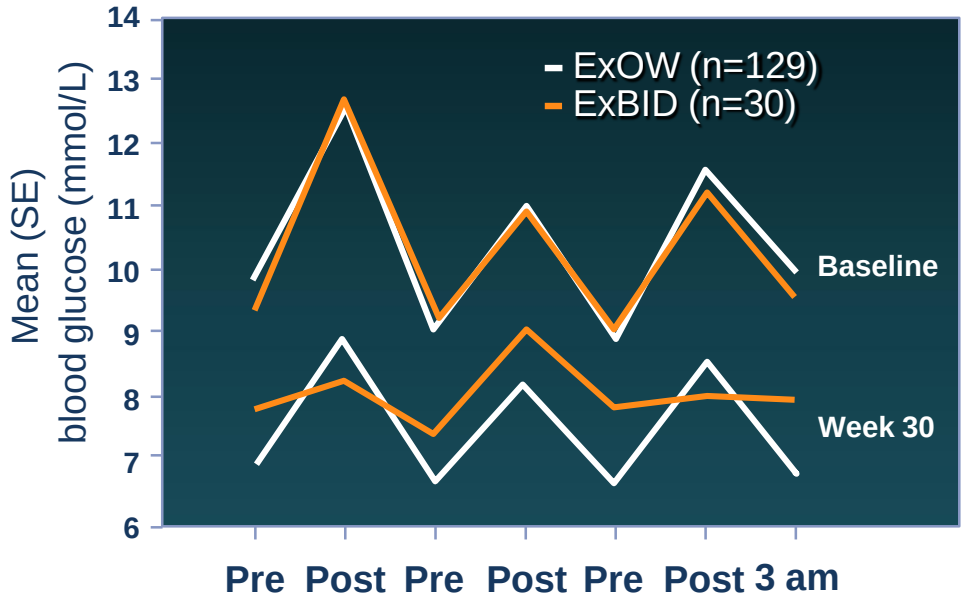
Migliore prestazione glicemia post-prandiale

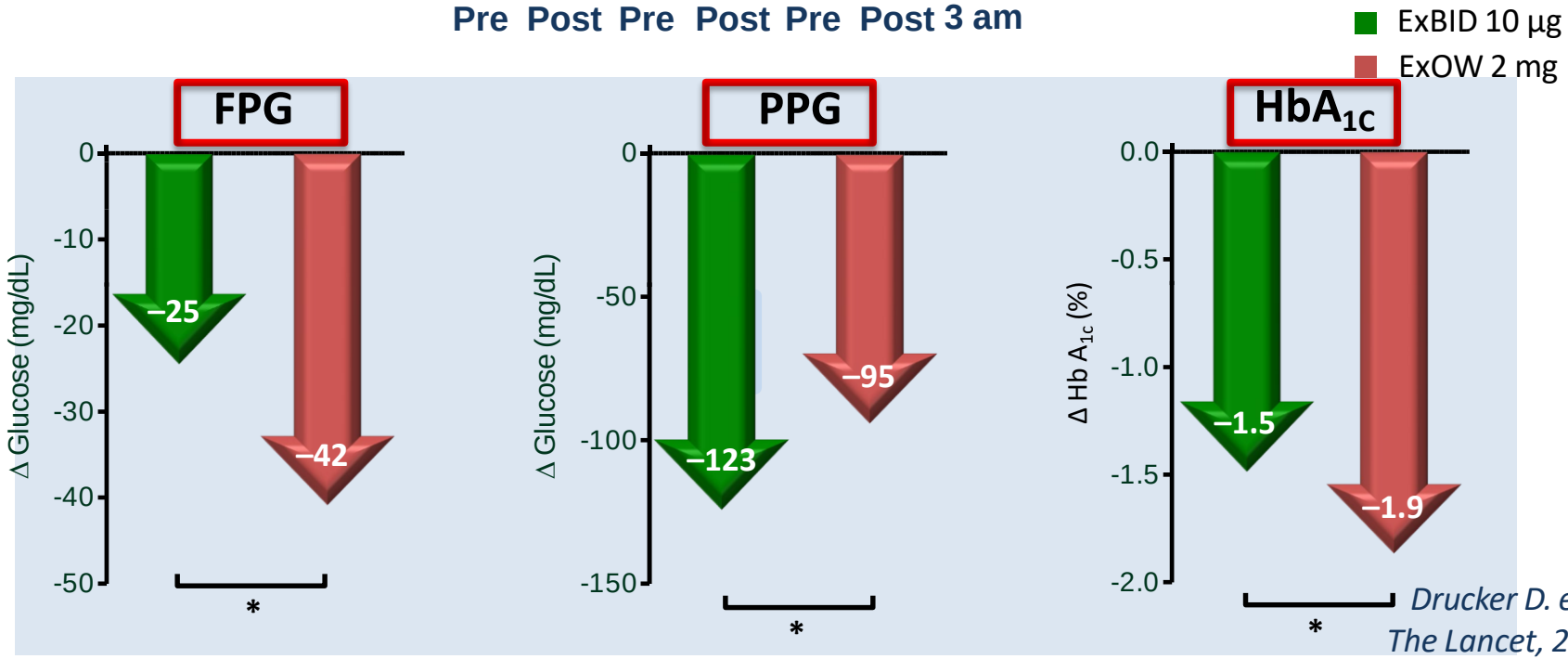
ANALOGHI A **LUNGA** DURATA D'AZIONE



Migliore prestazione glicemia a digiuno

Pazienti in terapia con ExOW e ExBID





*$P<0.05$

Drucker D. et al
The Lancet, 2008

Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide-LAR Liraglutide
Half-life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Eccellenza

Il più alto livello qualitativo raggiungibile

Nuovi interrogativi

GLP-1Ra per il peso?

Cominciare prima possibile per preservare beta cellula?

Azione sul cuore?

2008

oggi

Azione sul fegato?

Effetto sull'endotelio?

GLP-1Ra per i più gravi?

