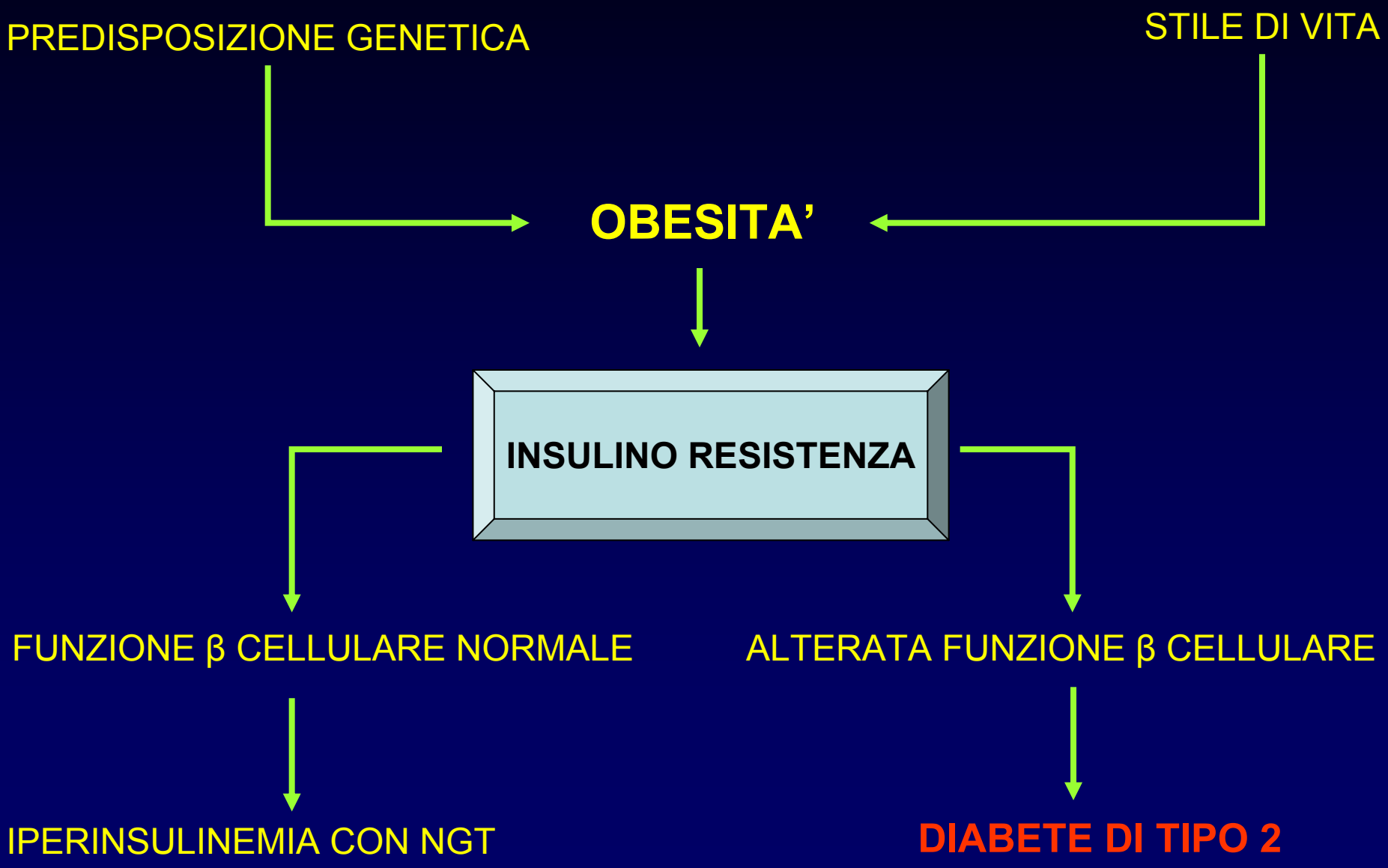
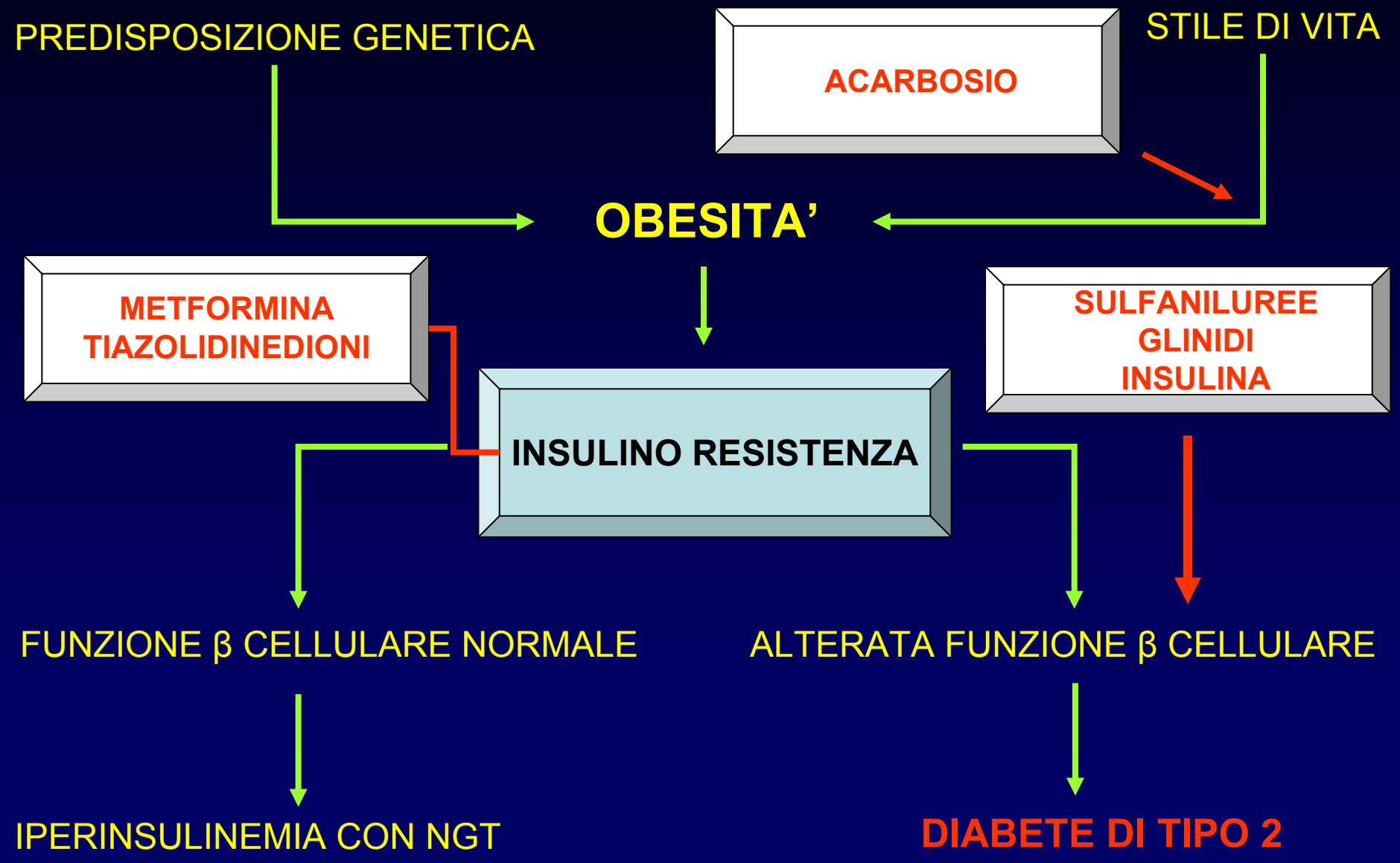
Patogenesi del Diabete di Tipo 2

