Endocrinologia e Intestino

Roberto Trevisan

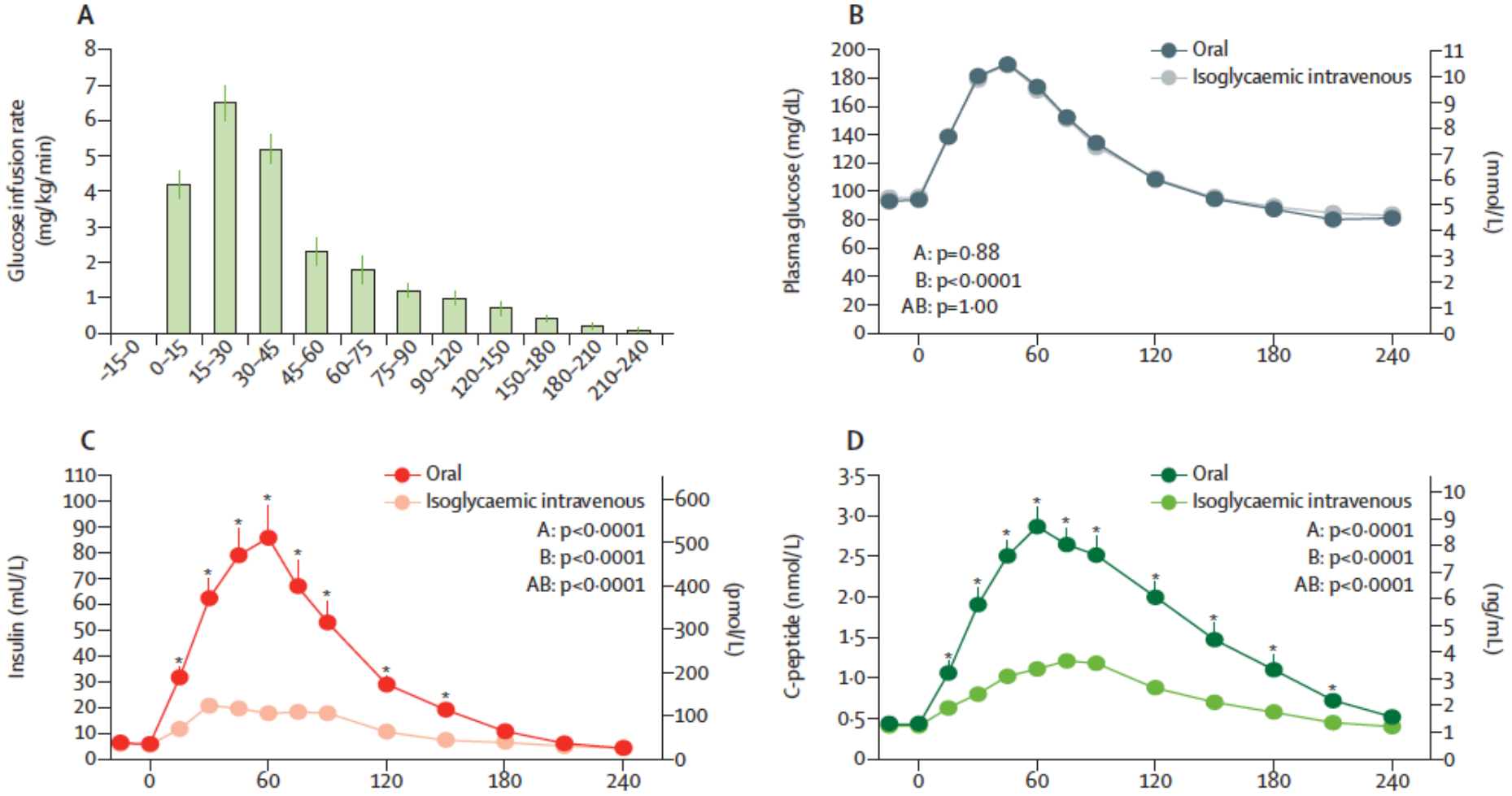
UOC Malattie Endocrine 1 – Diabetologia

ASST Papa Giovanni XXII, Bergamo

INCRETINE E INTESTINO
Un nuovo organo endocrino
The Duodenum as a Key Player in Metabolic Diseases

1

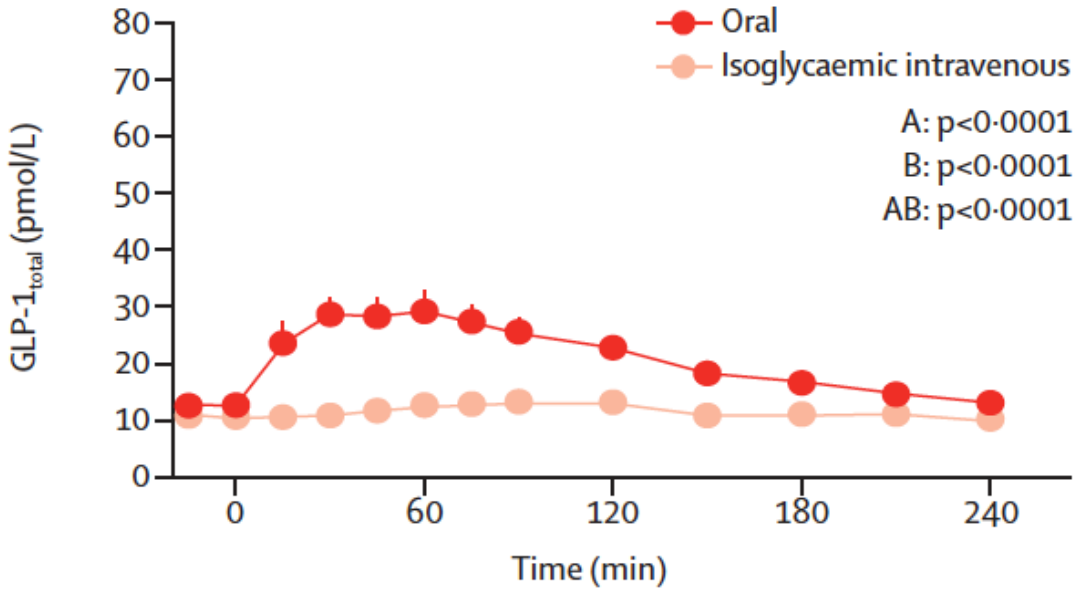
Incretin effect in healthy individuals

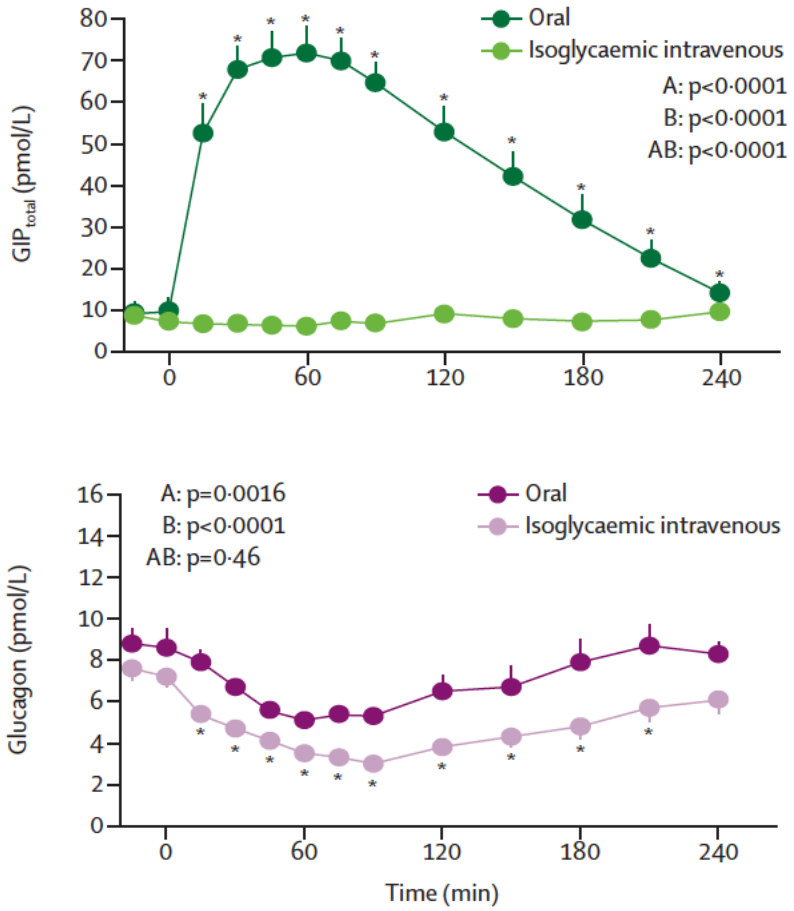


Lancet Diabetes Endocrinol 2016; 4: 525–36

2

Incretin effect in healthy individuals

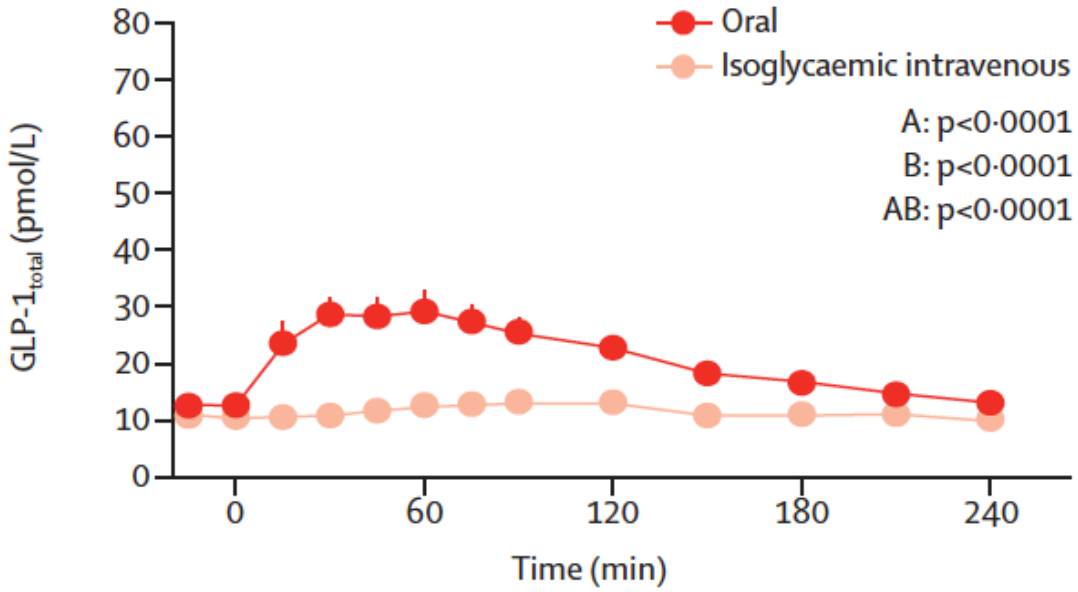


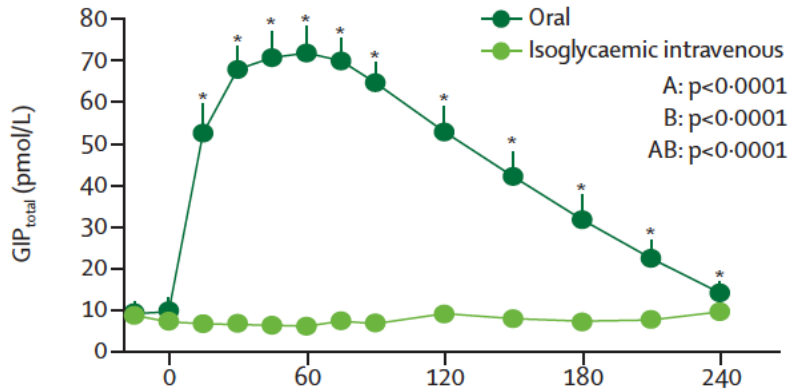


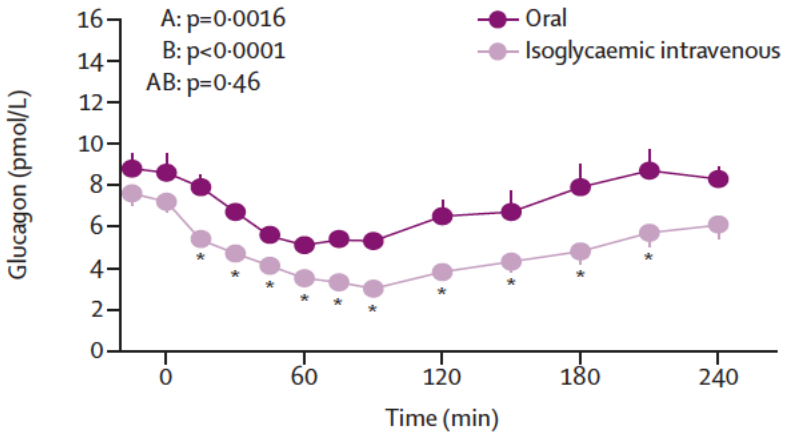
Lancet Diabetes Endocrinol 2016; 4: 525–36