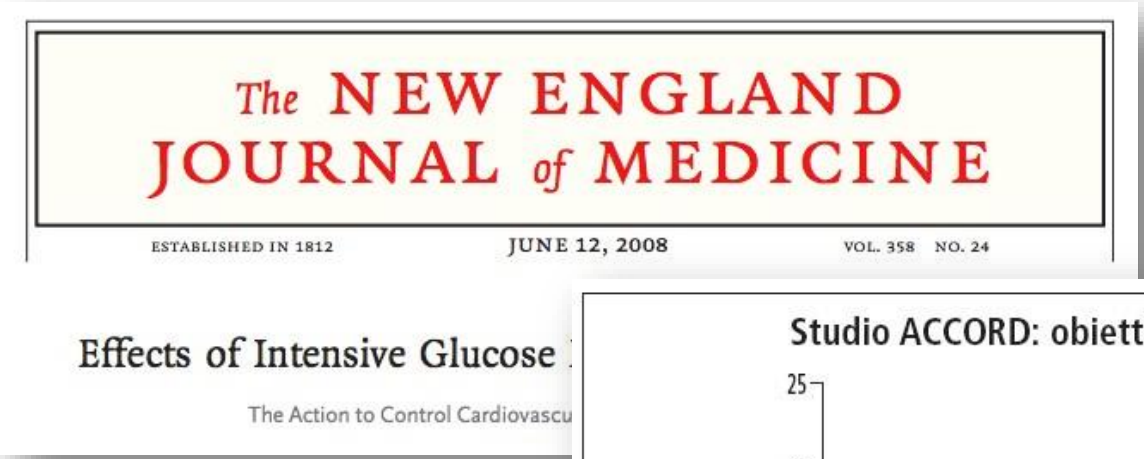
LA CAUSA PIÙ IMPORTANTE DI MORBILITÀ E MORTALITÀ NEL DM2 È SICURAMENTE RAPPRESENTATA DALLE MALATTIE CV

TRATTAMENTO OTTIMALE DEL DM2 → ABBATTERE IL RISCHIO CV

Livelli eccessivi di glicemia possono, attraverso vari meccanismi molecolari, innescare danno vascolare o accelerarne la progressione

Ridurre la glicemia a livelli simili a quelli osservati nei non diabetici può tradursi in una consistente riduzione del rischio CV?

Lezione da grandi trials


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose

The Action to Control Cardiovascu

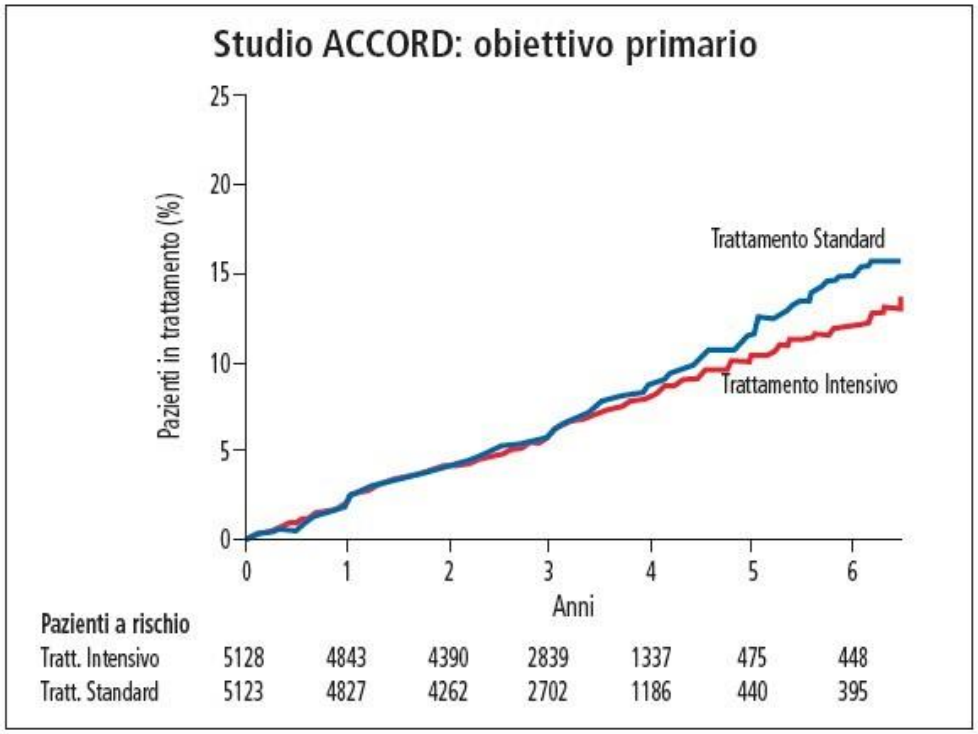


Figura 3. Studio ACCORD: incidenza % complicanze CV maggiori.

La terapia intensiva finalizzata al raggiungimento del target glicemico **aumenta il rischio di mortalità** e **non riduce gli eventi cardiovascolari**

I GLP-1 RA RIDUCONO il RISCHIO CV RESIDUO*?

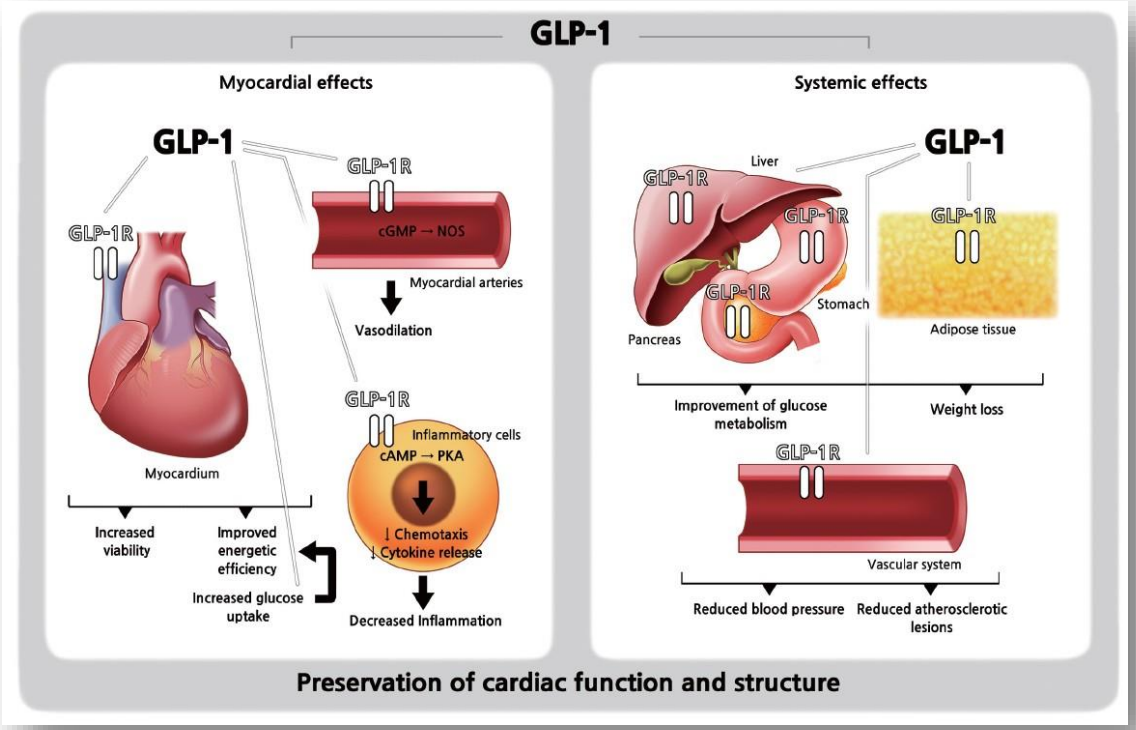
*Rischio di sviluppare eventi CV nonostante il raggiungimento dei target terapeutici