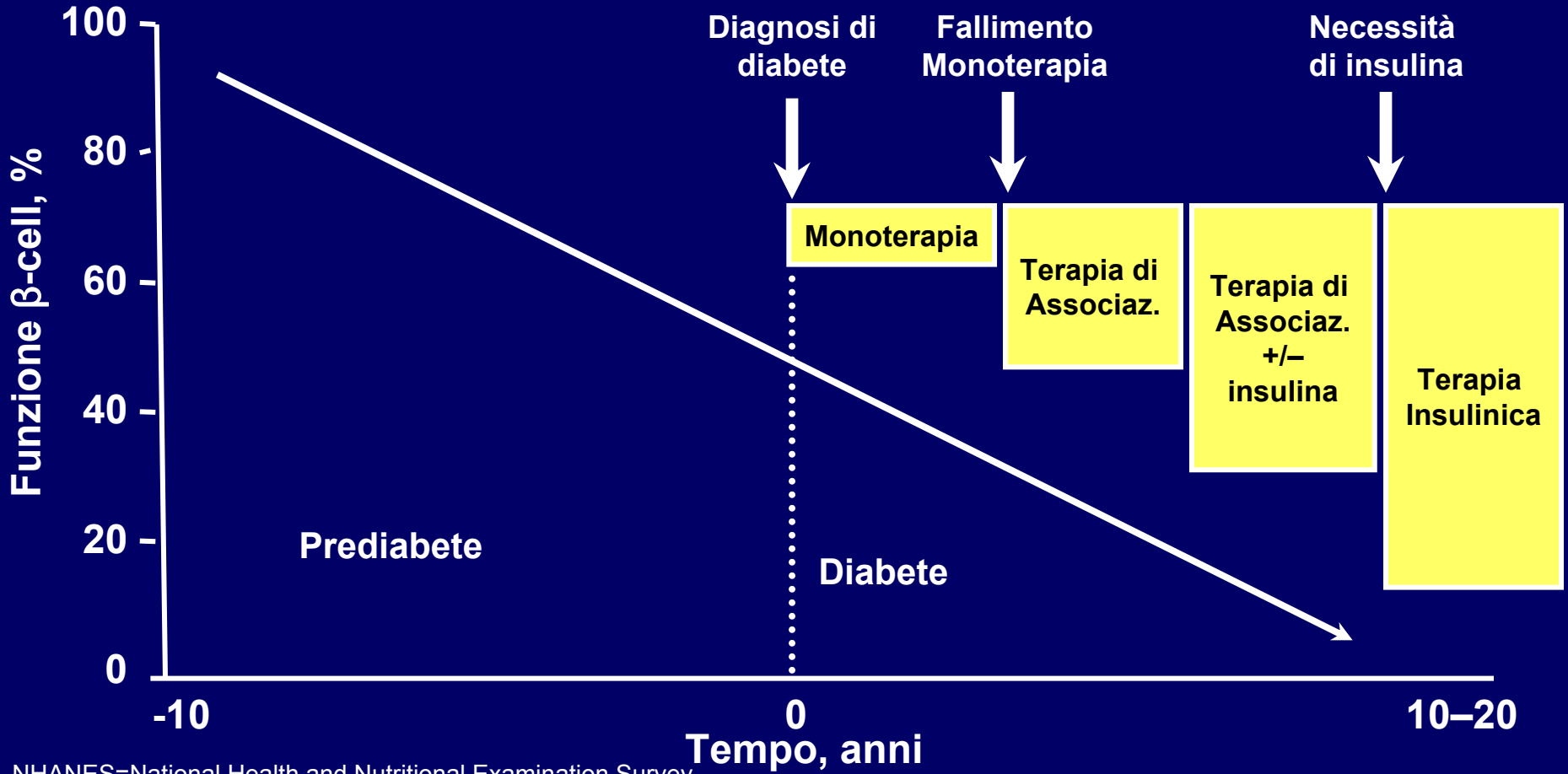


Armamentario Terapeutico del Diabete di Tipo 2



Con il progredire della malattia gli obiettivi del trattamento diventano più difficili da raggiungere