3

Incretin effect in healthy individuals

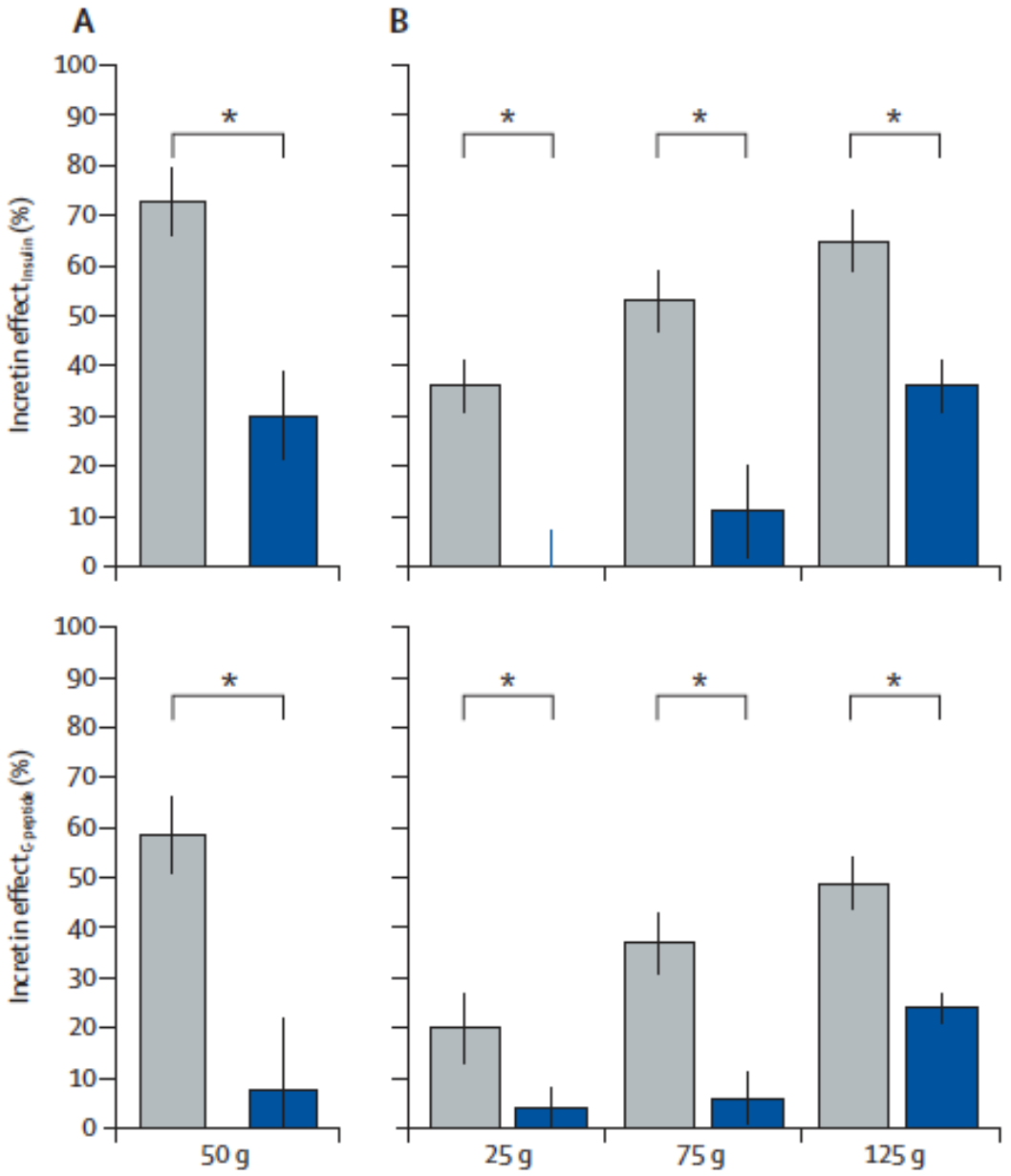






Lancet Diabetes Endocrinol 2016; 4: 525–36

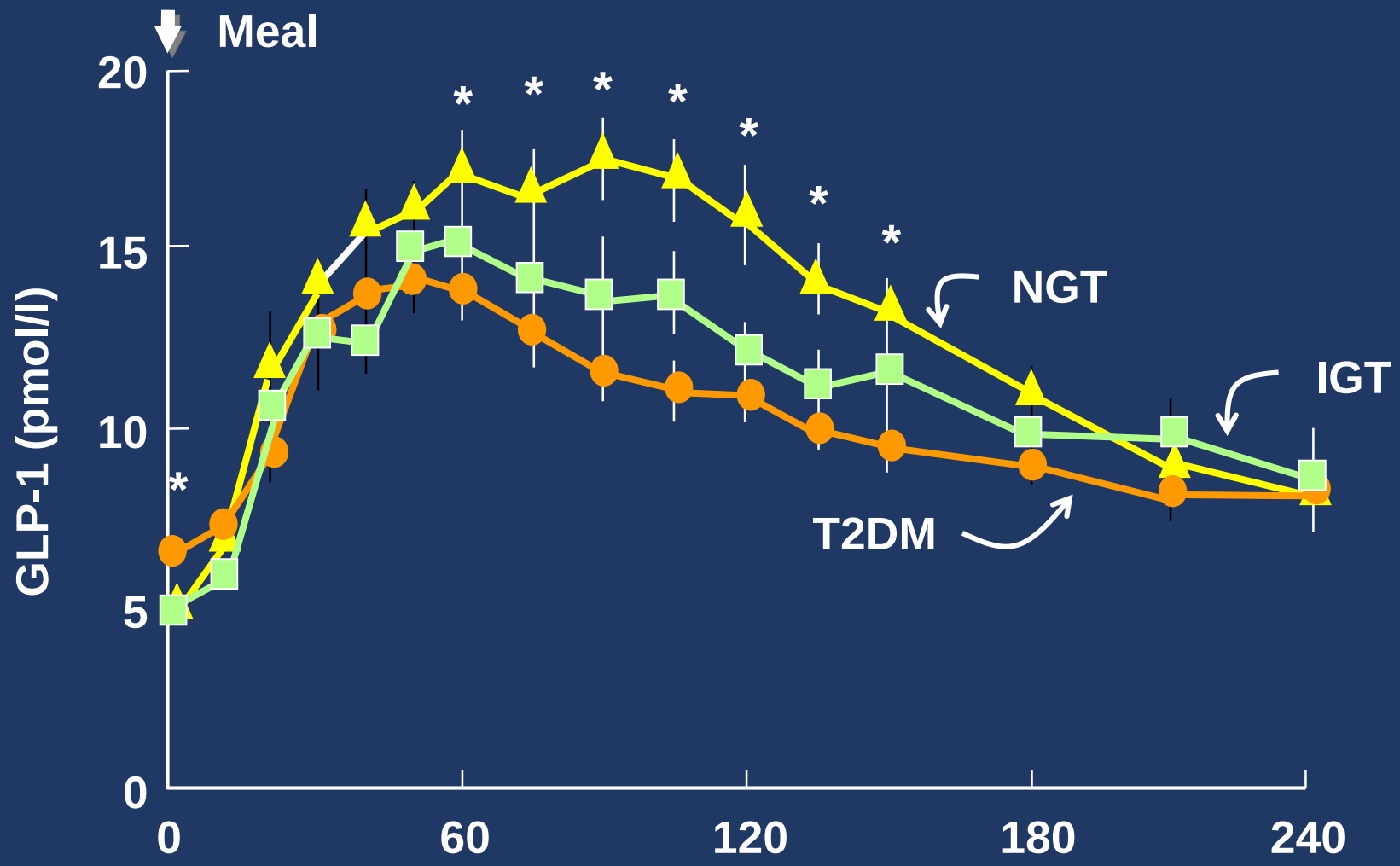
Incretin effect, calculated from insulin or C-peptide responses, in studies comparing healthy individuals with patients with Type 2 diabetes



Lancet Diabetes Endocrinol 2016; 4: 525–36

4

Postprandial GLP-1 levels are decreased in people with IGT and Type 2 diabetes

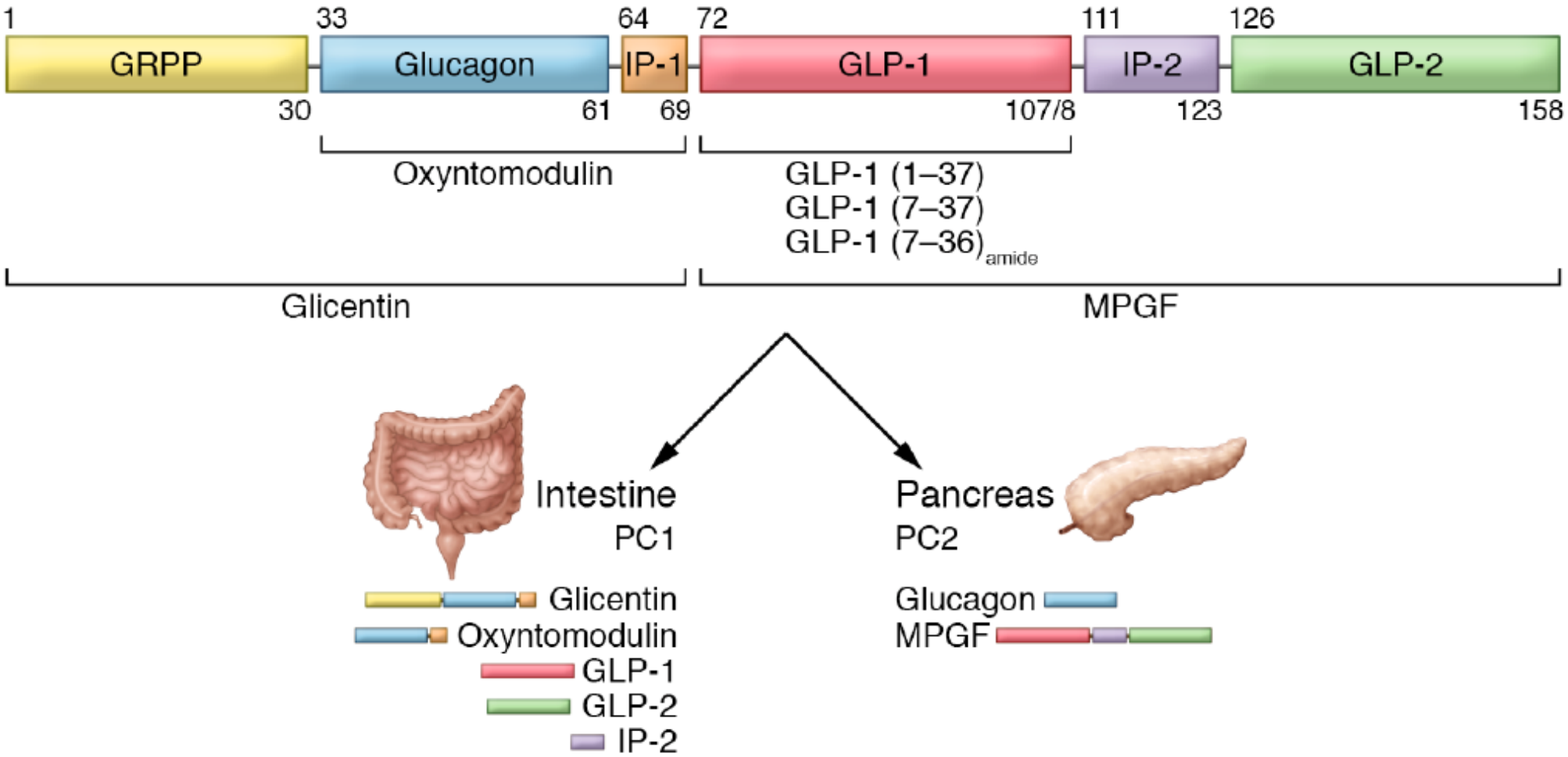


***P*<0.05 T2DM vs NGT**

Toft-Nielsen et al. *J Clin Endocrinol Metab.* 2001

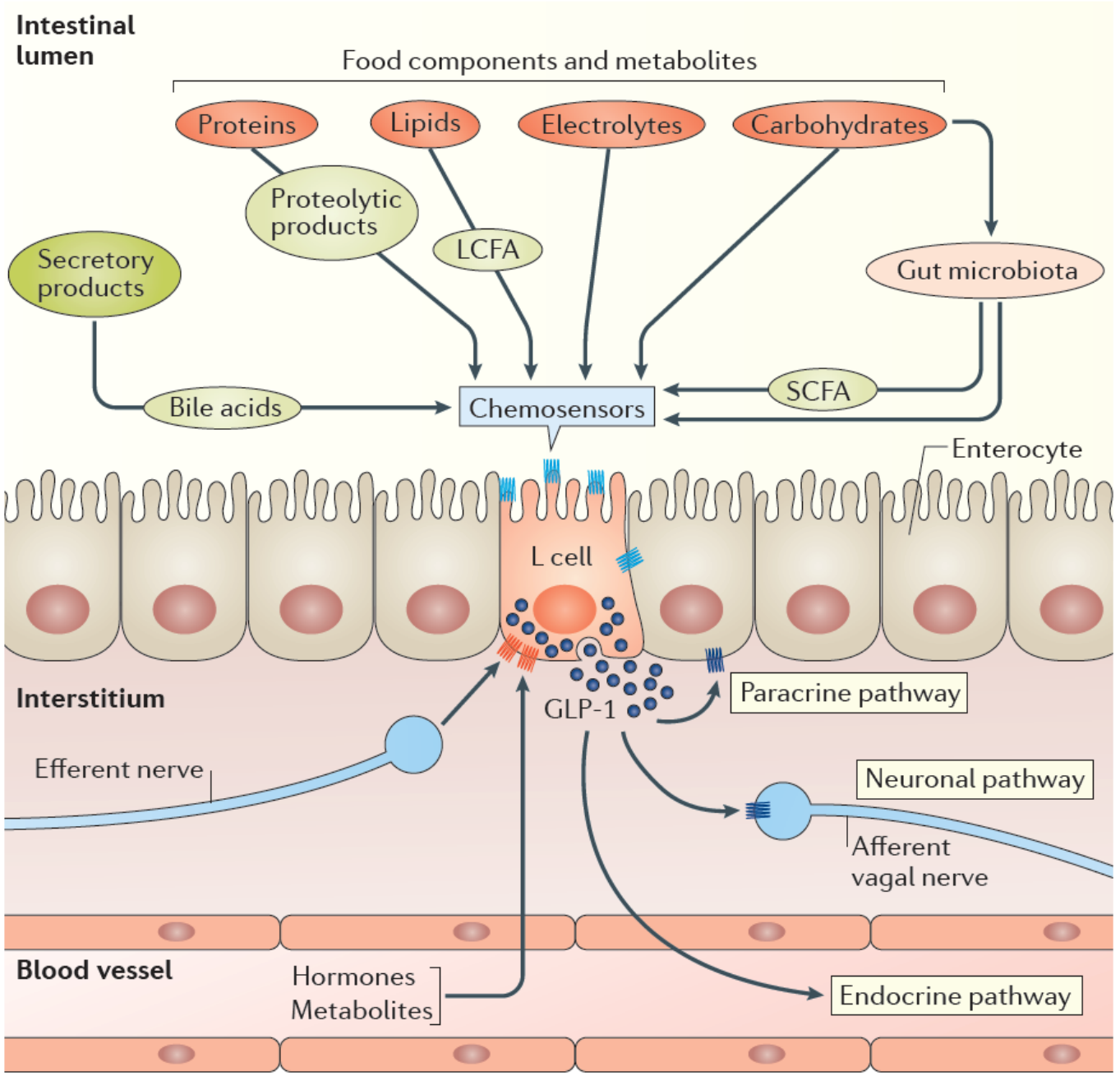
IGT=impaired glucose tolerance; NGT=normal glucose tolerance