Razionale per l'utilizzo

<u>Il GLP-1 possiede recettori in molti organi :</u>

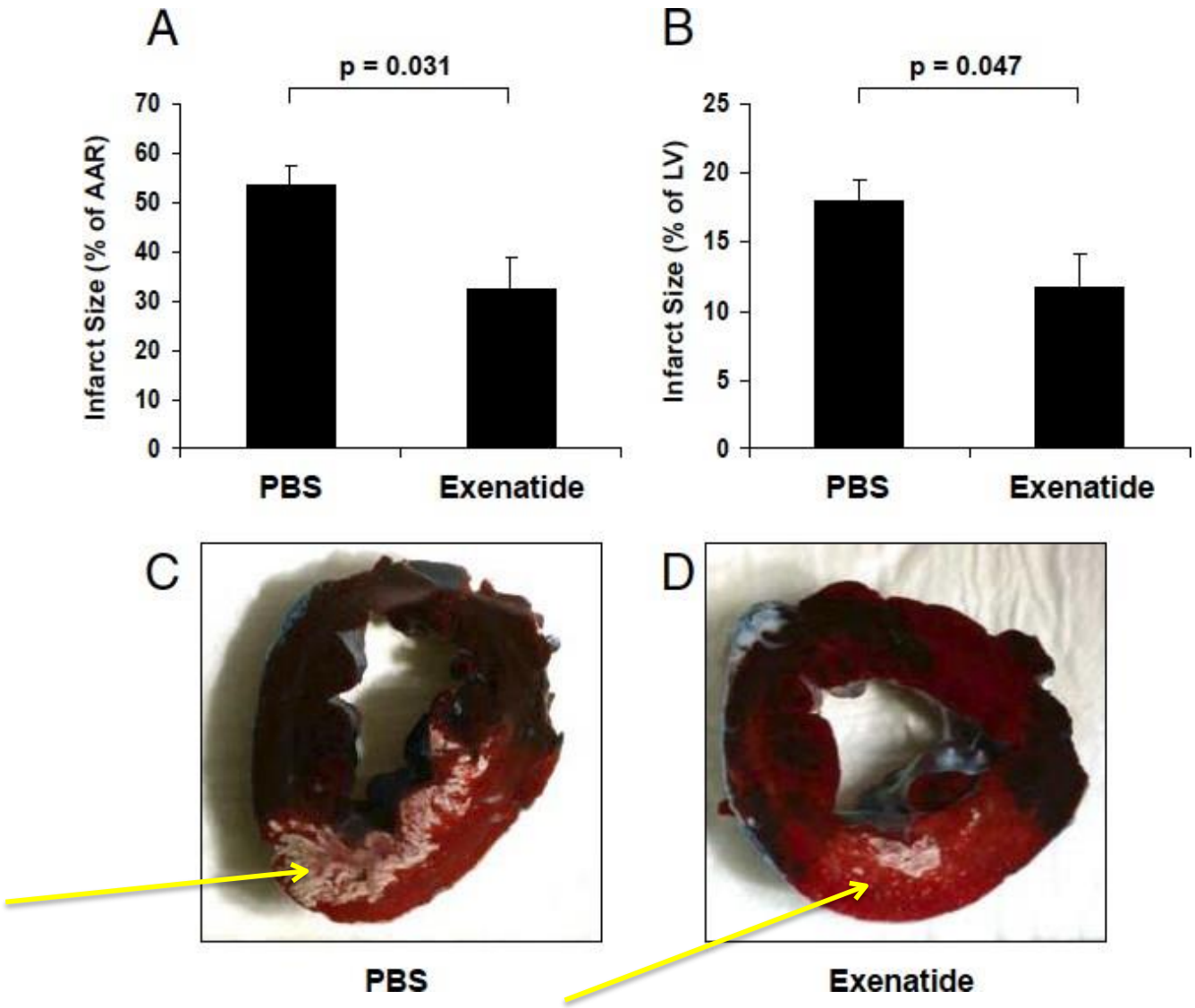
Tratto gastrointestinale
Polmone
Cuore
Vasi sanguigni
Fegato
Rene
Cervello….

Kang M.Y. **Endocrinol Metab.** 2016



Endocrinol Metab 2016;31:258-274
http://dx.doi.org/10.3803/EnM.2016.31.2.258
pISSN 2093-596X · eISSN 2093-5978

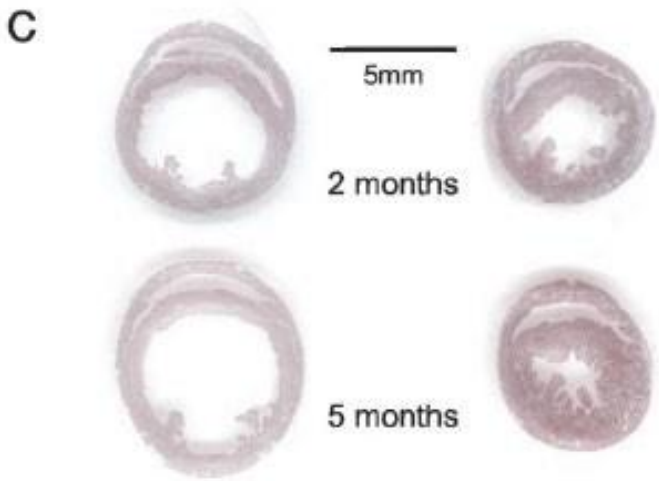
Exenatide Reduces Infarct Size in a porcine model