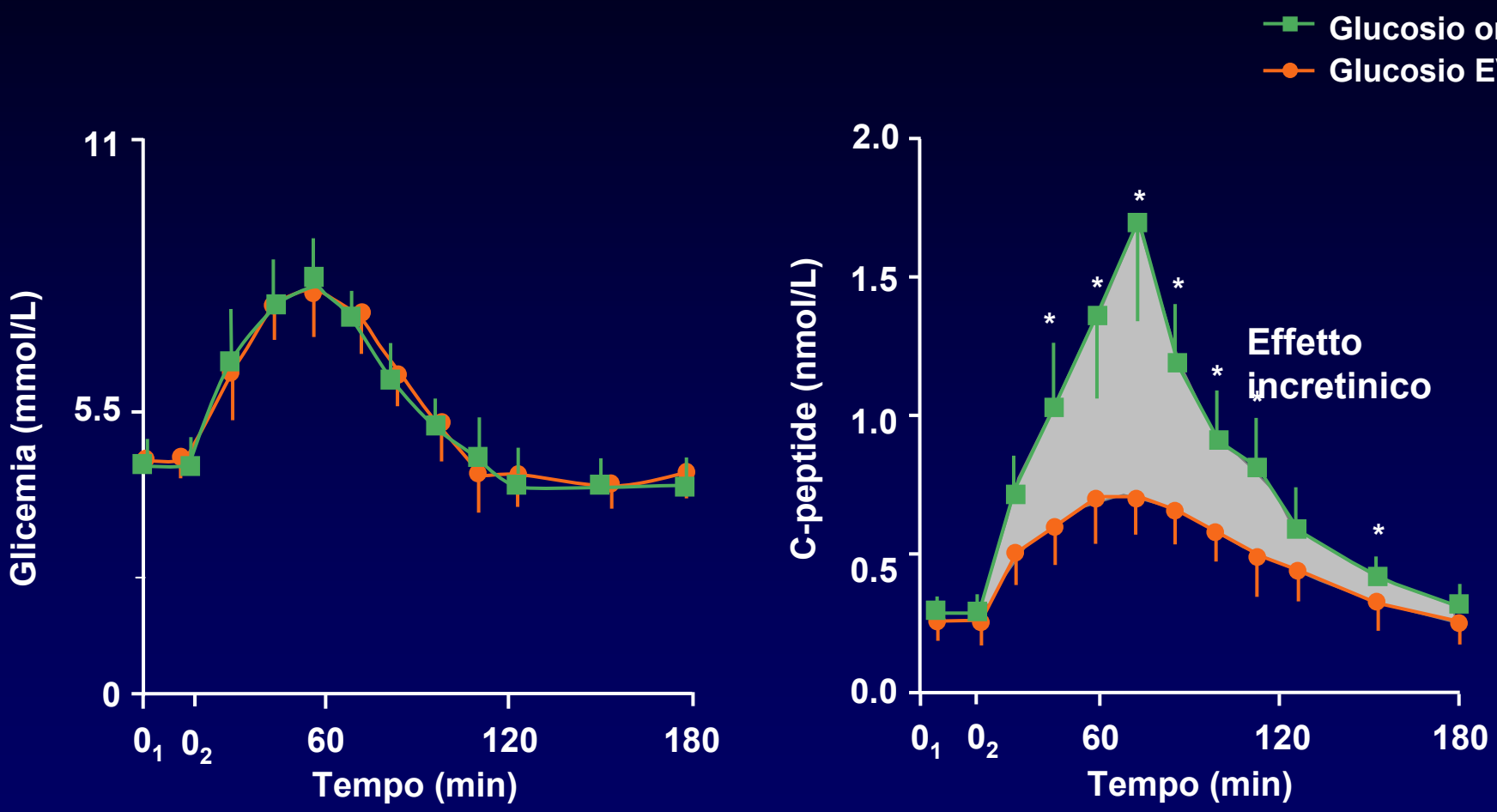
Parametri (NHANES)	
% Pazienti con HbA_{1c}<7%	49.8% (2001–2002)
Valori medi di HbA_{1c}	7.9% (1999–2000)



NHANES=National Health and Nutritional Examination Survey.

Lebovitz HE. *Med Clin N Am*. 2004;88:847–863; Turner RC et al. *JAMA*. 1999;281:2005–2012; UKPDS 16. *Diabetes*. 1995;44:1249–1258; Warren RE. *Diabetes Res Clin Pract*. 2004;65:S3–S8; Resnick HE et al. *Diabetes Care*. 2006;29:531–537; Koro CE et al. *Diabetes Care*. 2004;27:17–20.

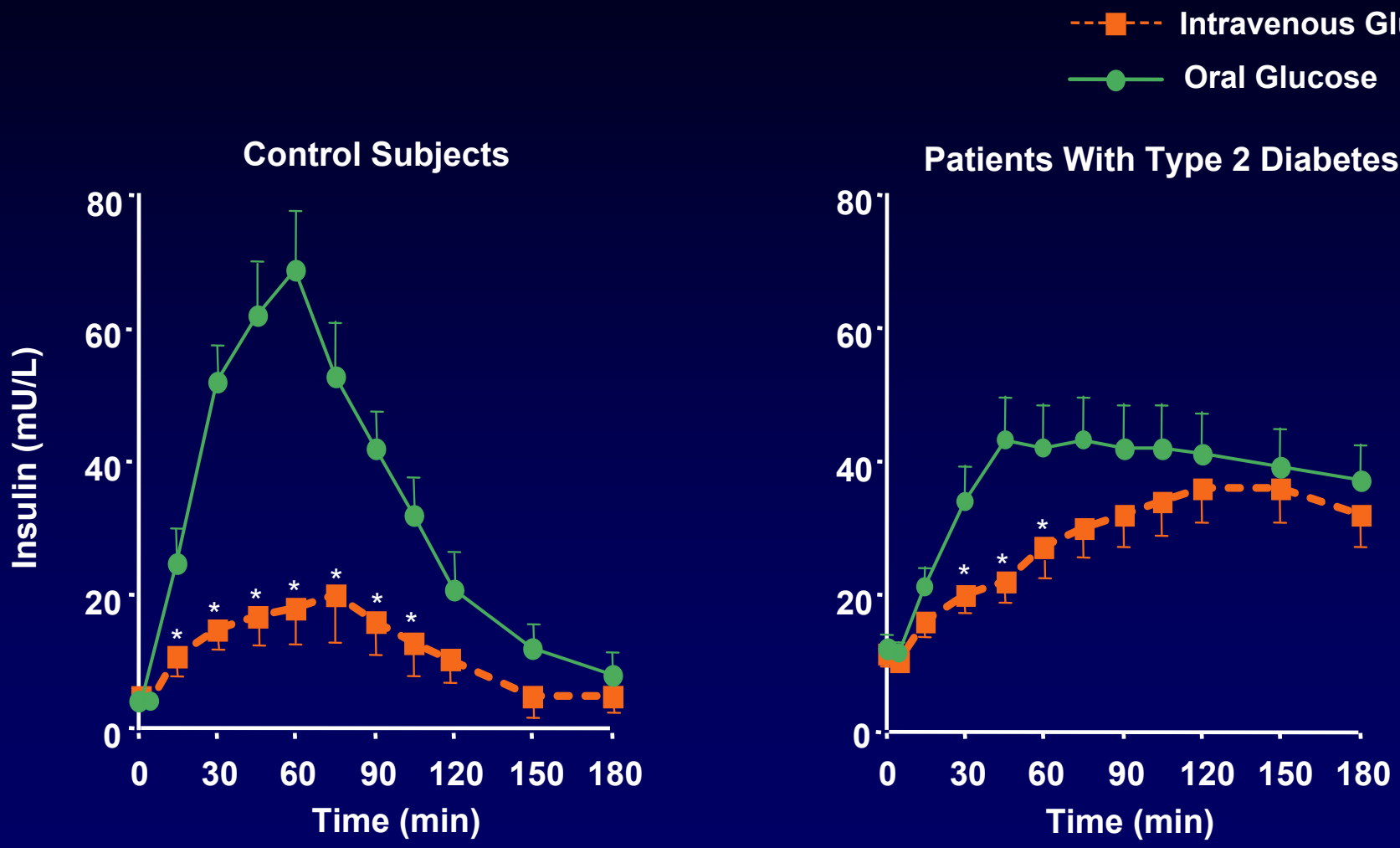
L'effetto incretinico: differente risposta al glucosio orale ed EV



Mean ± SE; N = 6; *$P \leq .05$; 0_1-0_2 = glucose infusion time.

Nauck MA, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab.* 1986;63:492-498. Copyright 1986, The Endocrine Society.

The Incretin Effect Is Reduced in Patients With Type 2 Diabetes



*$P \leq .05$ compared with respective value after oral load.