Structure and processing of human proglucagon

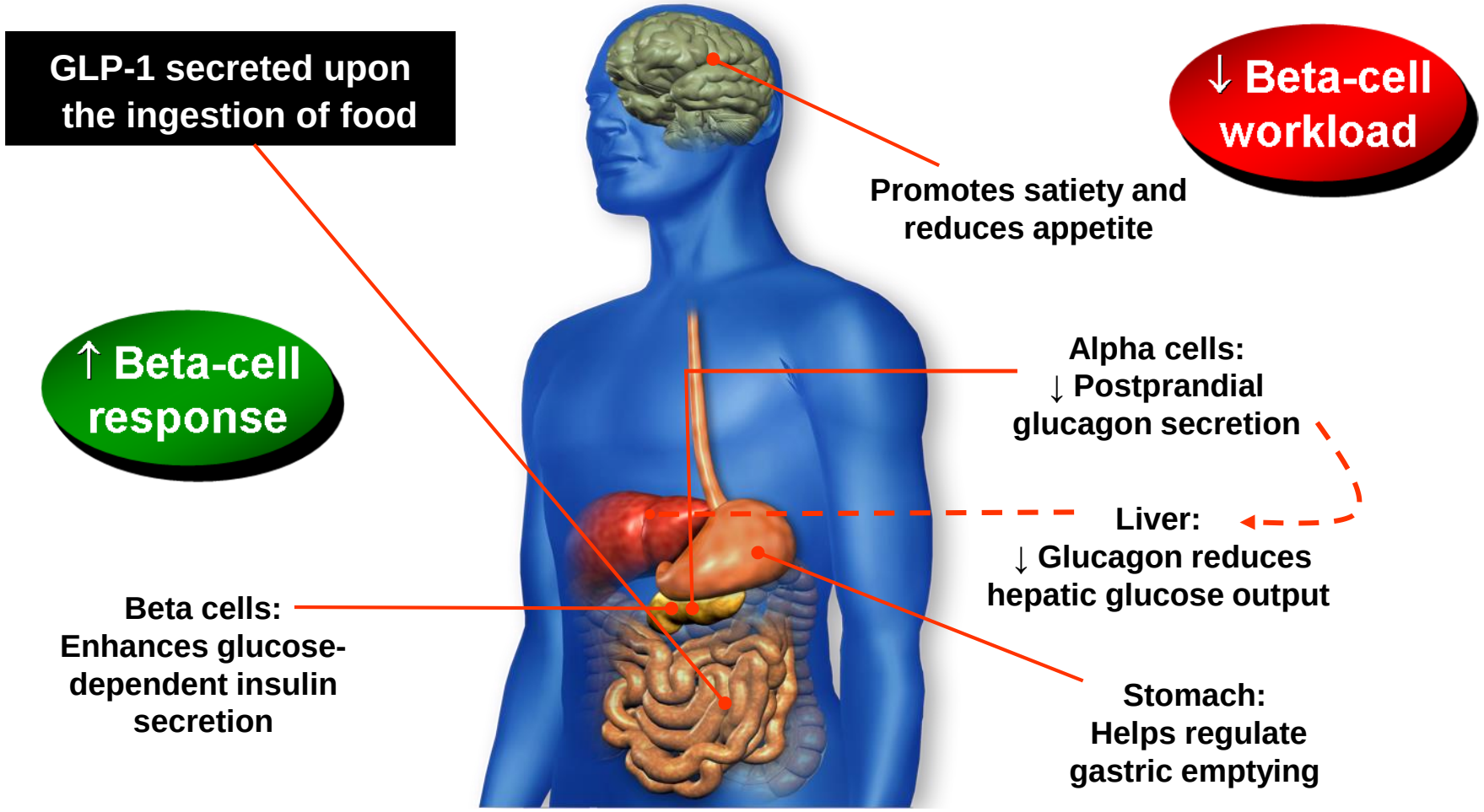


J Clin Invest. 2017;127(12):4217-4227

The sensory and secretory function of the L cell

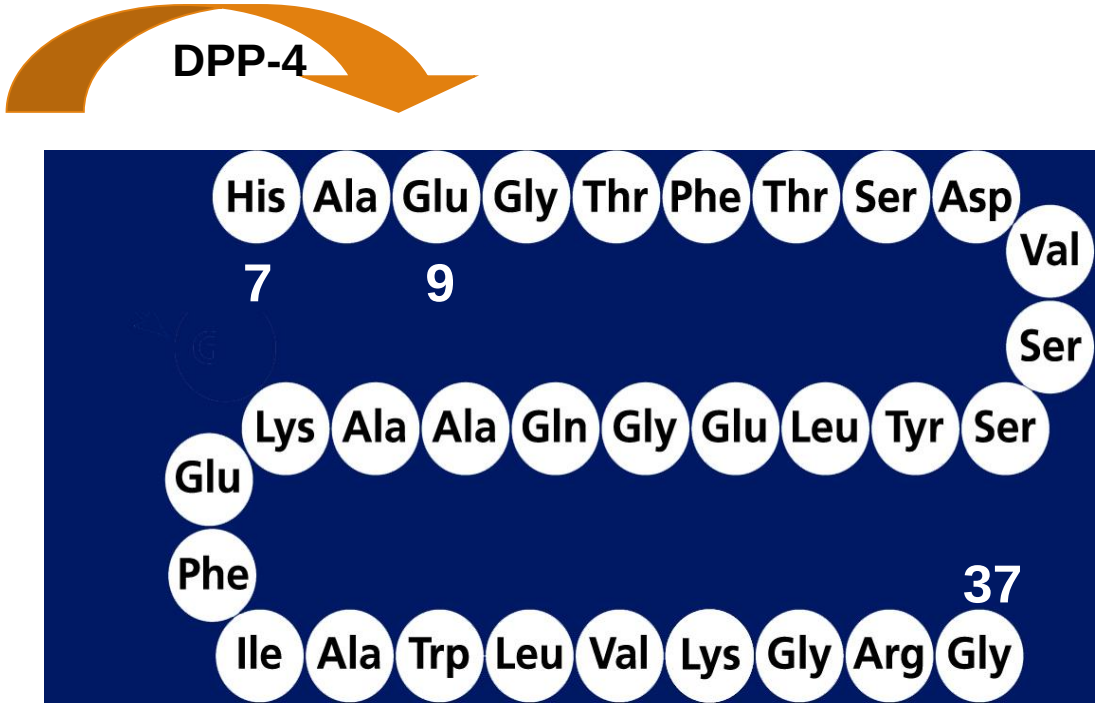


GLP-1 actions in humans



Flint et Al. *J Clin Invest*. 1998;101:515-520.; Larsson et Al.*Acta Physiol Scand*. 1997;160:413-422.; Nauck MA et Al. *Diabetologia*. 1996;39:1546-1553.; Drucker DJ *Diabetes.* 1998;47:159-169.

Il GLP-1 nativo è degradato rapidamente dalla DPP-4

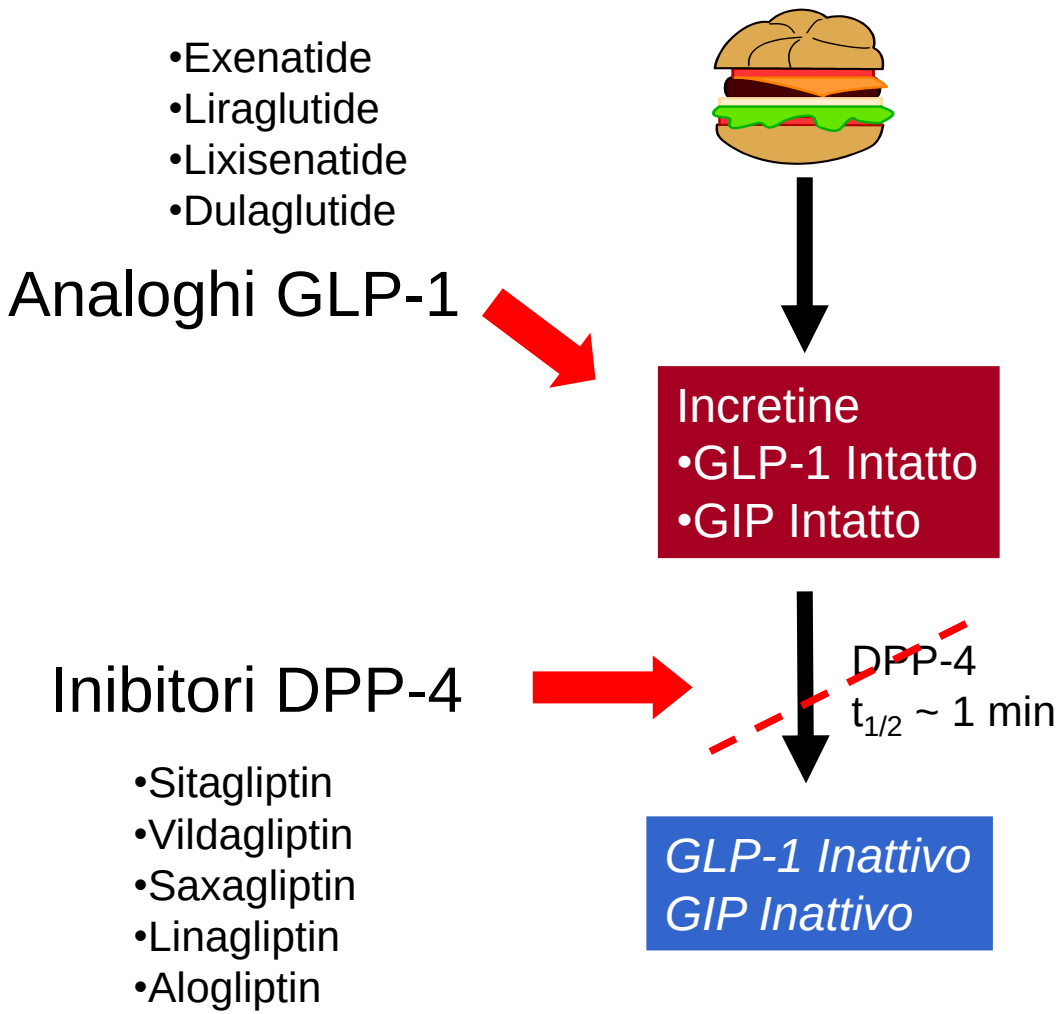


$T_{½}$=1–2 minuti
MCR=5–10 L/min

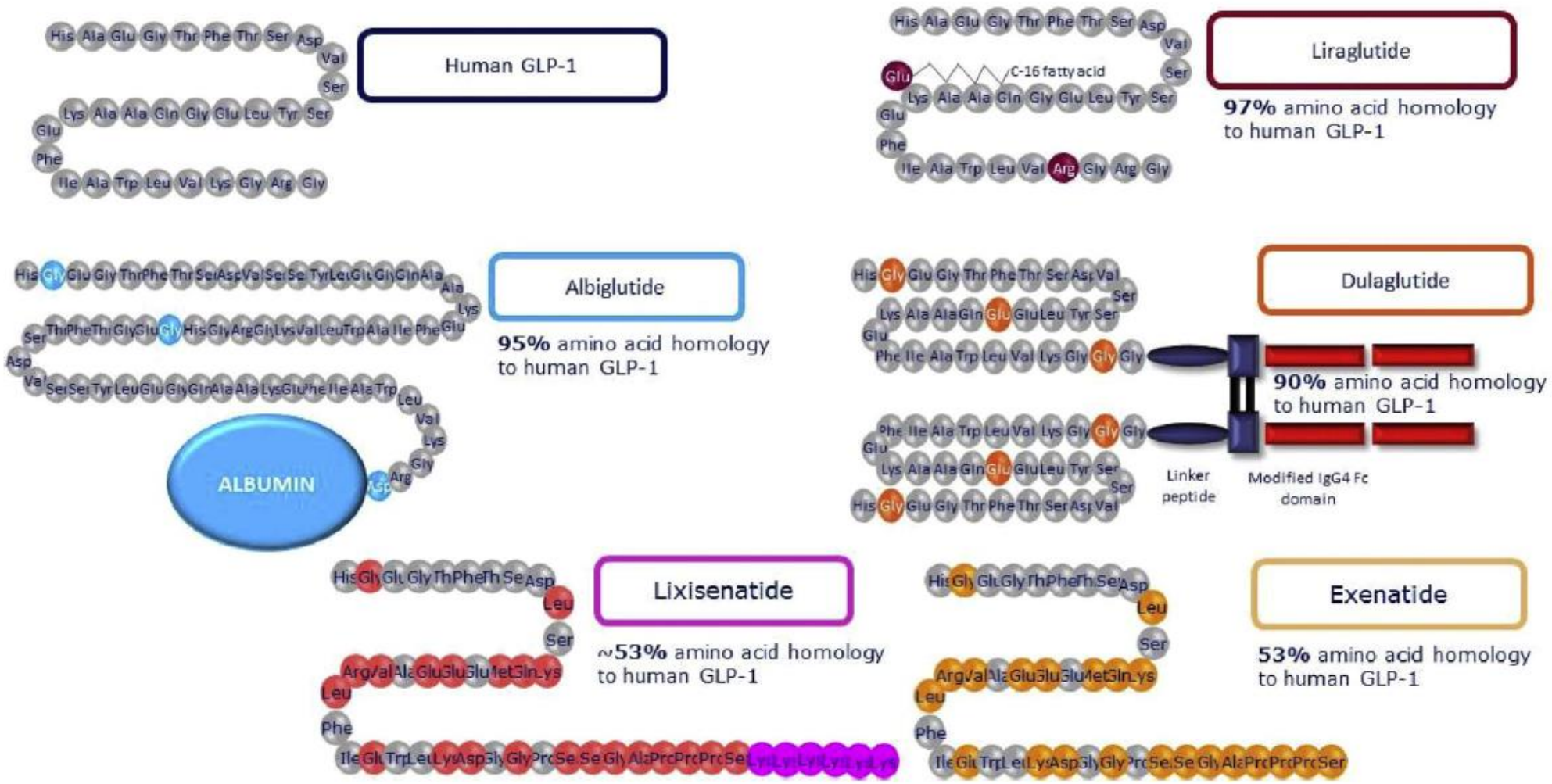
MCR=metabolic clearance rate.

Vilsbøll T et al. *J Clin Endocrinol Metab*. 2003;88:220–224.

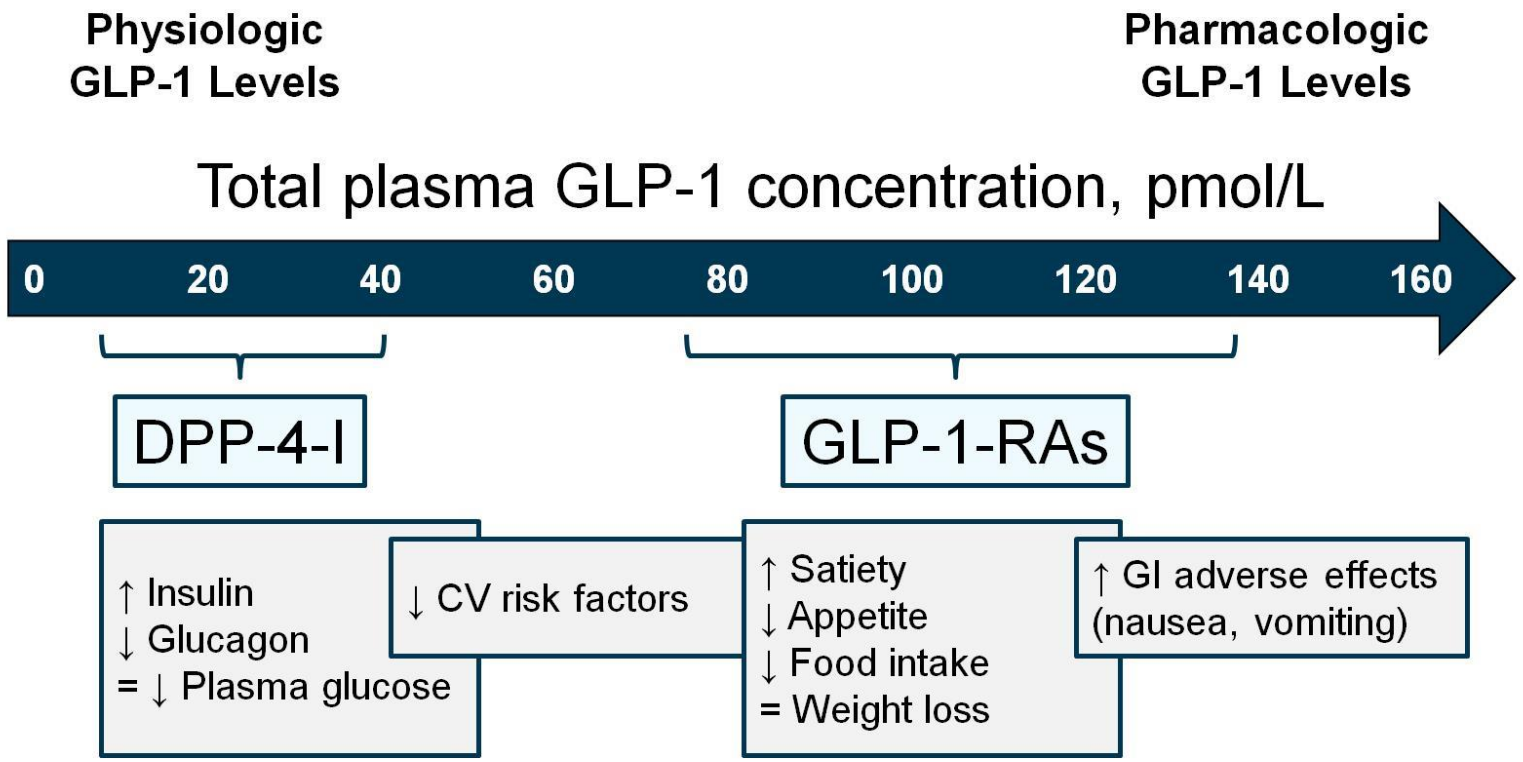
I nuovi farmaci che aumentano il GLP-1



Structural modifications of available glucagon-like peptide-1 receptor agonists

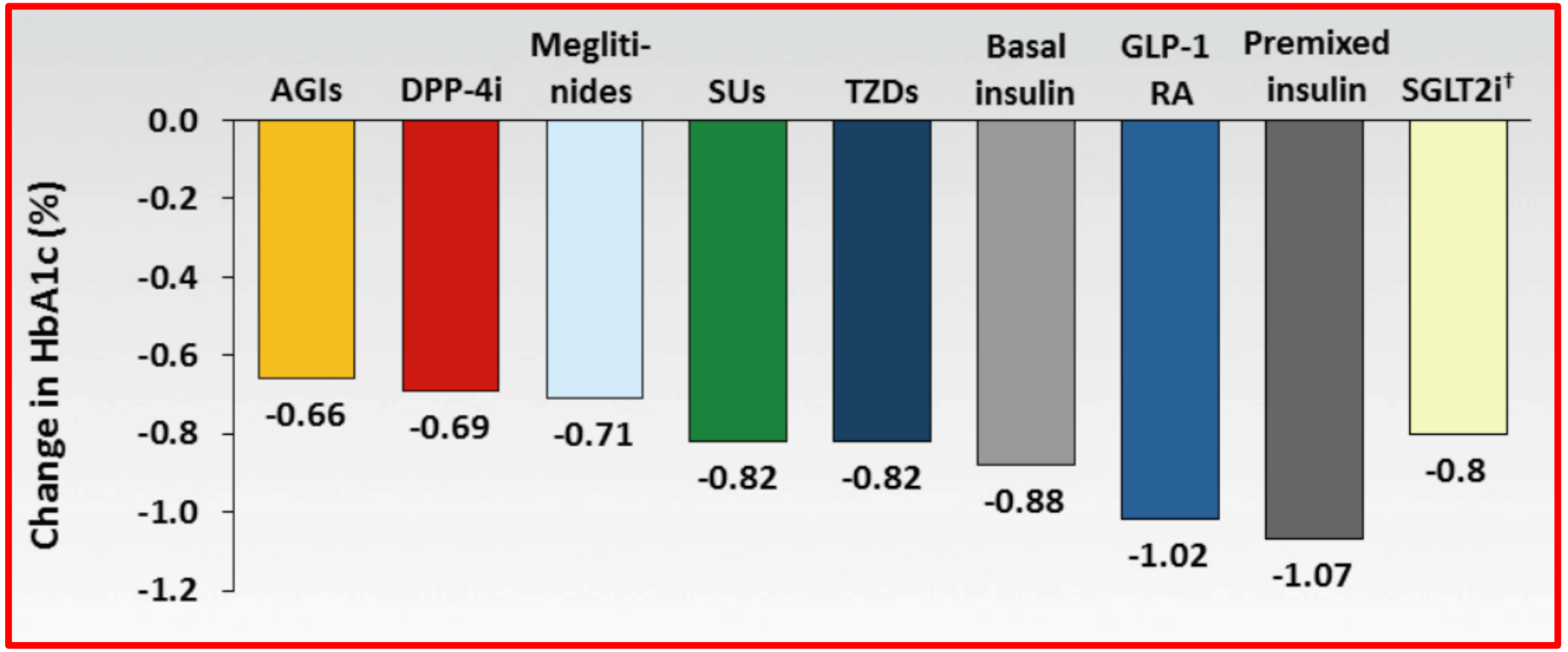


Dose-Related Effects of GLP-1



Courtesty of Vilsbøll T.