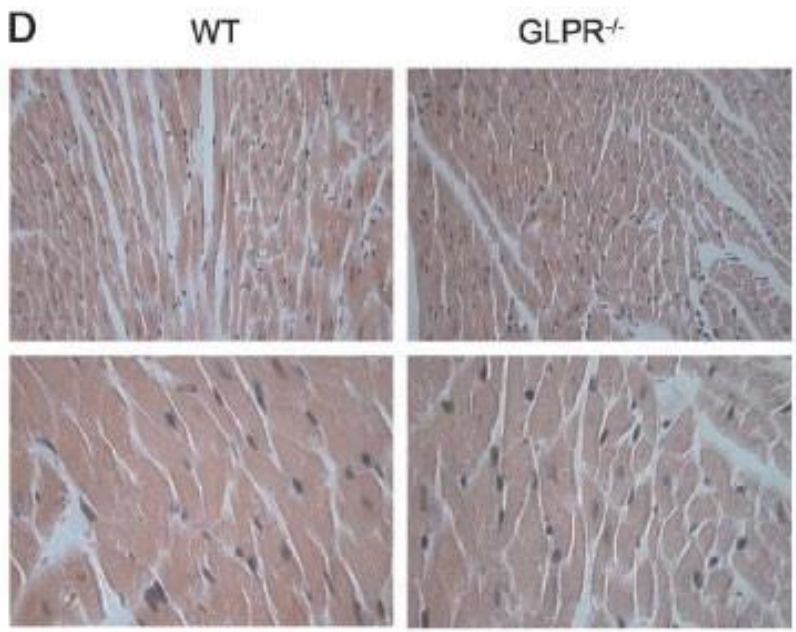


Timmers L. **JACC** 2009

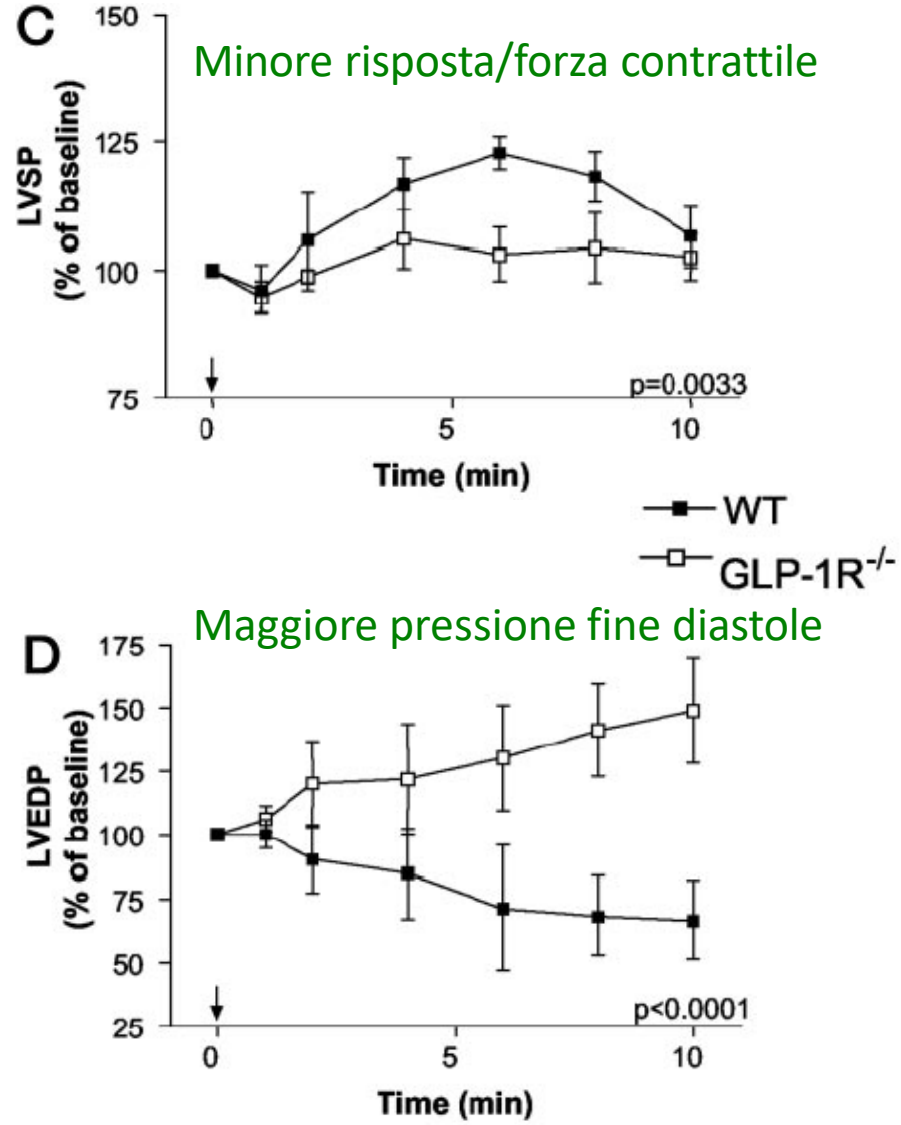
Sezioni di ventricolari

Risposta allo stress da ipo





istologia



Gros R. **Endocrinology** 2003

European Heart Journal (2012) **33**, 1491–1499
doi:10.1093/eurheartj/ehr309

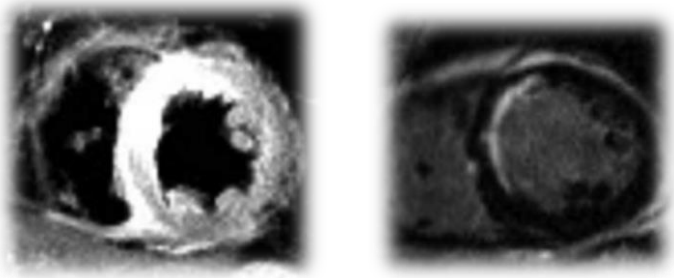
CLINICAL RESEARCH
Acute coronary syndromes