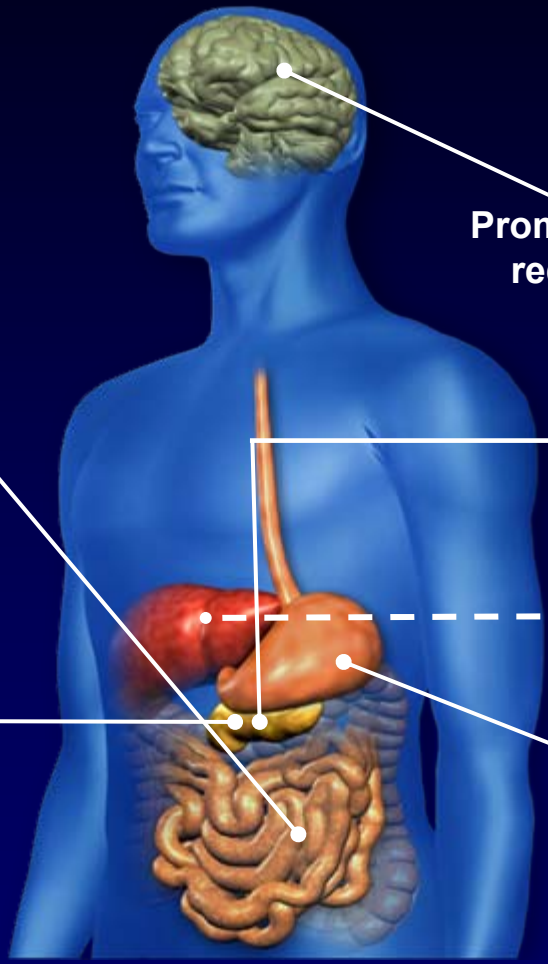
Nauck MA, et al. *Diabetologia*. 1986;29:46-52. Reprinted with permission from Springer-Verlag © 1986.

Le 2 incretine principali sono il GLP-1 ed il GIP

- Sono state identificate due incretine principali :
  - Glucagon-like peptide 1 (GLP-1)
    - Sintetizzato e rilasciato dalle cellule L dell'ileo
    - Siti d'azione multipli: cellule β e α , tratto GI, CNS, polmone e cuore
    - Le azioni sono mediate da recetori specifici
  - Glucose-dependent insulinotropic polypeptide (GIP)
    - Sintetizzato e rilasciato dalle cellule K del digiuno
    - Sito d'azione: prevalentemente β cellule pancreatiche; agisce anche sugli adipociti
    - Le azioni sono mediate da recettori specifici
- Il GLP-1 è responsabile della maggior parte dell'effetto incretinico

Wei Y, et al. *FEBS Lett.* 1995;358:219-224.; Drucker DJ. *Diabetes Care*. 2003;26:2929-2940.; Kieffer TJ, et al. *Endocr Rev.* 1999;20:876-913.; Thorens B. *Diabete Metab.* 1995;21:311-318.

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload

Promotes satiety and reduces appetite

↑ Beta-cell response

Alpha cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

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

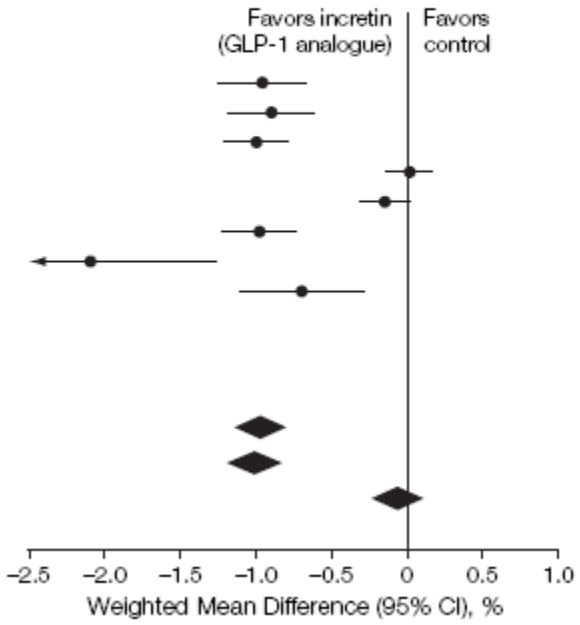
Name	Description	Structure
GLP-1	Physiological peptide	^{7}HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR^{36}
Liraglutide (NN2211)	GLP-1 analogue	^{7}HAEGTFTSDVSSYLEGQAA**K**EFIAWLV**R**GR**G**^{37} **E** — **C-16 fatty acid chain**
Exendin/exenatide (Byetta)	GLP-1 mimetic	^{1}H**G**EGTFTSD**L**S**K**Q**M**E**EE**A**V**R**L**F**I**E**W**L**K**N**G**GPSSGAPPPS**^{39}

Weighted Mean Difference in Change in Hemoglobin A1c Percentage Value for GLP-1 Analogues vs Control in Adults With Type 2 Diabetes

Figure 2. Weighted Mean Difference in Change in Hemoglobin A_{1c} Percentage Value for GLP-1 Analogues vs Control in Adults With Type 2 Diabetes

Source	Study Duration, wk	No. of Participants	Weighted Mean Difference (95% CI) for Change in Hemoglobin A_{1C}, %
Buse et al,[11] 2004	30	252	−0.96 (−1.24 to −0.68)
DeFronzo et al,[12] 2005	30	226	−0.90 (−1.18 to −0.62)
Kendall et al,[13] 2005	30	488	−1.00 (−1.21 to −0.79)
Heine et al,[14] 2005	26	535	0.02 (−0.12 to 0.16)
Nauck et al,[15] 2007	52	501	−0.15 (−0.32 to 0.01)
Zinman et al,[16] 2007	16	233	−0.98 (−1.21 to −0.74)
Kim et al,[17] 2006	15	29	−2.10 (−2.93 to −1.27)
Madsad et al,[18] 2004	12	57	−0.75 (−1.10 to −0.40)

Comparisons	No. of Studies			I^2, %
GLP-1 vs placebo[11-13,16-18]	6	1285	−0.97 (−1.13 to −0.81)	44
Exenatide vs placebo[11-13,16]	5	1228	−1.01 (−1.18 to −0.84)	45
Exenatide vs insulin[14,15]	2	1036	−0.06 (−0.22 to 0.10)	59



Amori, R. E. et al. JAMA 2007;298:194-206.