Meta-analysis: A1c Reductions With Antihyperglycemic Agents Added to Metformin

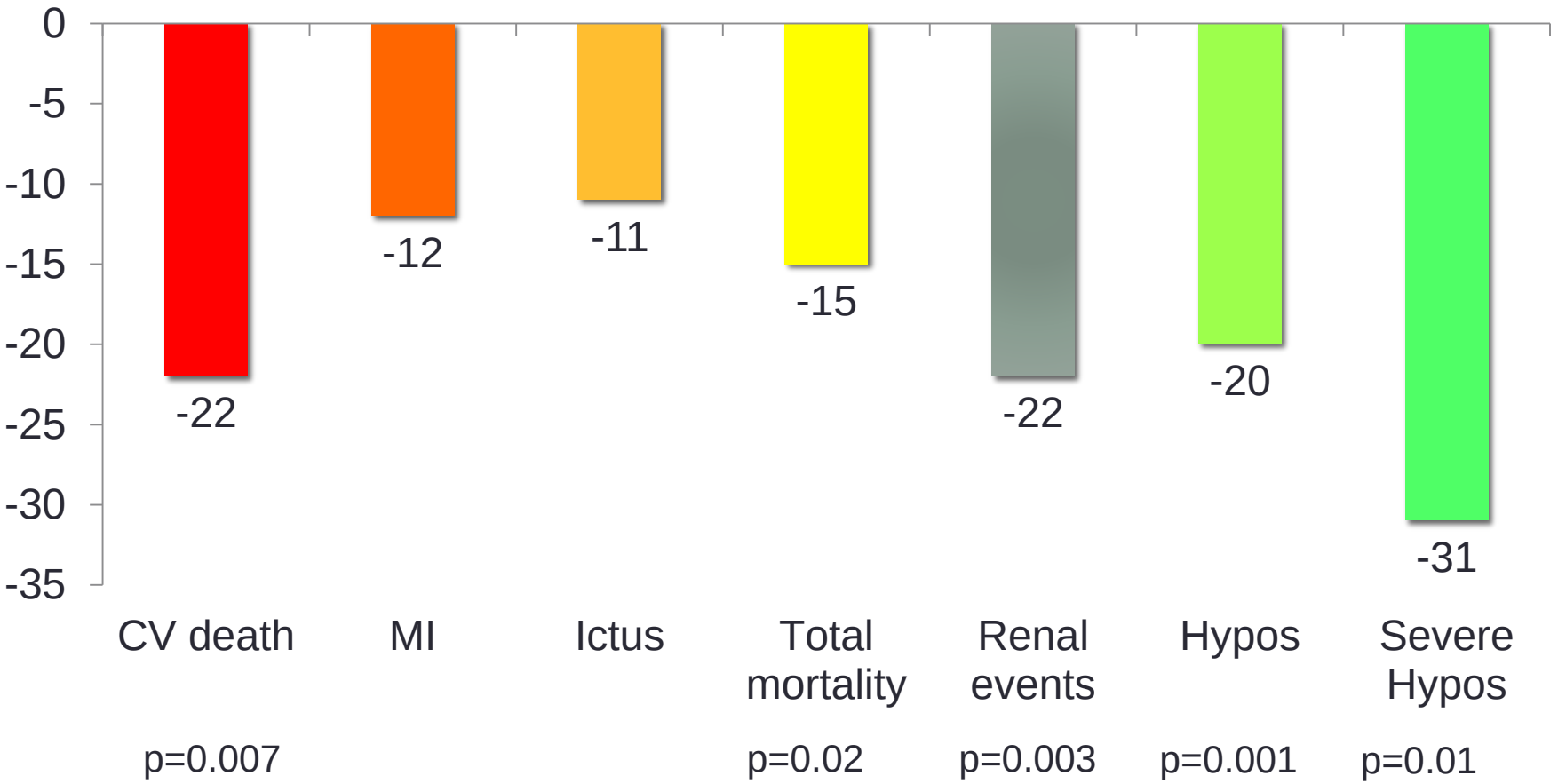


Liu SC et al. Diabetes Obes Metab 2012; 14: 810-820
Fujita Y et al. J Diabetes Investig 2014; 5: 265-275

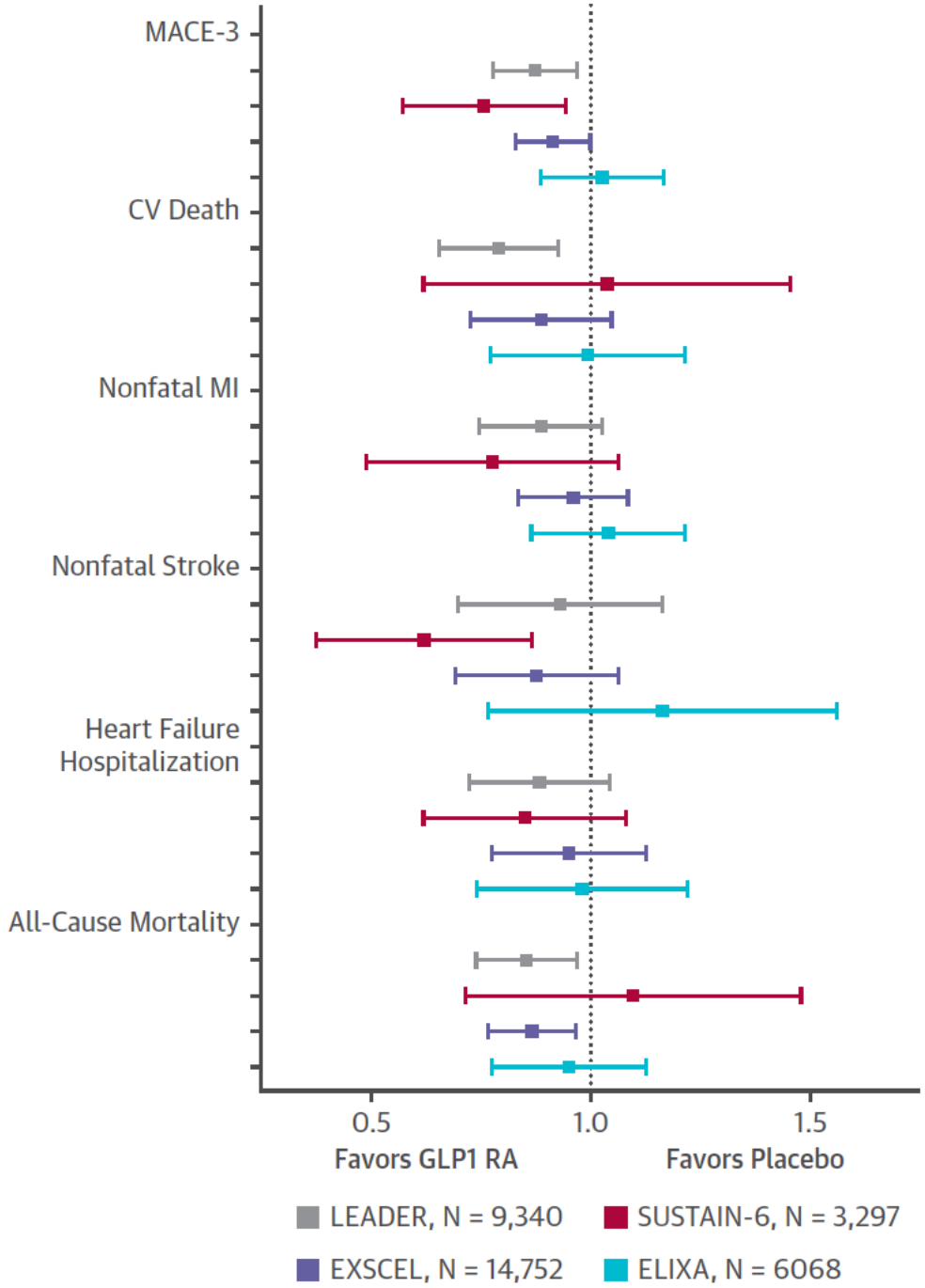
Marso SP et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1603827.

LEADER Results

% HR reduction in clinical outcomes with Liraglutide vs Placebo



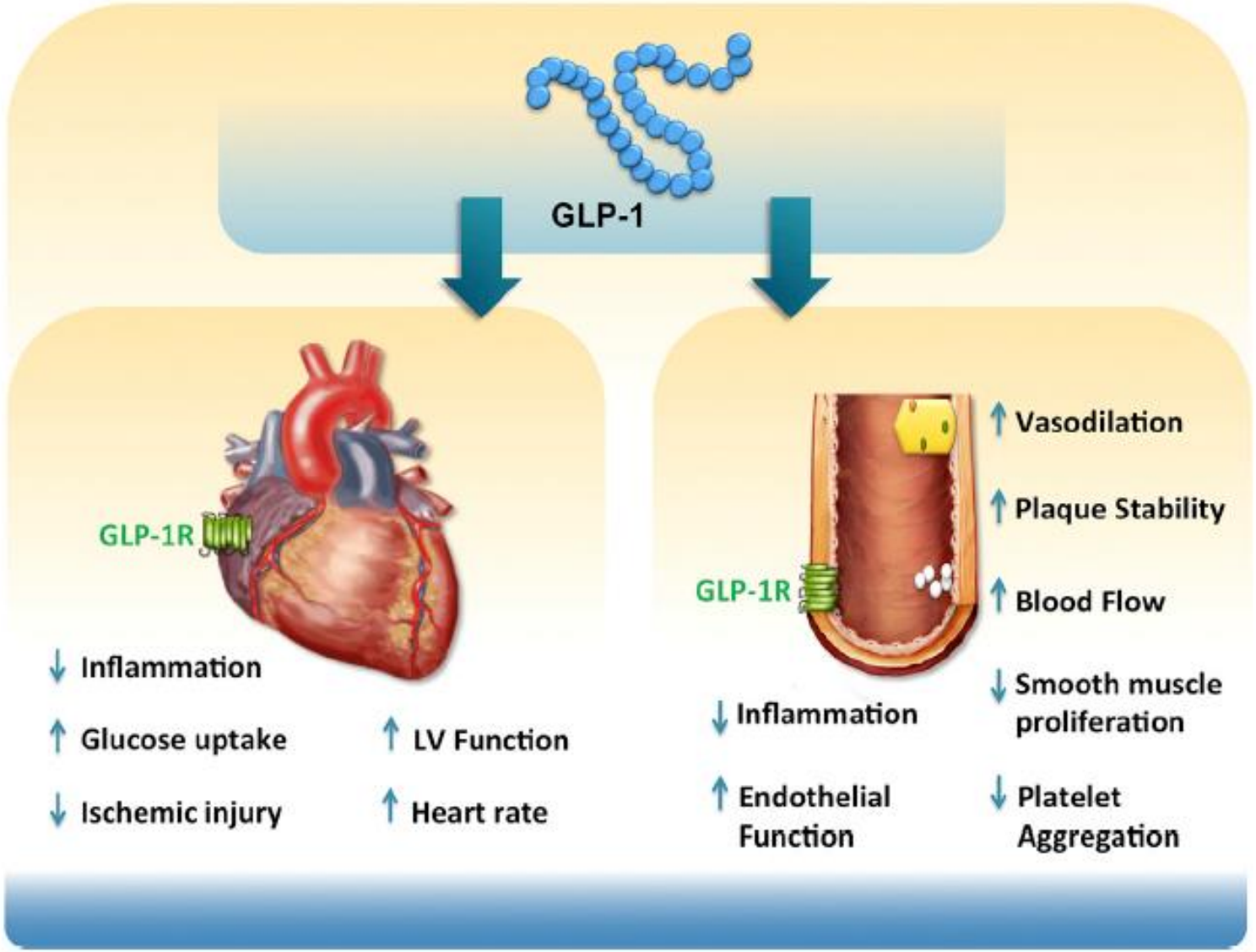
Summary of Reductions in Major Adverse Cardiac Events in Recent GLP-1 RA Trials