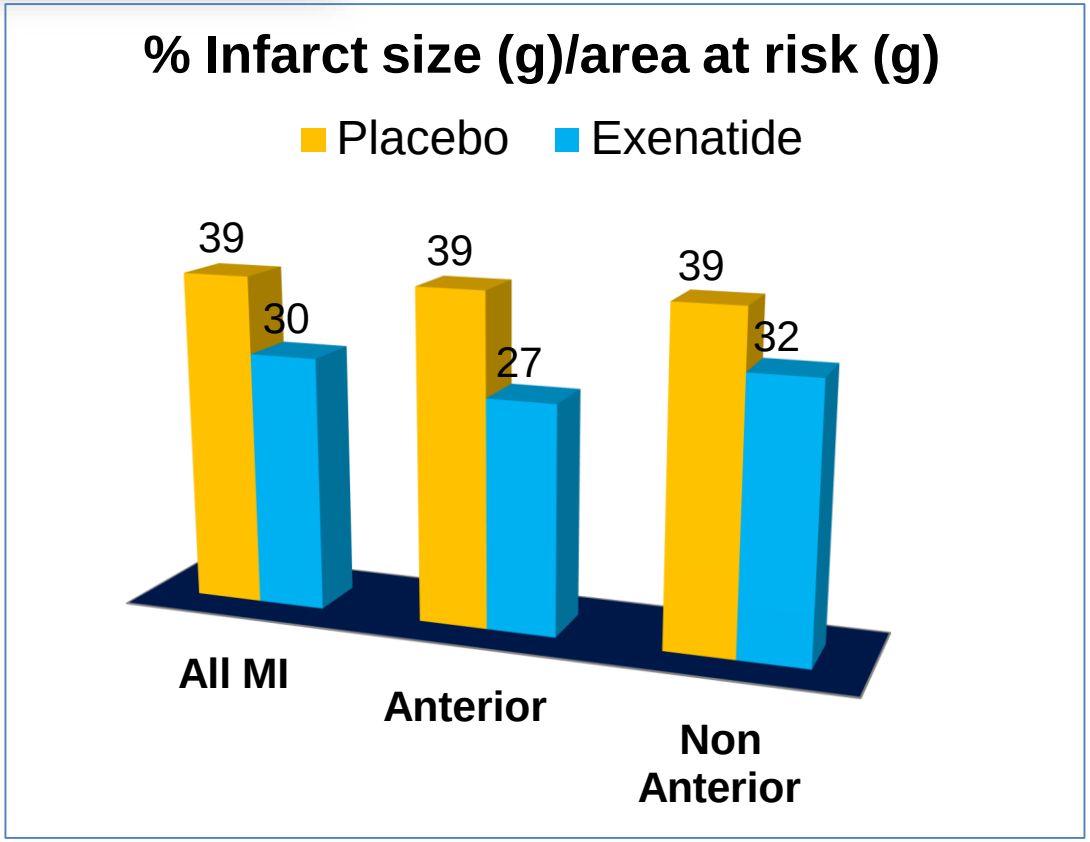
Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction

Jacob Lønborg[1]*, Niels Vejlstrup[1], Henning Kelbæk[1], Hans Erik Bøtker[2], Won Yong Kim[2], Anders B. Mathiasen[1], Erik Jørgensen[1], Steffen Helqvist[1], Kari Saunamäki[1], Peter Clemmensen[1], Lene Holmvang[1], Leif Thuesen[2], Lars Romer Krusell[2], Jan S. Jensen[3], Lars Køber[1], Marek Treiman[4], Jens Juul Holst[4], and Thomas Engstrøm[1]