JAMA

Summary of Adverse Events in Patients With Type 2 Diabetes Treated With Incretin-Based vs Non-Incretin-Based Therapy

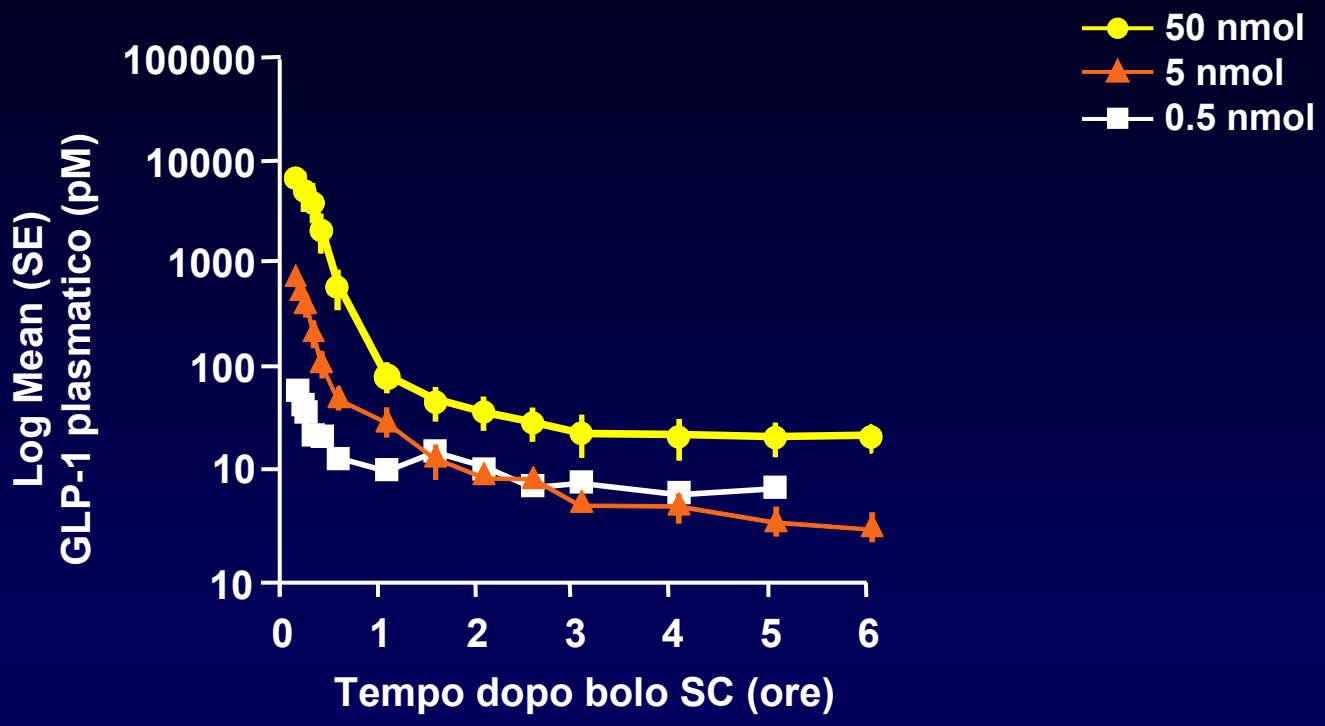
Amori, R. E. et al. JAMA 2007;298:194-206.

JAMA

Note Pratiche

- Gli incretino mimetici sono ausili terapeutici efficaci e utili in associazione alla terapia con ADO
- Ci sono prove robuste che indicano che la terapia con questi farmaci induce calo ponderale di circa 3 kg
- Gli incretino mimetici sono efficaci solo in presenza di iperglicemia
- L'uso di incretino mimetici può dar origine alla produzione di anticorpi

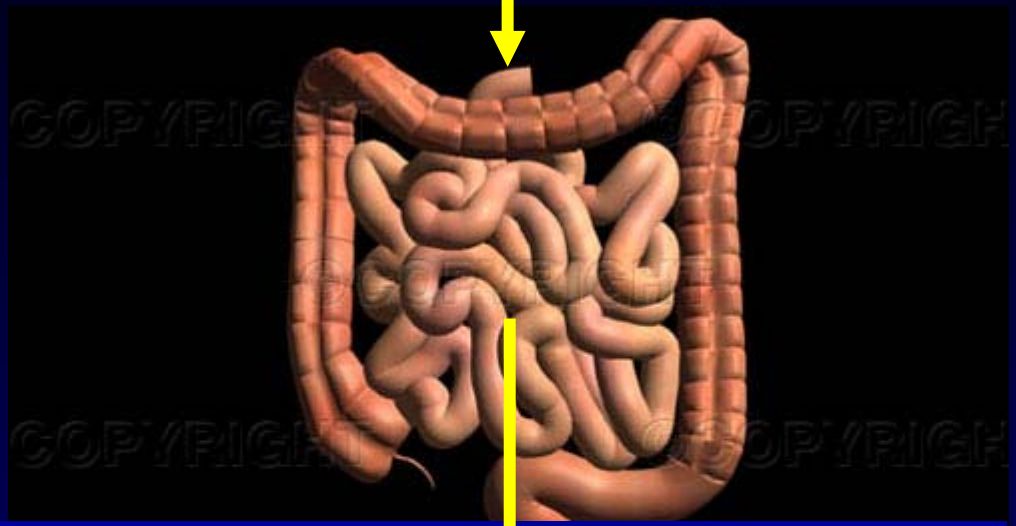
La rapida degradazione del GLP-1 ad opera della DPP-IV ne limita la durata d'azione



La Dipeptidil peptidasi-IV (DPP-IV) degrada il GLP-1

Mean ± SEM;N = 4-7 (rats); *P* <.05.
Adapted from Parkes D, et al. *Drug Dev Res.* 2001;53:260-267.; Eng J, et al. *J Biol Chem.* 1992;267:7402-7405.
Reprinted with permission from John Wiley and Sons Inc.

CIBO



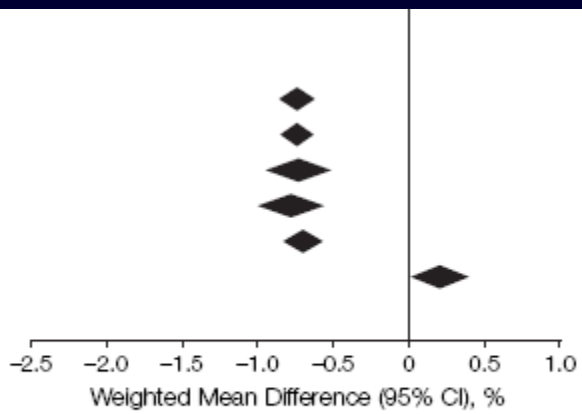
GLP-1 ATTIVO → AZIONI BIOLOGICHE

DPP-IV →

GLP-1 FORMA TRONCATA INATTIVA

Weighted Mean Difference in Change in Hemoglobin A1c Percentage Value for DPP4 inhbitors vs Control in Adults With Type 2 Diabetes

Comparisons	No. of Studies			I^2, %
DPP4 vs placebo[20-24,26-33,35,37,39]	16	4190	−0.74 (−0.85 to −0.62)	77
Sitagliptin vs placebo[20-24,26,27]	7	2404	−0.74 (−0.84 to −0.63)	54
Vildagliptin vs placebo[28-33,35,37,39]	9	1786	−0.73 (−0.94 to −0.52)	85
Duration 12 wk vs placebo[20,26-30,39]	7	1095	−0.78 (−1.00 to −0.56)	82
Duration 12-24 wk vs placebo[21-24,31-33,35,37]	9	3095	−0.70 (−0.83 to −0.58)	72
DPP4 vs hypoglycemic agent[25,34,36,38]	4	2899	0.21 (0.02 to 0.39)	66