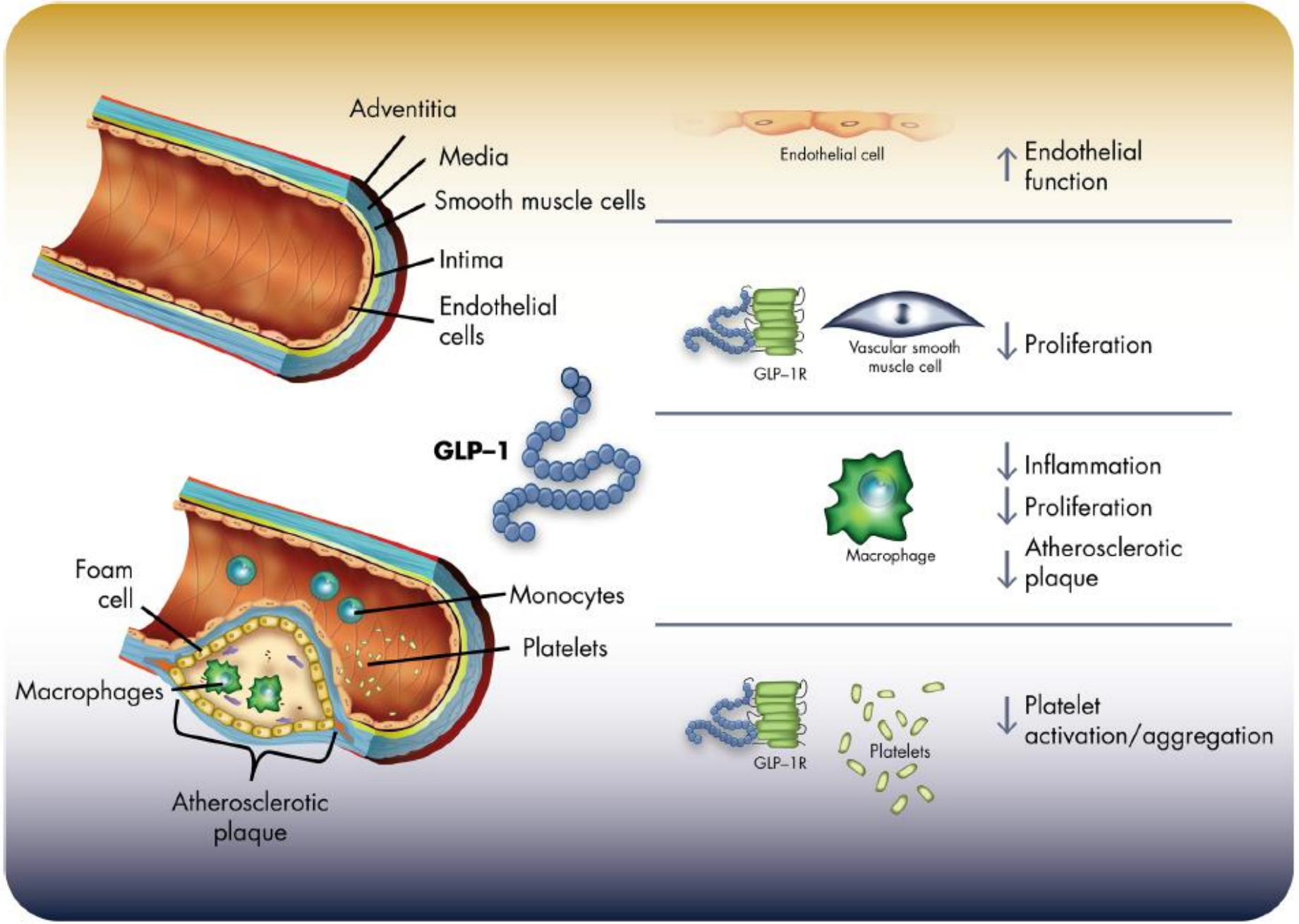
JACC VOL. 72, NO. 15, 2018

Cell Metabolism 2016

Direct and Indirect Actions of GLP-1 in the Heart and Blood Vessels

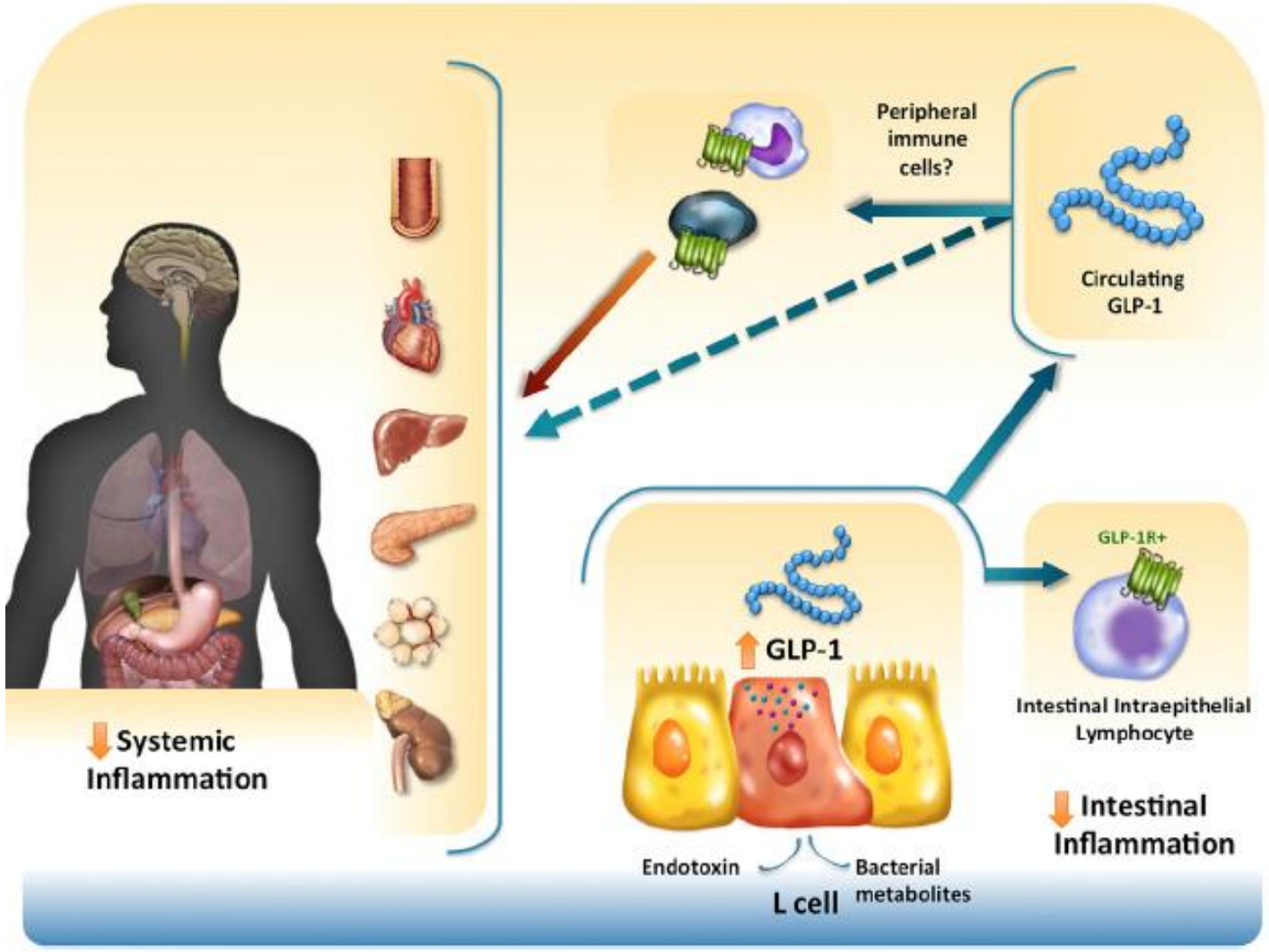


The vascular biology of GLP-1 action.



Endocrine Reviews, December 2016, 37(6):554–583

Mechanisms Linking GLP-1 to Modulation of Inflammation



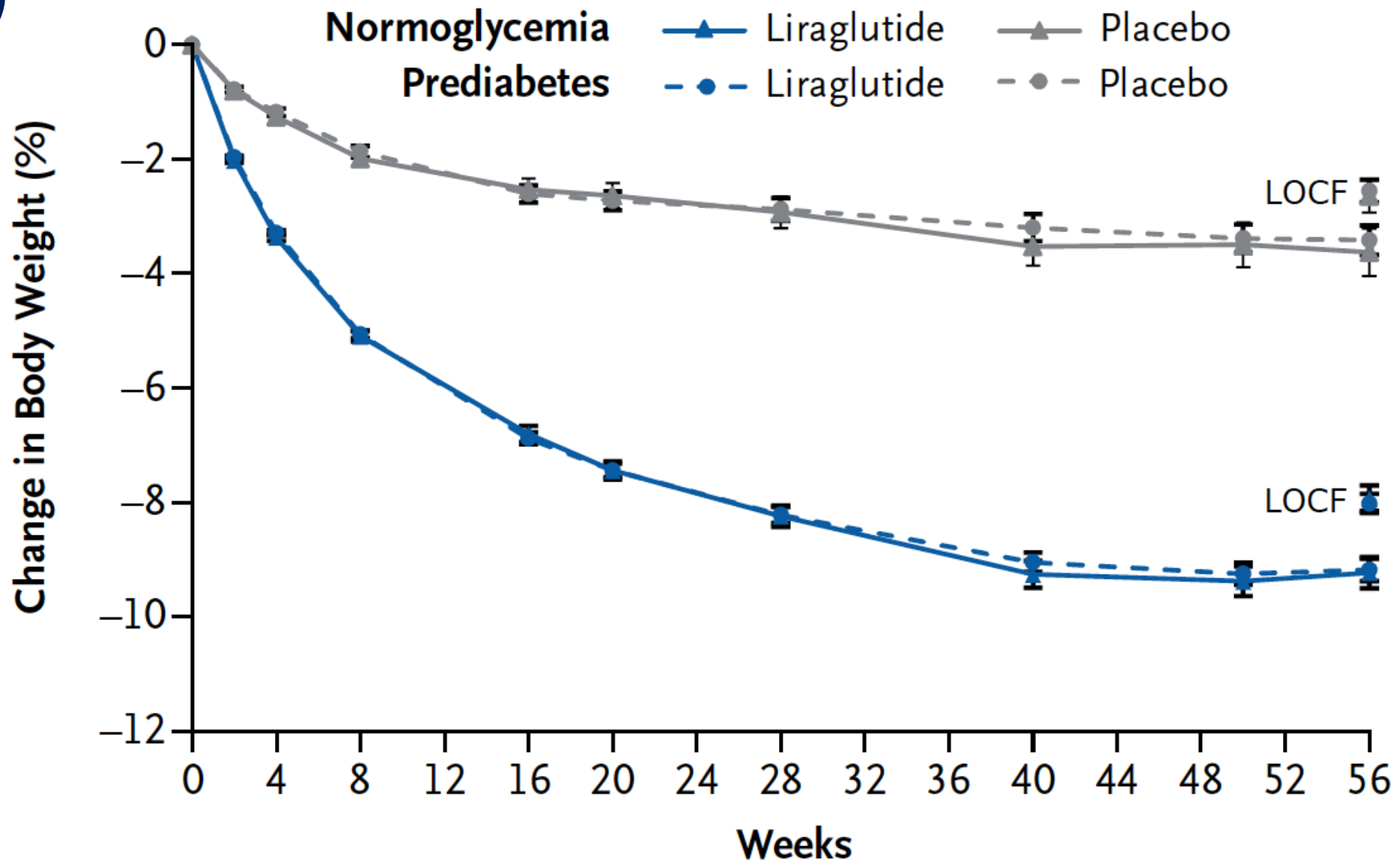
Cell Metabolism 2016

The NEW ENGLAND JOURNAL of MEDICINE

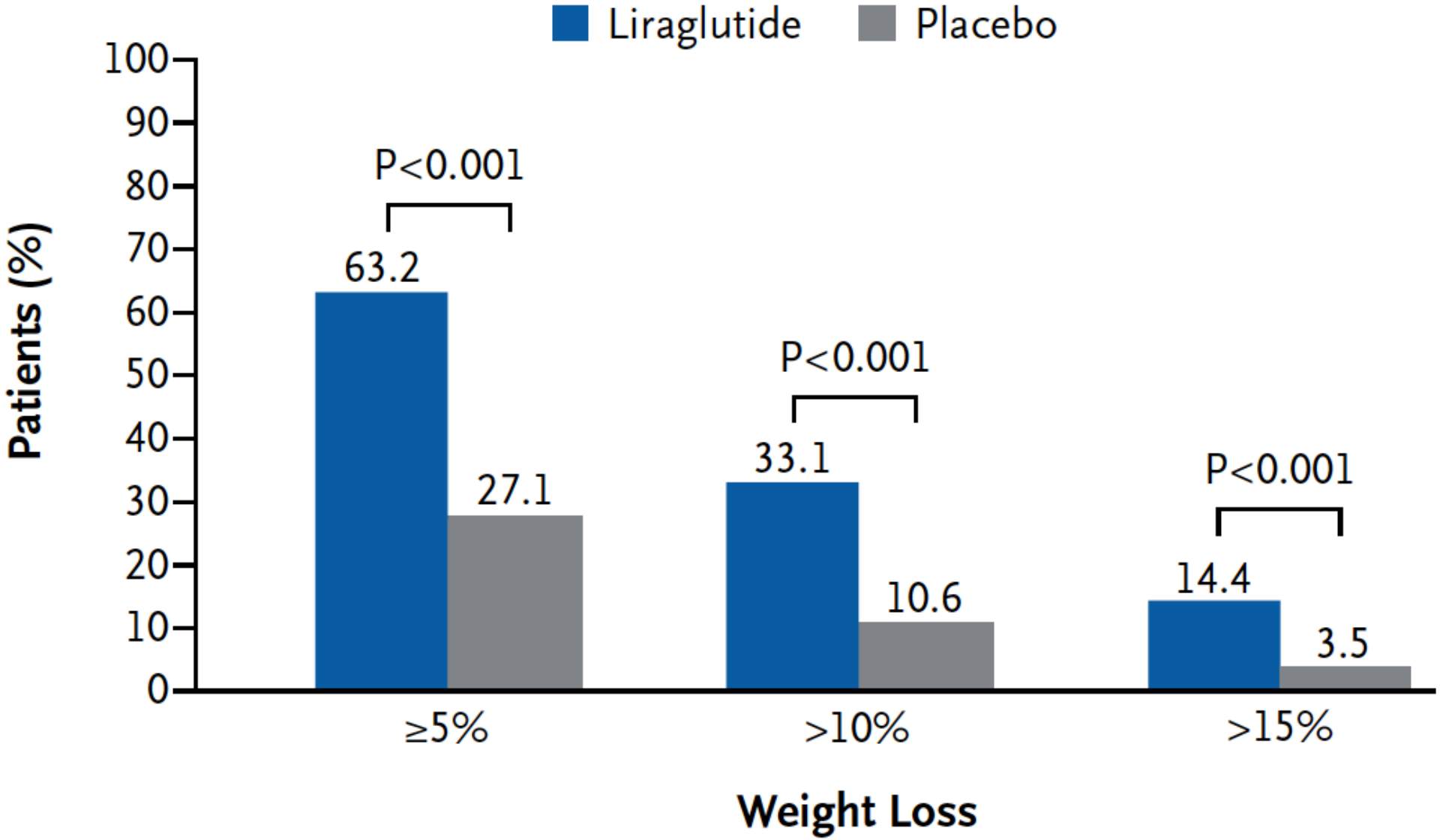
ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group*



N Engl J Med 2015;373:11-22.



N Engl J Med 2015;373:11-22.

Table 3. Adverse Events and Serious Adverse Events.*

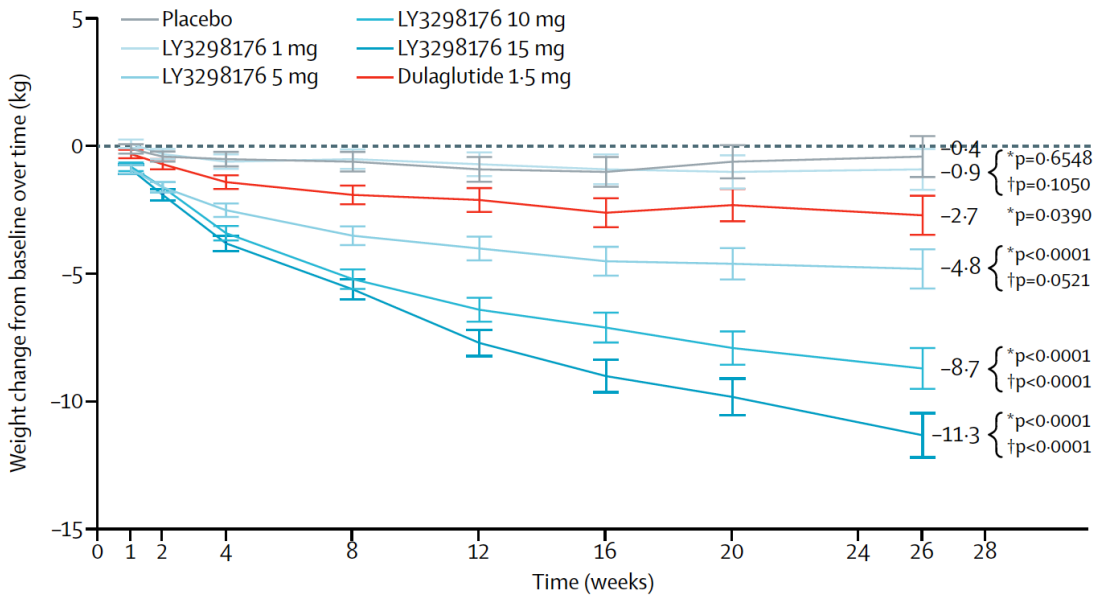
Event	Liraglutide (N=2481)			Placebo (N=1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5

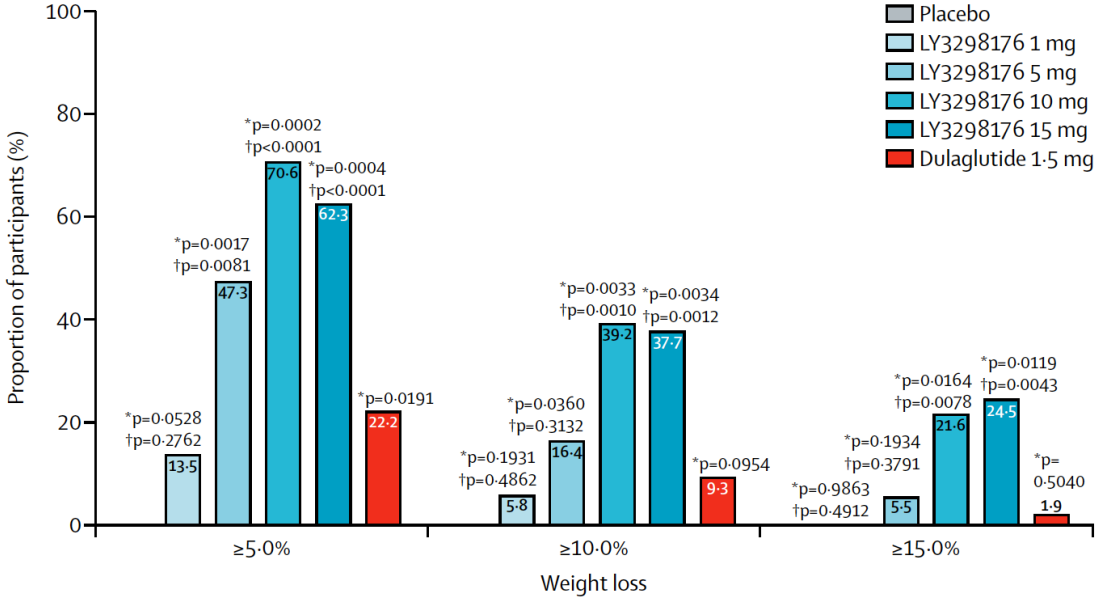
N Engl J Med 2015;373:11-22.