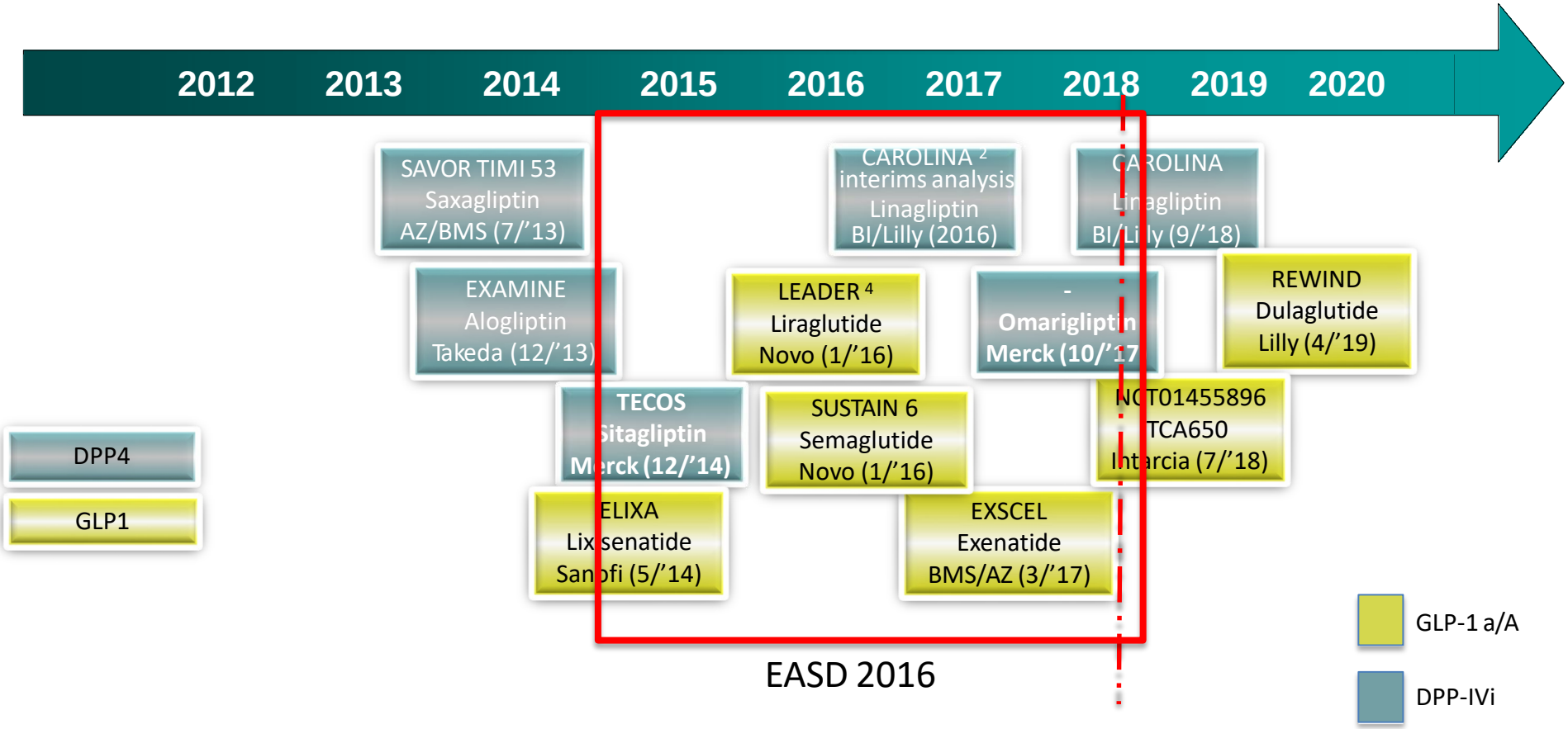
Riduzione area infartuale

in 172 pazienti con **IMA con STEMI**, in corso di trombolisi **(pPCI)** randomizzati a **placebo** o **Exenatide**





trials clinici disegnati per la sicurezza CV

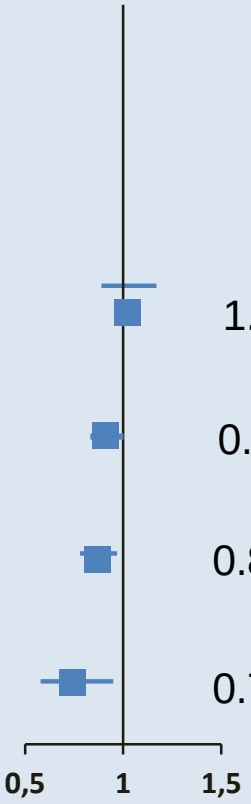


Cardiovascular Outcomes trial for diabetes [1]

[1] Expected dates for completion of primary endpoint (source: clinicaltrials.gov, accessed 04/2013)
[2] Interims data ~2016; 2nd Linagliptin CV outcomes trial vs PBO (CARMELINA) expected to start in 2013, per primary CI (tbc) results in 2018
[3] Per Janssen commentary at FDA ACM, next CV meta-analysis planned after 500 events- expected in 2015
[4] per Novo interims analysis possible in 2014/15 if required for review of obesity sNDA

I TRIAL DI OUTCOME CV CON GLP-1R AGONISTI IN PZ CON DM2 HANNO MOSTRATO RISULTATI ETEROGENEI

Trial	Outcome	HR (95% CI)
ELIXA (N=6068)[1] Lixisenatide vs placebo	Time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	1.02 (0.89, 1.17)
EXSCEL (N=14,752)[2] Exenatide vs placebo	3P-MACE: CV death, Non Fatal-MI, Non Fatal-stroke	0.91 (0.83, 1.00)
LEADER (N=9340)[3] Liraglutide vs placebo	3P-MACE: CV death, Non Fatal-MI, Non Fatal-stroke	0.87 (0.78, 0.97)
SUSTAIN-6 (N=3297)[4] Semaglutide vs placebo	3P-MACE: CV death, Non Fatal-MI, Non Fatal-stroke	0.74 (0.58, 0.95)



1. Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; 2. Holman RR, et al. N Engl J Med 2017;377:1228–1239; 3. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 4. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

LEADER ADA 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Valutare gli effetti a lungo termine di **Liraglutide** su Eventi cardiovascolari

SUSTAIN-6 EASD 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

Valutare la non inferiorità di **Semaglutide** vs placebo Per la sicurezza cardiovascolare

Studies endpoints
LEADER and SUSTAIN-6

LEADER more than **9000** patients
3,8 anni

SUSTAIN-6 more than **3000** patients
104 settimane

Primary endpoint	**Time to first MACE primary outcome composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary endpoints	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary and peripheral revascularisation*, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome • Efficacy endpoints • Microvascular endpoints • Safety/tolerability

- *All events were EAC-confirmed except peripheral revascularisation. BW, body weight; CV, cardiovascular; EAC, (external) event adjudication committee; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction.
  Marso *et al. NEJM june and september 2016*

LEADER ADA 2016

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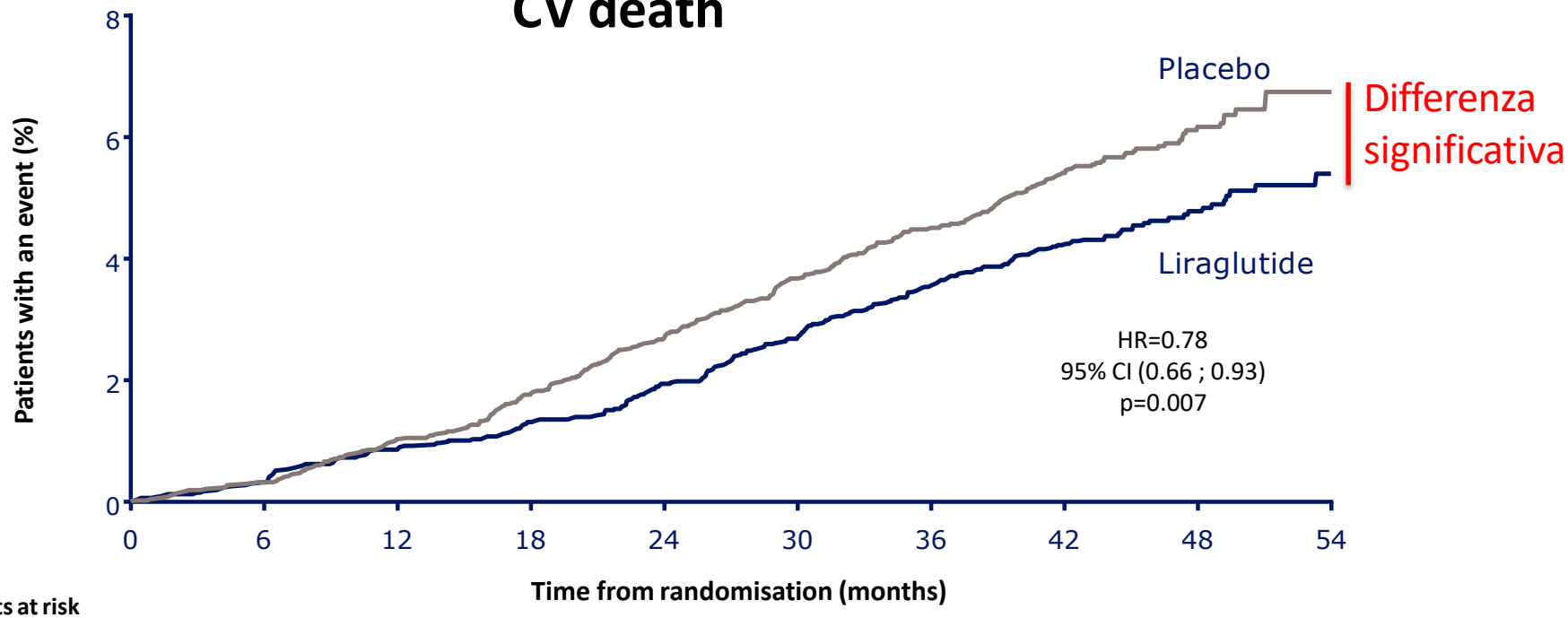
CV death