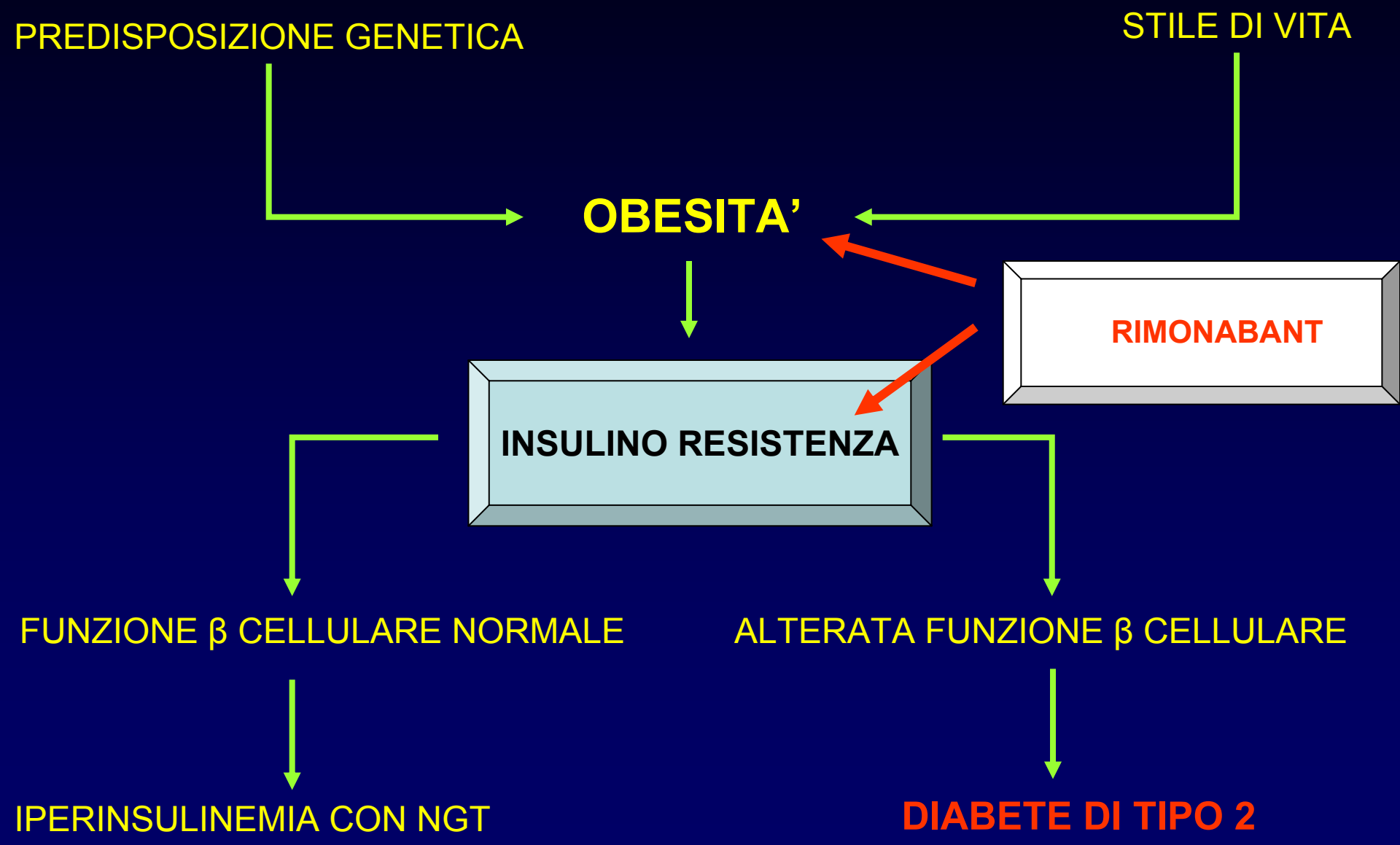


The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance. CI indicates confidence interval; DPP4, dipeptidyl peptidase 4.

Amori, R. E. et al. JAMA 2007;298:194-206.

JAMA

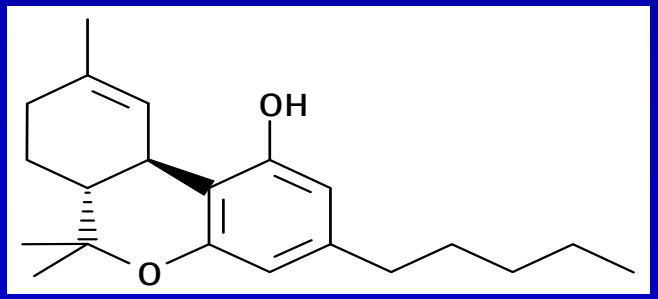
Patogenesi del Diabete di Tipo 2: il ruolo degli antagonisti degli endocannabinoidi



GLP-1R Agonists vs DPP-4 Inhibitors

	GLP-1R Agonists	DPP-4 Inhibitors
Administration	Injection	Orally Available
GLP-1 concentrations	Pharmacological	Physiological
Mechanisms of action	GLP-1	GLP-1 + GIP
Activation of portal glucose sensor	No	Yes
↑Insulin secretion	+++	+
↓Glucagon secretion	++	++
Gastric emptying	Inhibited	+/-
Weight loss	Yes	No
Expansion of beta-cell mass		
In preclinical studies	Yes	Yes
Nausea and vomiting	Yes	No
Potential immunogenicity	Yes	No