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

Juan Pablo Frias, Michael A Nauck, Joanna Van, Mark E Kutner, Xuewei Cui, Charles Benson, Shweta Urva, Ruth E Gimeno, Zvonko Milicevic, Deborah Robins, Axel Haupt

Bodyweight outcomes of treatment with LY3298176 at week 26





Lancet 2018; 392: 2180–93

Secretion of incretin hormones and quantification of the incretin effect after different bariatric surgeries for type 2 diabetes

	Eff ects on exposure of intestinal segments to nutrients	**GLP-1**	
Roux-en-Y gastric bypass	Duodenum and upper jejunum exposed to gastrointestinal secretory products only; lower small intestine (more L cells producing GLP-1) exposed to nutrients earlier and more extensively than without surgery	Significantly increased ↑↑↑	Significant increase in incretin effect (calculated from C-peptide) after surgery and greatly augmented GLP-1 response
Vertical sleeve gastrectomy	Acceleration of gastric emptying and more rapid exposure of the upper gut to nutrients	Significantly increased ↑↑	incretin effect improved significantly, but not as much as with gastric bypass

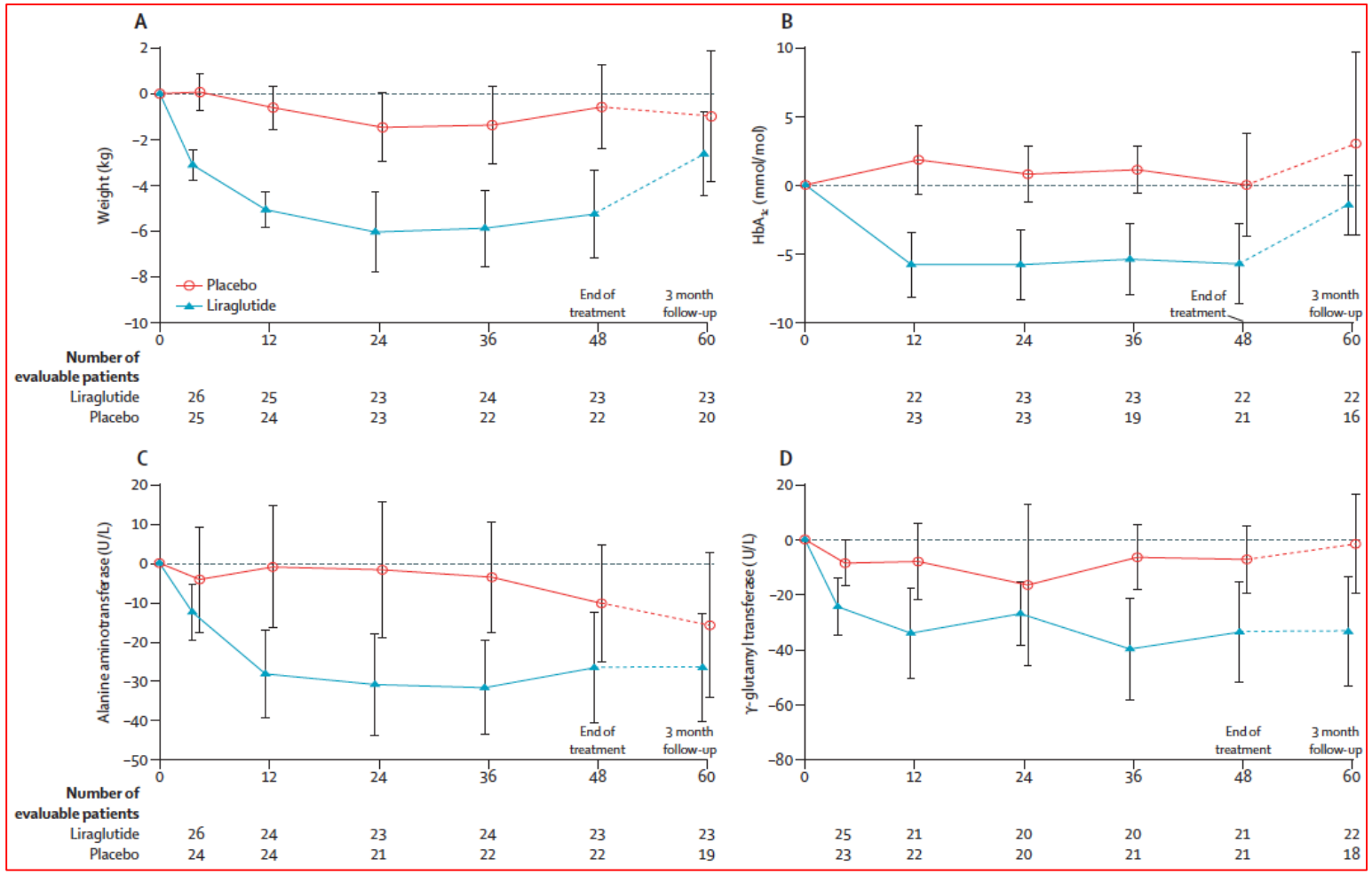
Lancet Diabetes Endocrinol 2016; 4: 525–36

Table 3 Potential GI therapeutic indications for glucagon-like peptide 1 based therapies

Condition	(potential) Mechanisms	Level of evidence
Dumping syndrome	Gastric emptying ↓	*Case series*[67]
Functional dyspepsia	Gastric emptying ↓ Gastric acid secretion ↓	*Hypothesised*
Constipated IBS	Colon circular muscle tone ↓ Visceral sensitivity ↓	*Clinical trials:* improved defaecation pattern, pain relief[80 91]
Short bowel syndrome	Gastric and bowel motility ↓	*Clinical trials:* reduced diarrhoea, improved nutritional status[93 94]
Mucositis and IBD	Inflammatory parameters ↓ Mucosal apoptosis ↓ Mucosa proliferation ↑	*Animal studies*: prevention of loss in mucosal mass in experimental mucositis[89 97]
NAFLD	Weight ↓ Hepatic insulin sensitivity ↑ Hepatic de novo lipogenesis ↓ Fatty acid oxidation ↑	*Clinical trials:* reduction in steatosis and steatohepatitis[148 155]
Cholangiopathies	Cholangiocyte proliferation ↑ Cholangiocyte apoptosis ↓ Bile acid production ↓	*Hypothesised*[168]

Smits MM, et al. Gut 2016;65:702–711.

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study



Lancet 2016; 387: 679–90

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide *vs* placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

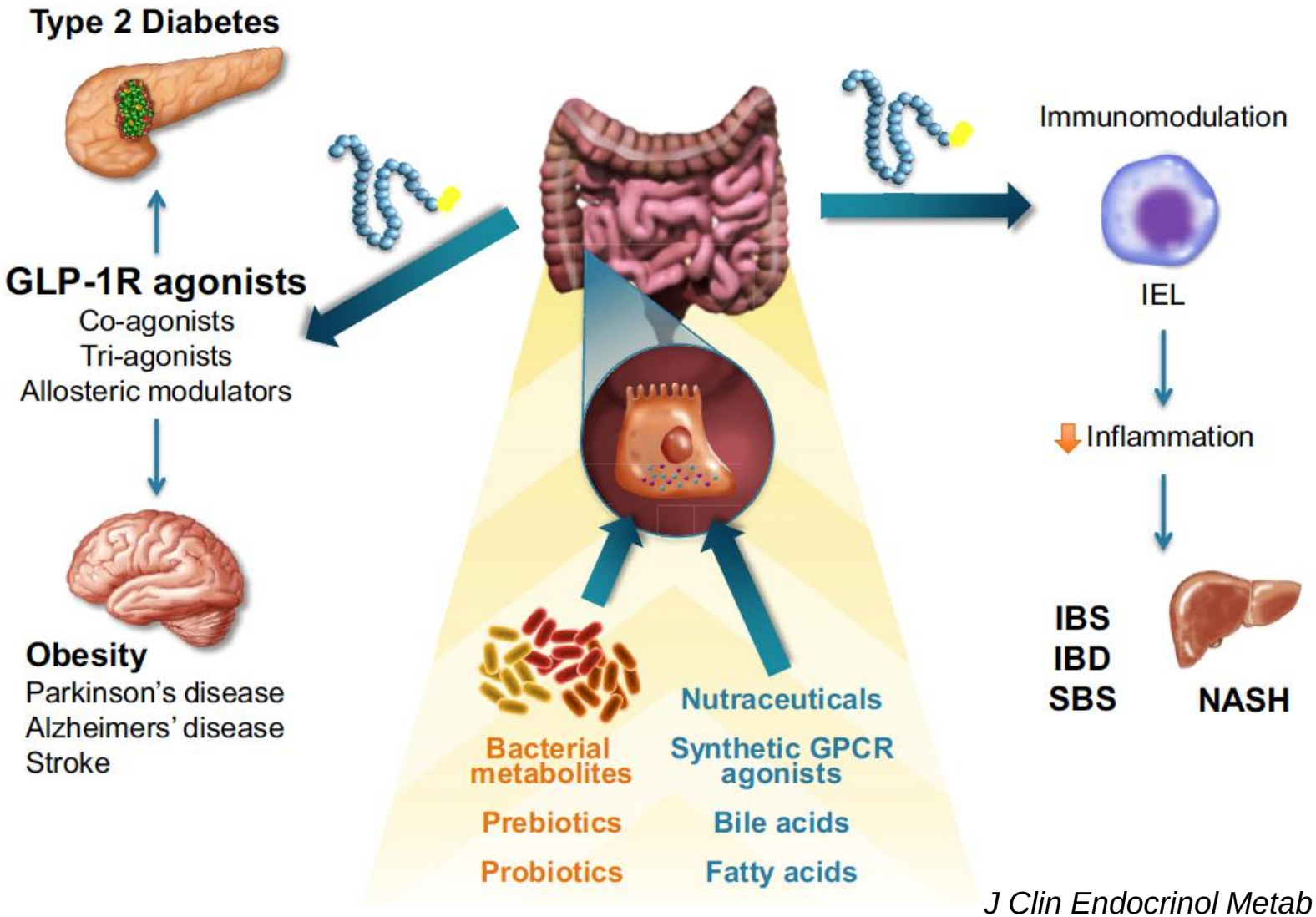
Lancet 2016; 387: 679–90

Table 4 Side effects of GLP-1 based therapies

Side effect	Frequency		Potential mechanism
	GLP-1RA	DPP-4I	
GI			
Nausea	+++	++	Gastric emptying ↓, activation nausea centres
Vomiting	++	+	Gastric emptying ↓, activation nausea centres
Diarrhoea	+++	+	Unknown
Constipation	++	+	Intestinal motility ↓
Flatulence	++	+	Unknown
Gastric reflux	++	+/++	Unknown
Pancreatitis	+/—	+/—	Unknown
Cholelithiasis	+/—	?	Weight loss, bile acid production ↓, gallbladder motility ↓
Other			
Hypoglycaemia*	+/++	+/++	Insulin secretion ↑, intestinal glucose uptake ↓
Nasopharyngitis	+	+	Unknown
Anaphylaxis	+/—	+/—	Immunoreactive
Prerenal failure	+/—	+/—	Dehydration by vomiting, diuresis ↑

Smits MM, et al. Gut 2016;65:702–711.

Translational potential of the GLP-1-producing EEC



J Clin Endocrinol Metab 101: 778–786, 2016

CONCLUSIONE E PROSPETTIVE FUTURE

- I GLP1 agonisti sono in grado non solo di migliorare il controllo metabolico nel paziente diabetico, ma anche di ridurre il rischio CVD con meccanismi indipendenti dall'effetto sulla glicemia e sul peso corporeo.
- I GLP1 agonisti a dosaggi elevato sono dei potenti farmaci anti-obesità.
- I GLP1 agonisti potrebbero essere di beneficio a numerose patologie di interesse gastroenterologico, quali la dispepsia, la «dumping syndrome», il colon irritabile, le malattie infiammatorie, la sdr dell'intestino corto, la NASH e patologie colestatiche.

1

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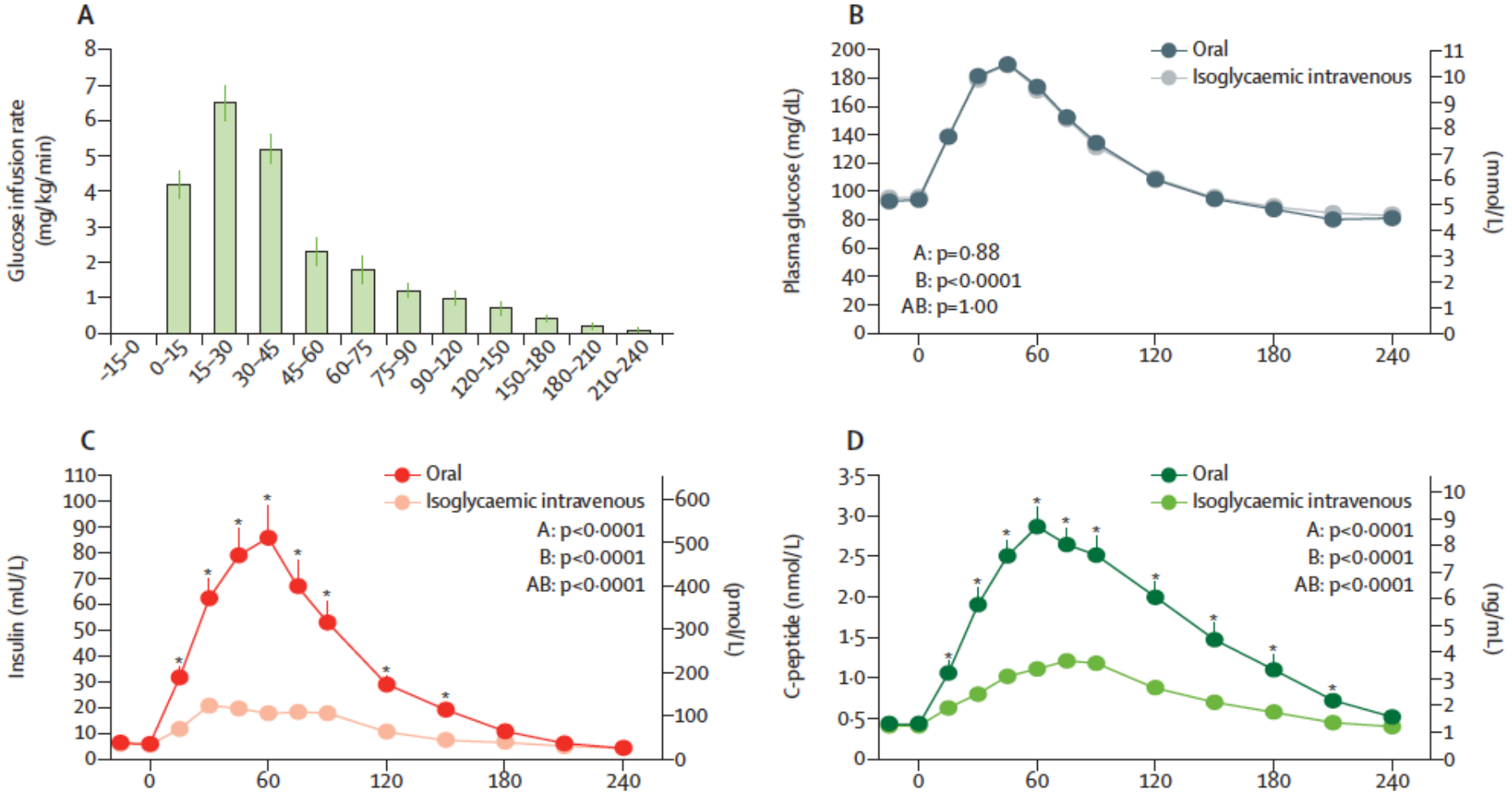