Patients at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

SUSTAIN-6 EASD 2016

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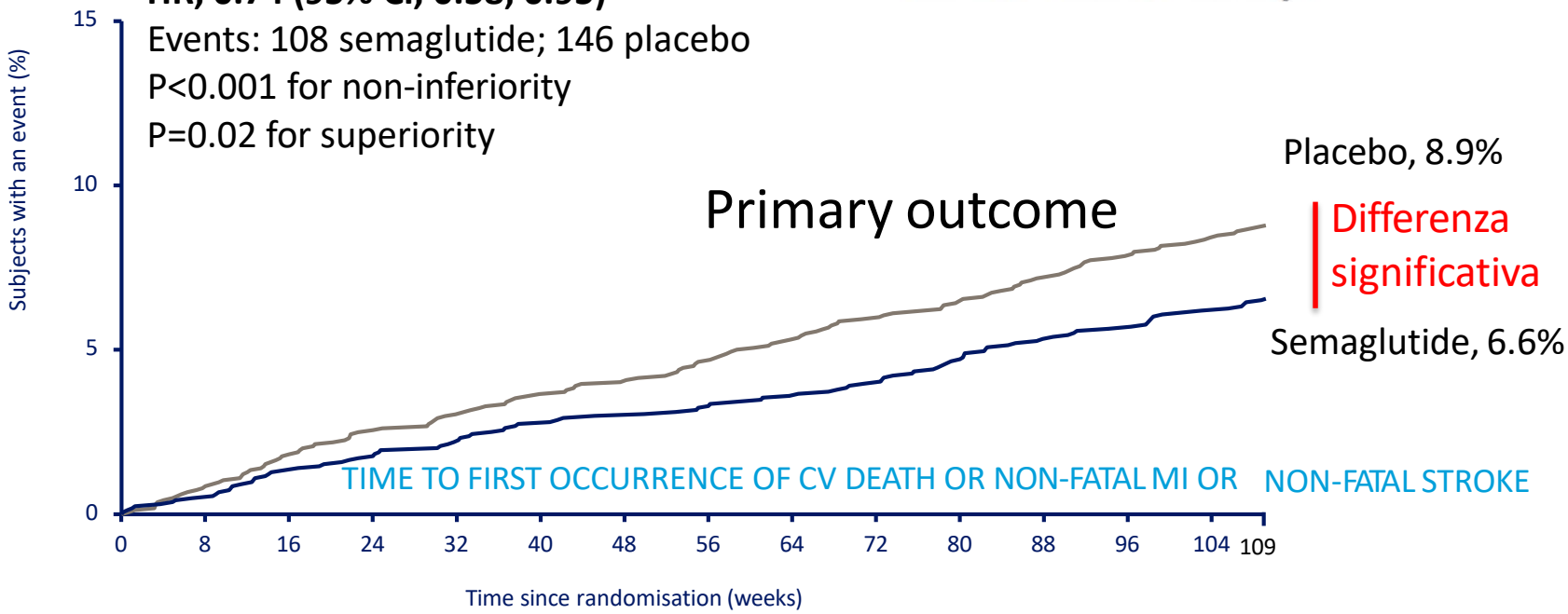
HR, 0.74 (95% CI, 0.58; 0.95)

Events: 108 semaglutide; 146 placebo

P<0.001 for non-inferiority

P=0.02 for superiority



Number of subjects at risk

Semaglutide	**1648**	**1619**	**1601**	**1584**	**1568**	**1543**	**1524**	**1513**
Placebo	1649	1616	1586	1567	1534	1508	1479	1466

RISCHIO CARDIOVASCOLARE RESIDUO

Abbiamo raggiunto l'obiettivo?

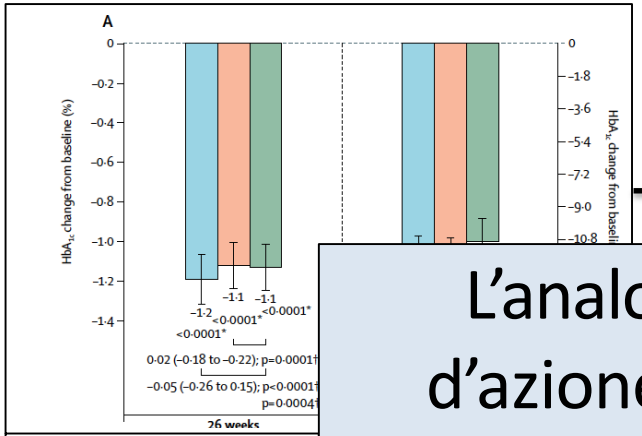
NO!