Endocannabinoids



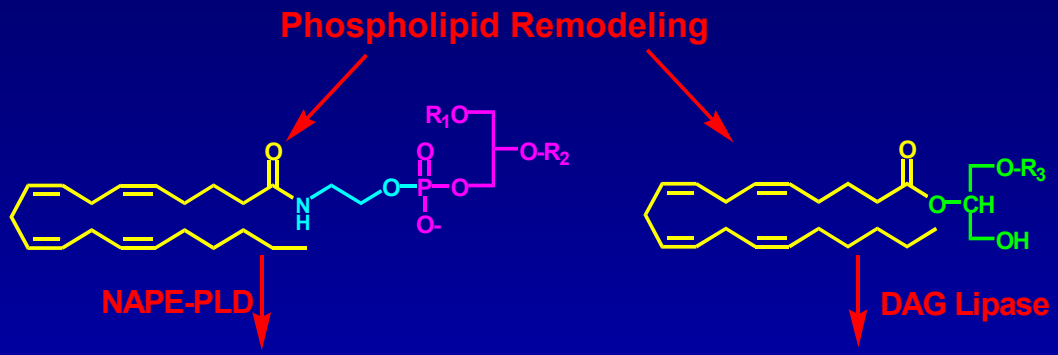
Δ^9-Tetrahydrocannabinol

1964: *(Gaoni and Mechoulam)*

ENDOCANNABINOIDS

are produced <u>on demand</u> from the cell membrane

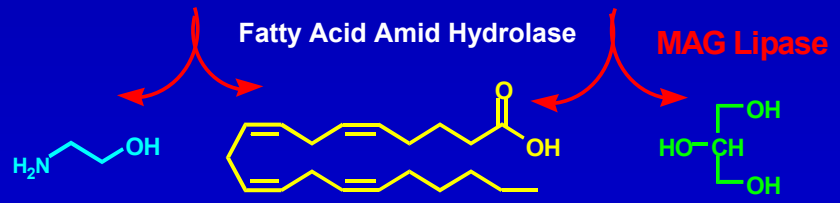
Phospholipid-derived precursors



Endocannabinoids

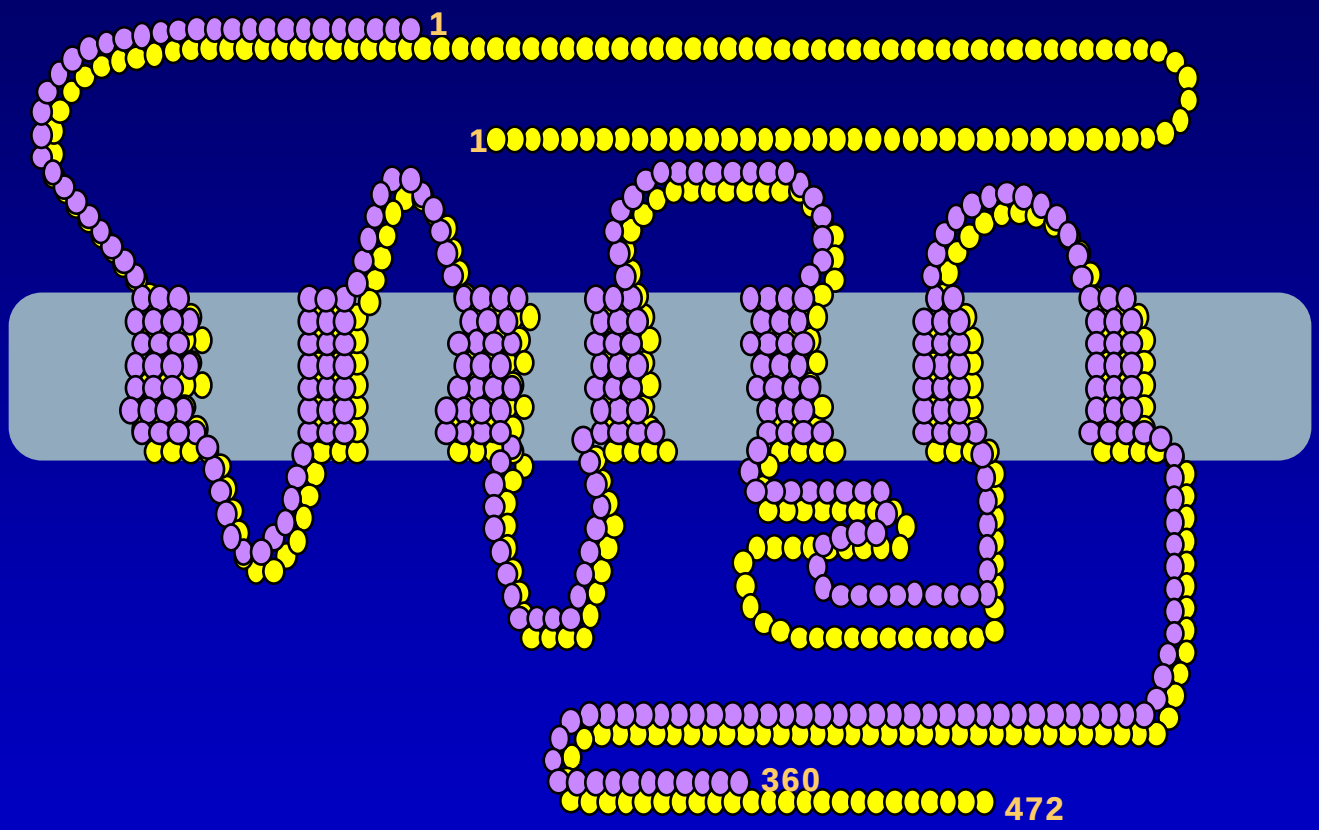
1992: *(Devane et al)*

Degradation products



are <u>immediately metabolized</u> after their action

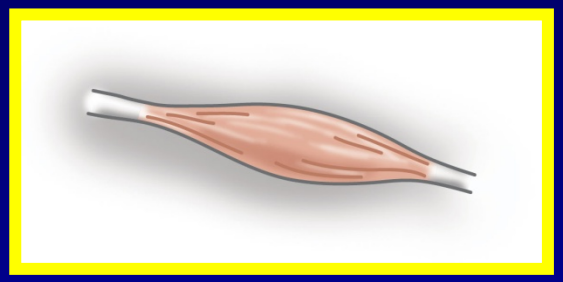
Cannabinoid Receptors



CB_1 1990: *(Matsuda et al)*