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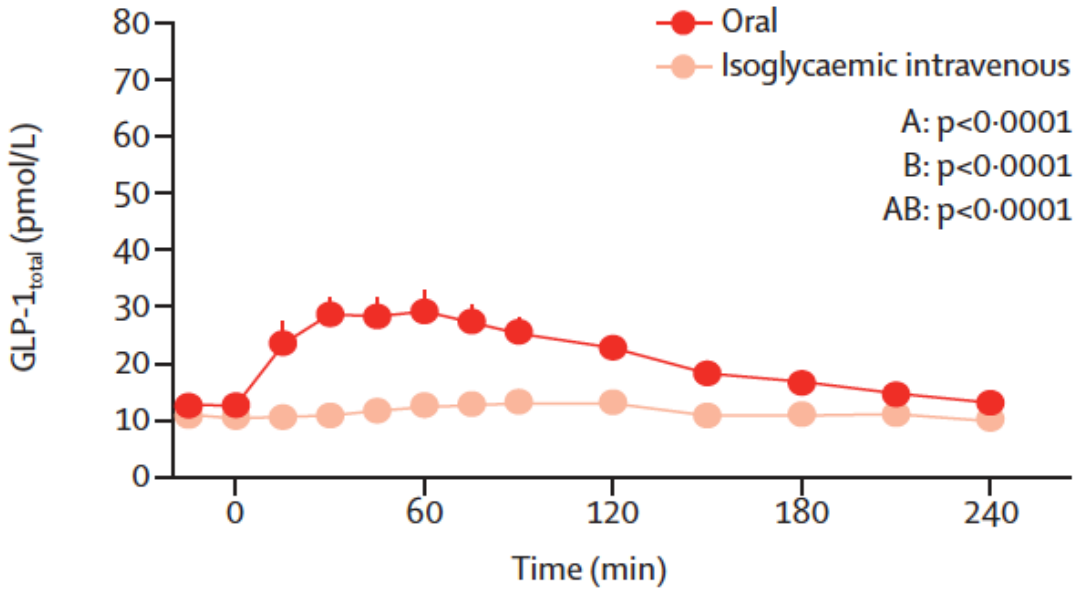

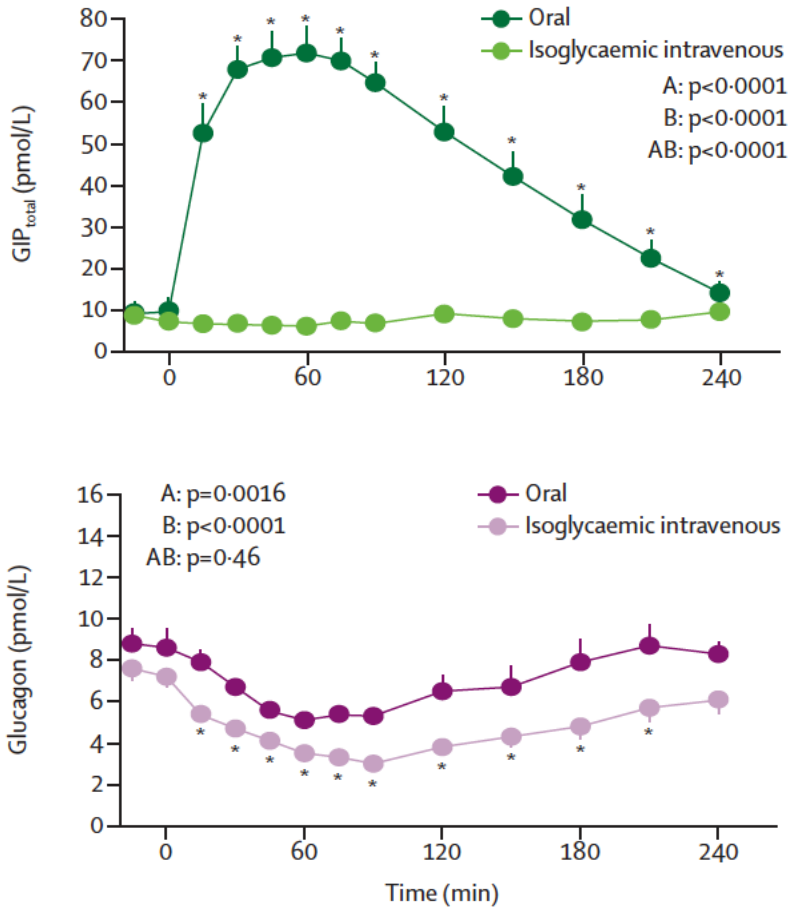

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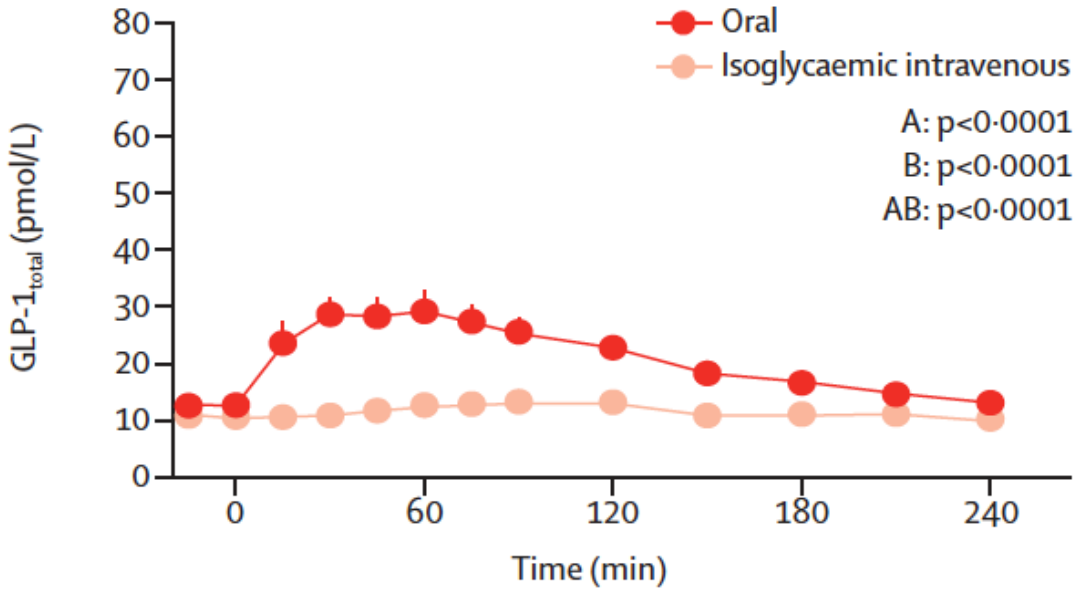

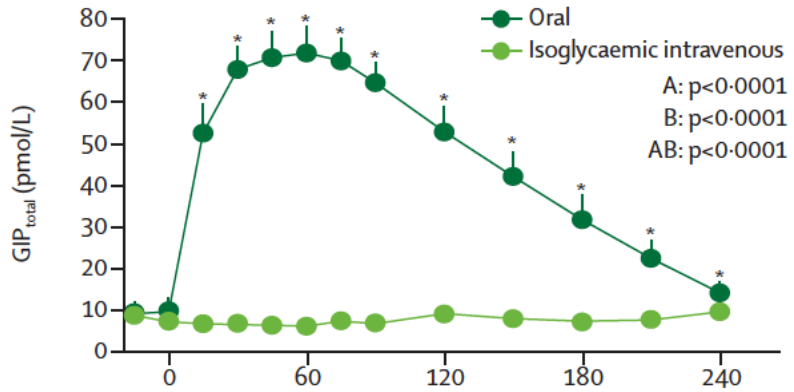

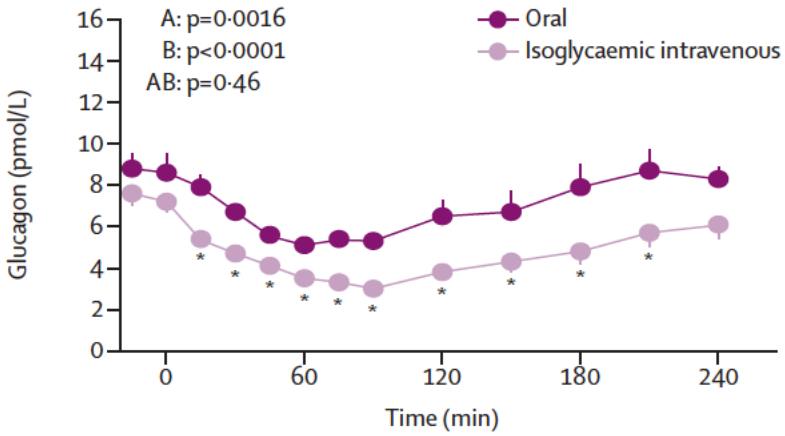

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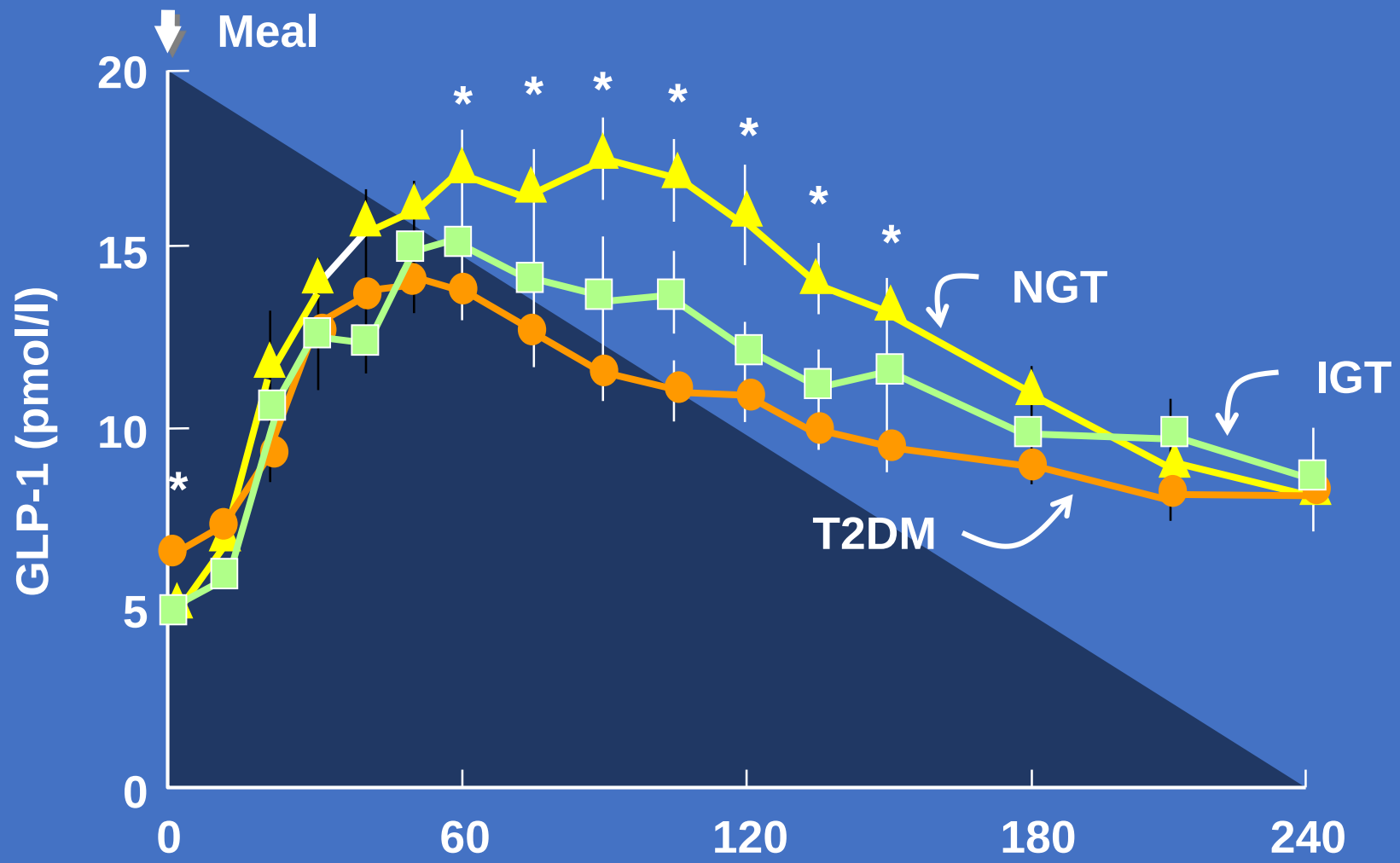
Postprandial GLP-1 levels are decreased in people with IGT and Type 2 diabetes

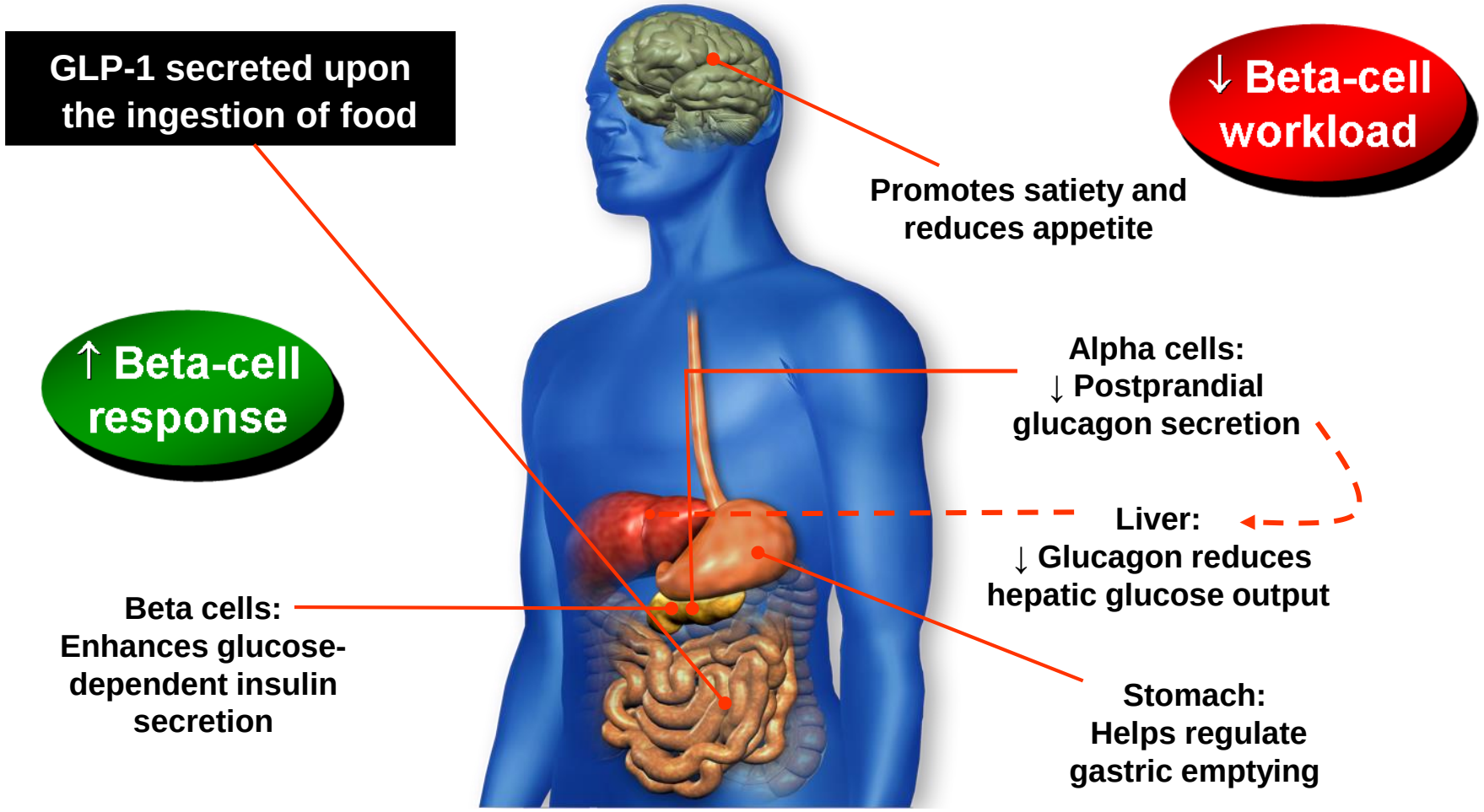


***P*<0.05 T2DM vs NGT**

Toft-Nielsen et al. *J Clin Endocrinol Metab.* 2001

IGT=impaired glucose tolerance; NGT=normal glucose tolerance

GLP-1 actions in humans



Flint et Al. *J Clin Invest*. 1998;101:515-520.; Larsson et Al.*Acta Physiol Scand*. 1997;160:413-422.; Nauck MA et Al. *Diabetologia*. 1996;39:1546-1553.; Drucker DJ *Diabetes.* 1998;47:159-169.