Il diabete è una patologia complessa

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fady T Botros

AWARD-7

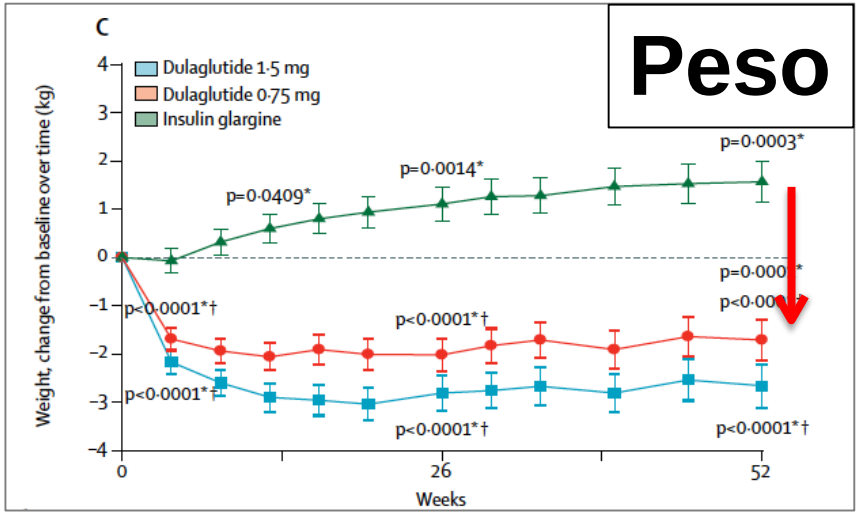


Dimostrazione di non inferiorità rispetto alla

L'analogo a lunga durata d'azione è efficace e sicuro

HbA1c

Peso



Glargine

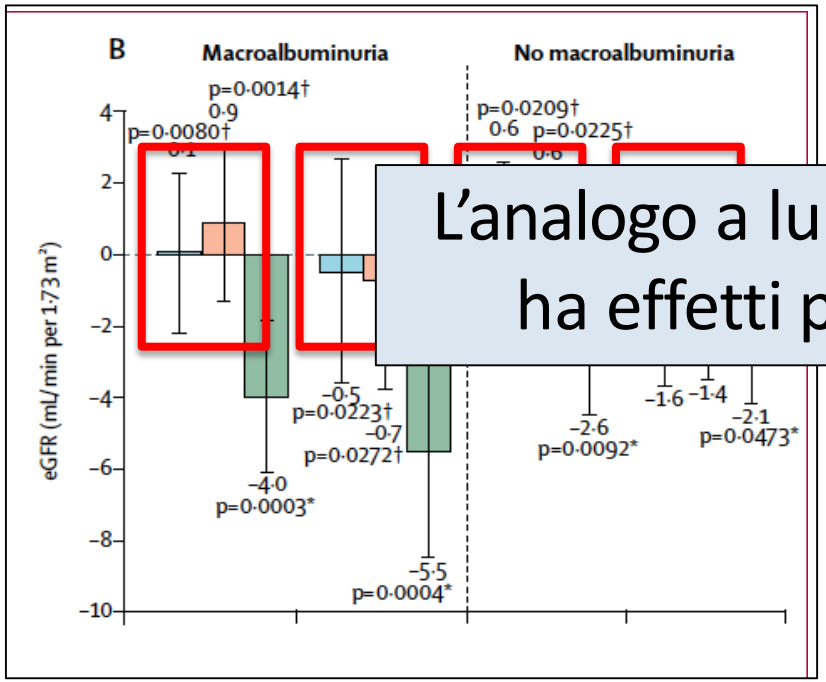
Dula 0.75

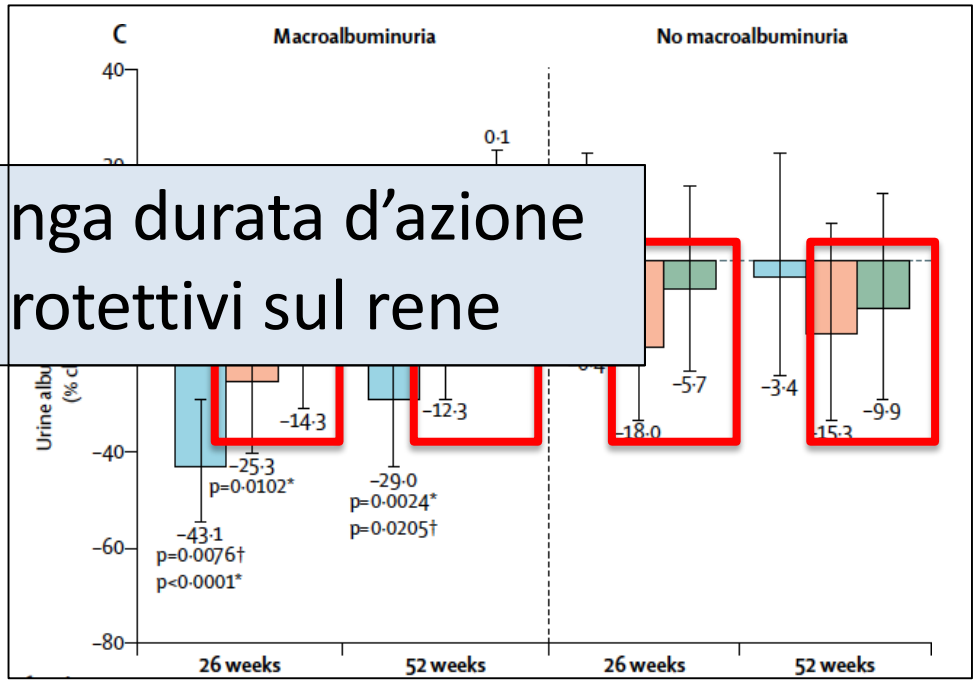
Dula 1.5

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fady T Botros

AWARD-7





L'analogo a lu nga durata d'azione ha effetti p rotettivi sul rene

eGFR

UACR

Dula 1.5 Dula 0.75 Glargine

CONCLUSIONI

Il deficit di GLP1 è una componente fondamentale nella patofisiologia del DM che contribuisce allo sviluppo di:

- deficit secretorio insulinico
- aumento del glucagone plasmatico
- iperglicemia post prandiale

Gli agonisti del GLP1R non solo riducono la glicemia ma migliorano alcuni parametri CV quali PA, colesterolo e il peso

E' stato inoltre dimostrato un effetto positivo sugli outcome CV e sul rischio di IMA

Gli effetti benefici sulla salute CV sono indipendenti dal controllo glicemico, ma di fondamentale importanza nella gestione del diabetico.

GRAZIE PER L’ATTENZIONE