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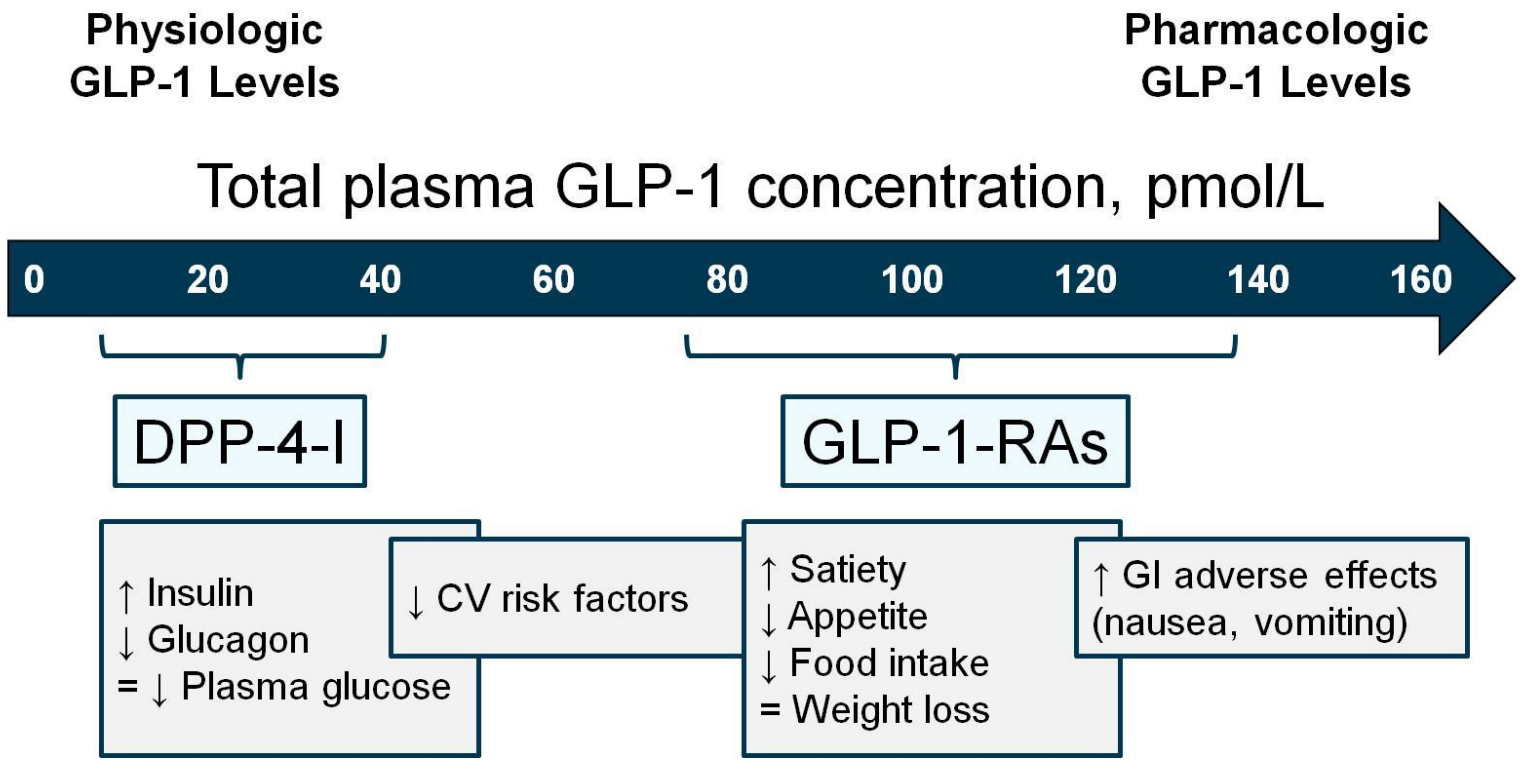
Dose-Related Effects of GLP-1

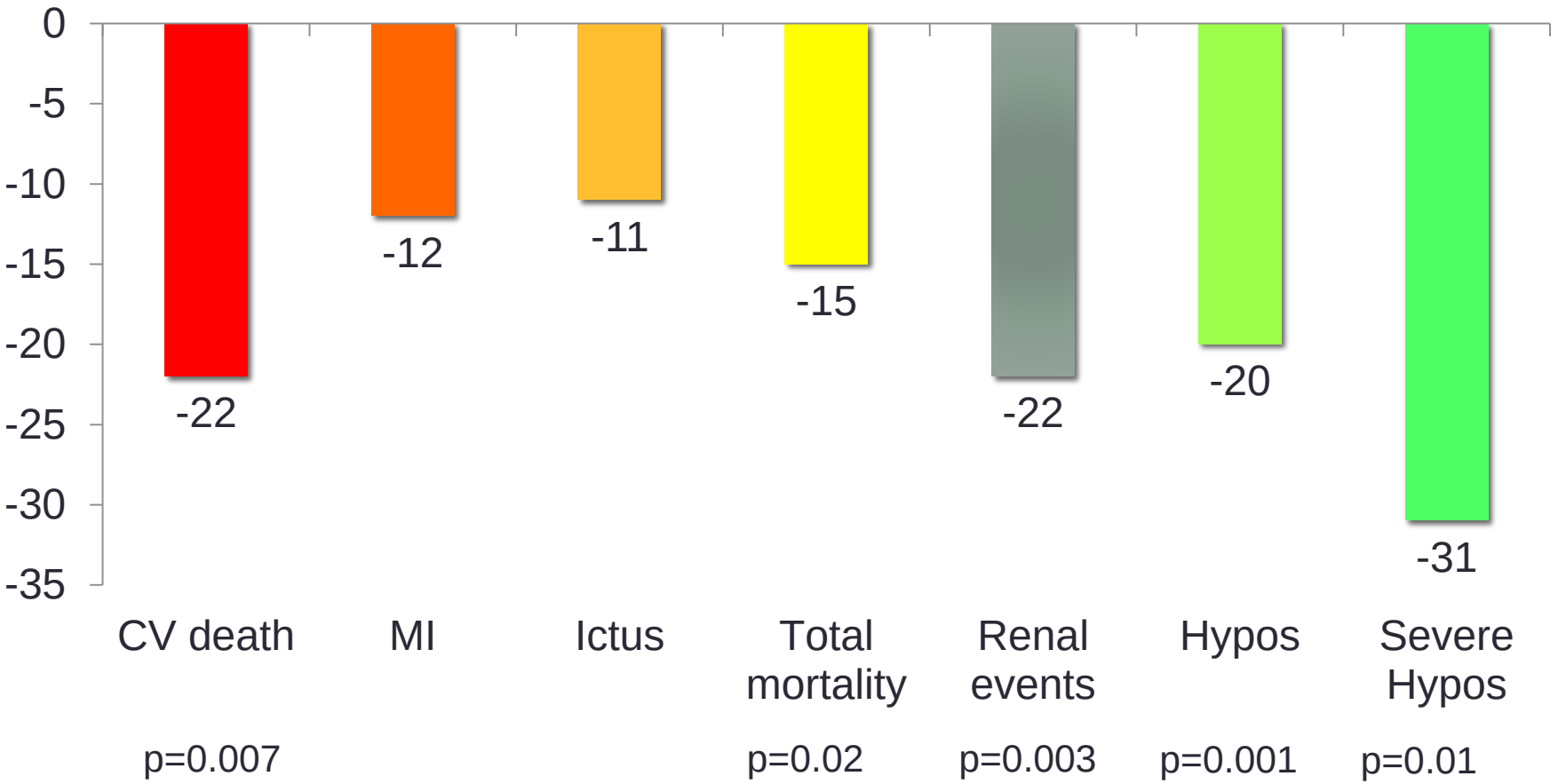


Courtesty of Vilsbøll T.

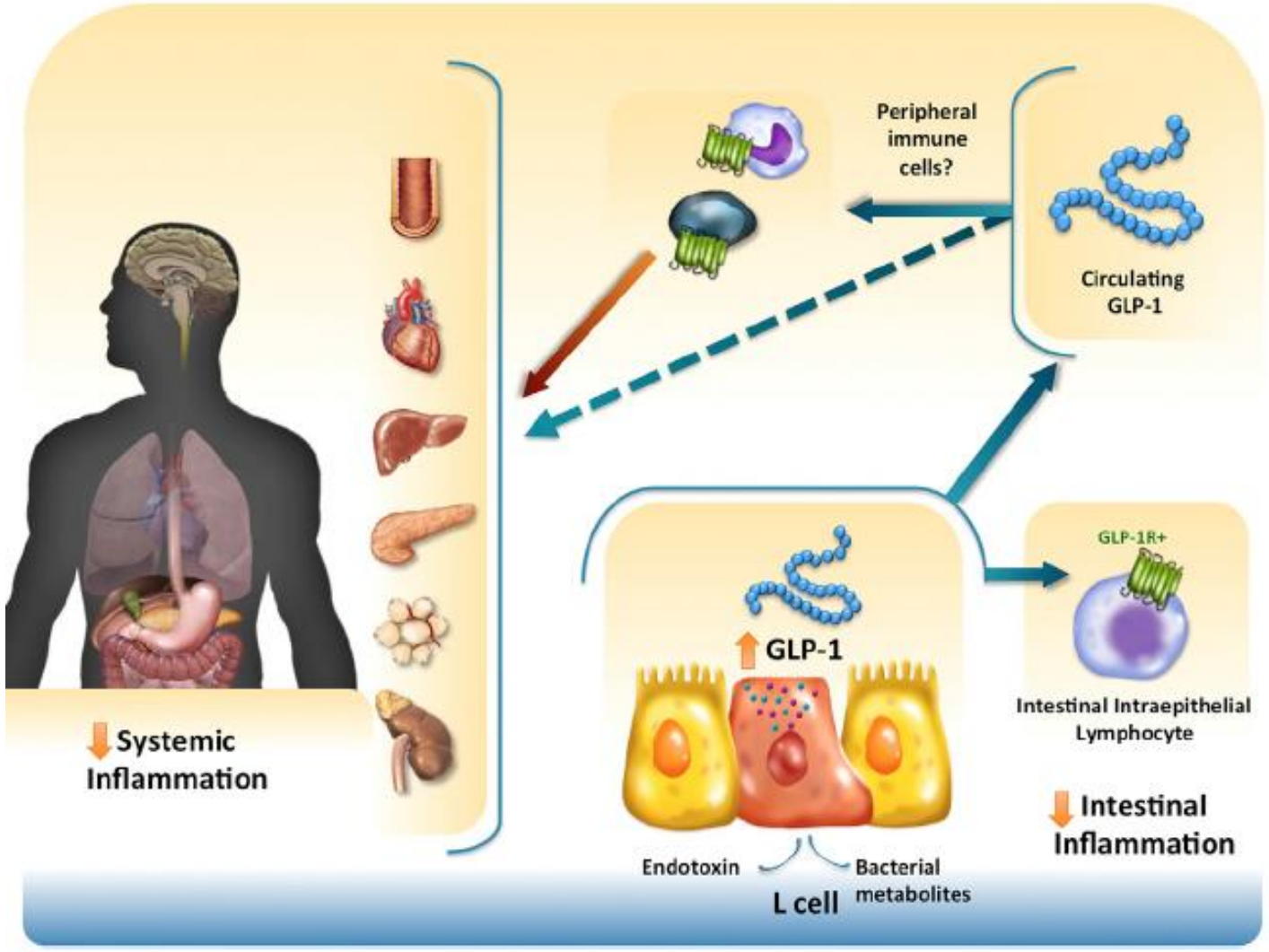
Marso SP et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1603827.

LEADER Results

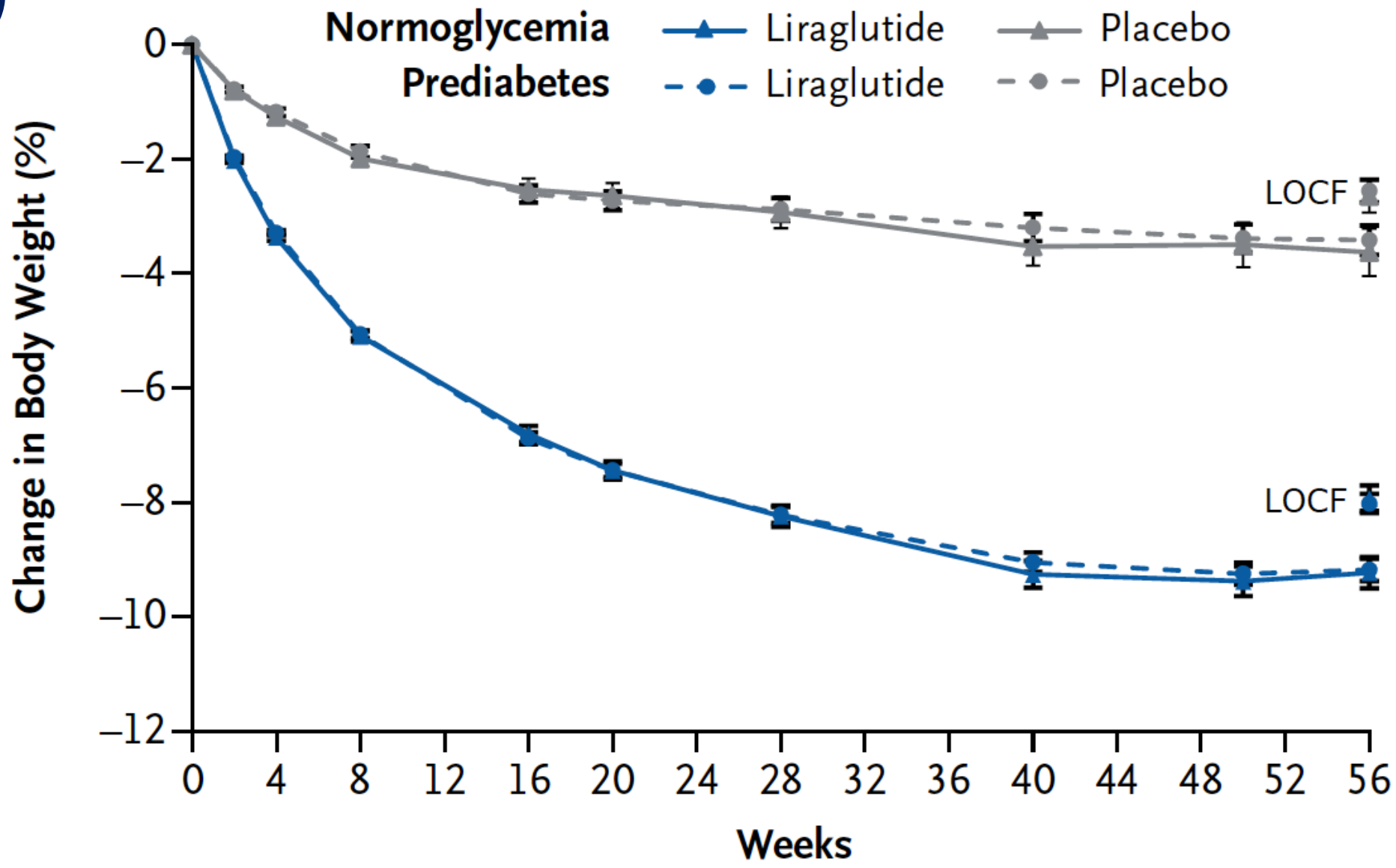
% HR reduction in clinical outcomes with Liraglutide vs Placebo



Mechanisms Linking GLP-1 to Modulation of Inflammation



Cell Metabolism 2016



N Engl J Med 2015;373:11-22.

Table 3 Potential GI therapeutic indications for glucagon-like peptide 1 based therapies

Condition	(potential) Mechanisms	Level of evidence
Dumping syndrome	Gastric emptying ↓	*Case series*[67]
Functional dyspepsia	Gastric emptying ↓ Gastric acid secretion ↓	*Hypothesised*
Constipated IBS	Colon circular muscle tone ↓ Visceral sensitivity ↓	*Clinical trials:* improved defaecation pattern, pain relief[80 91]
Short bowel syndrome	Gastric and bowel motility ↓	*Clinical trials:* reduced diarrhoea, improved nutritional status[93 94]
Mucositis and IBD	Inflammatory parameters ↓ Mucosal apoptosis ↓ Mucosa proliferation ↑	*Animal studies*: prevention of loss in mucosal mass in experimental mucositis[89 97]
NAFLD	Weight ↓ Hepatic insulin sensitivity ↑ Hepatic de novo lipogenesis ↓ Fatty acid oxidation ↑	*Clinical trials:* reduction in steatosis and steatohepatitis[148 155]
Cholangiopathies	Cholangiocyte proliferation ↑ Cholangiocyte apoptosis ↓ Bile acid production ↓	*Hypothesised*[168]

Smits MM, et al. Gut 2016;65:702–711.