CB_2 1993: *(Munro et al)*

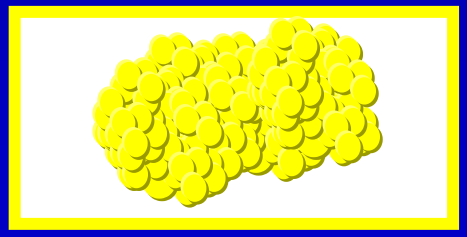
Muscles
Increased CB1 expression



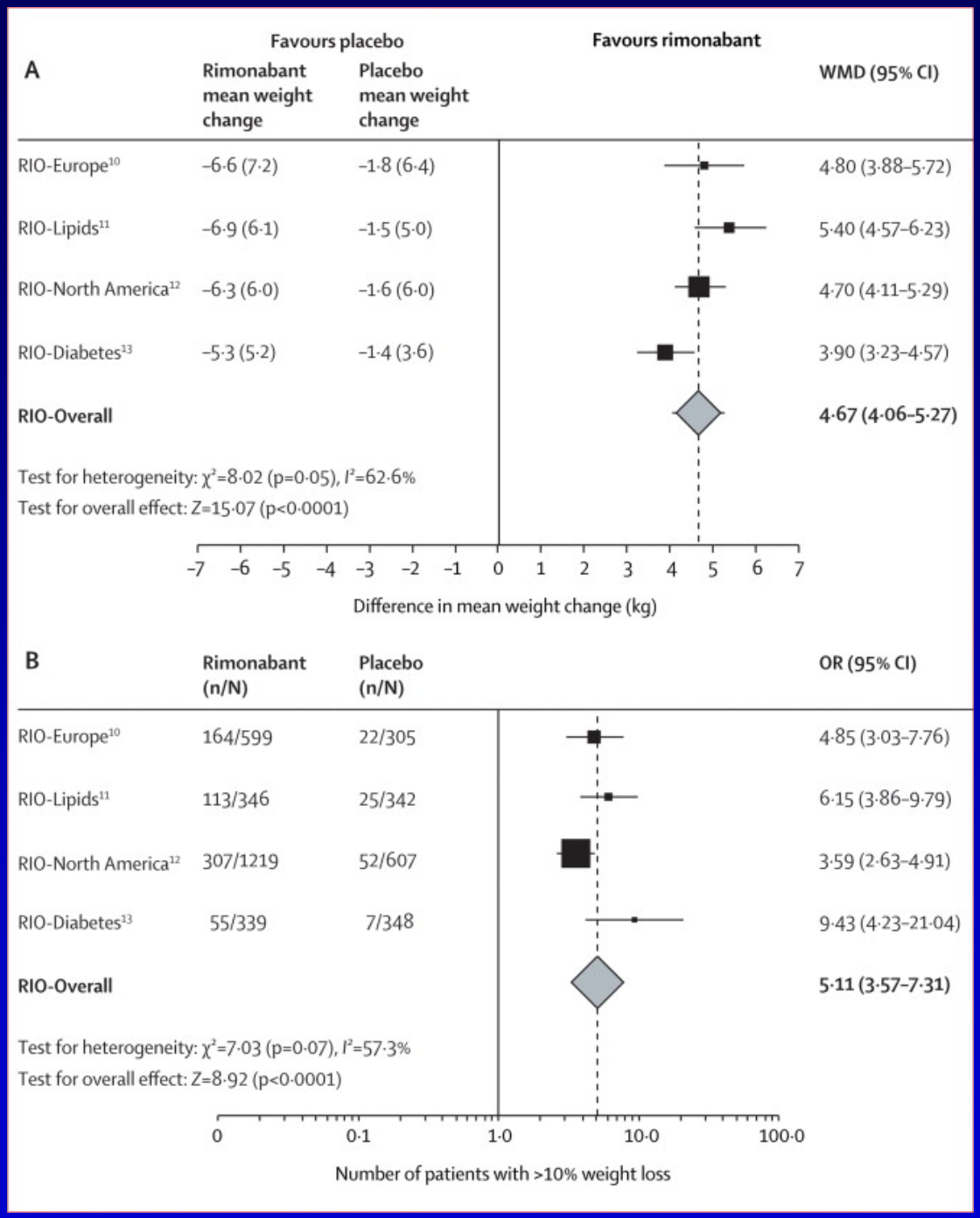
Hypothalamus
Increased endocannabinoid production

Evidence of endocannabinoid system overaction associated to obesity

Liver
Increased endocannabinoid production
Increased CB1 expression



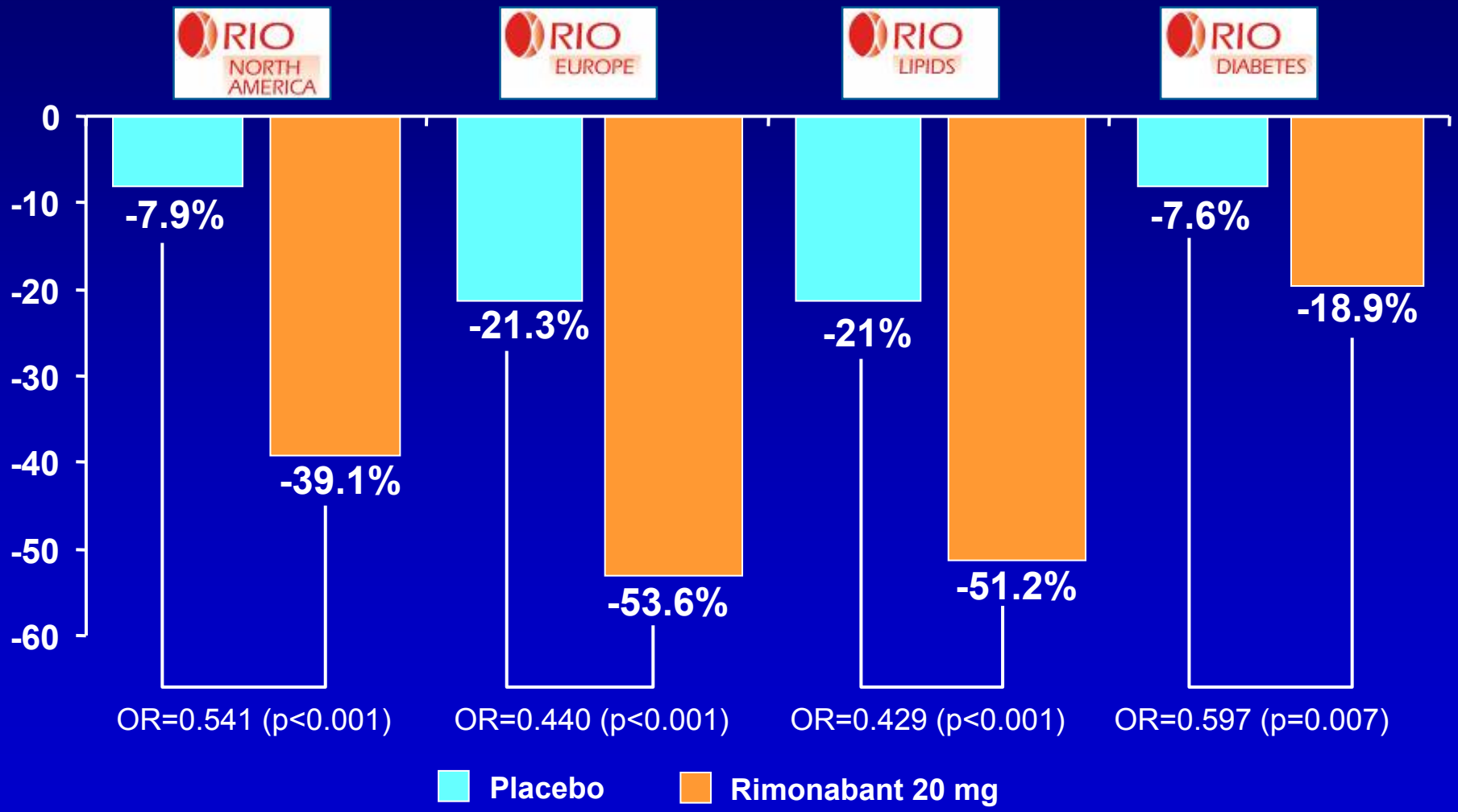
Adipose tissue
Increased CB1 expression



Christensen et al. Lancet 2007

Reduction in metabolic syndrome at 1 year

As defined by NCEP ATP III criteria



ITT, LOCF

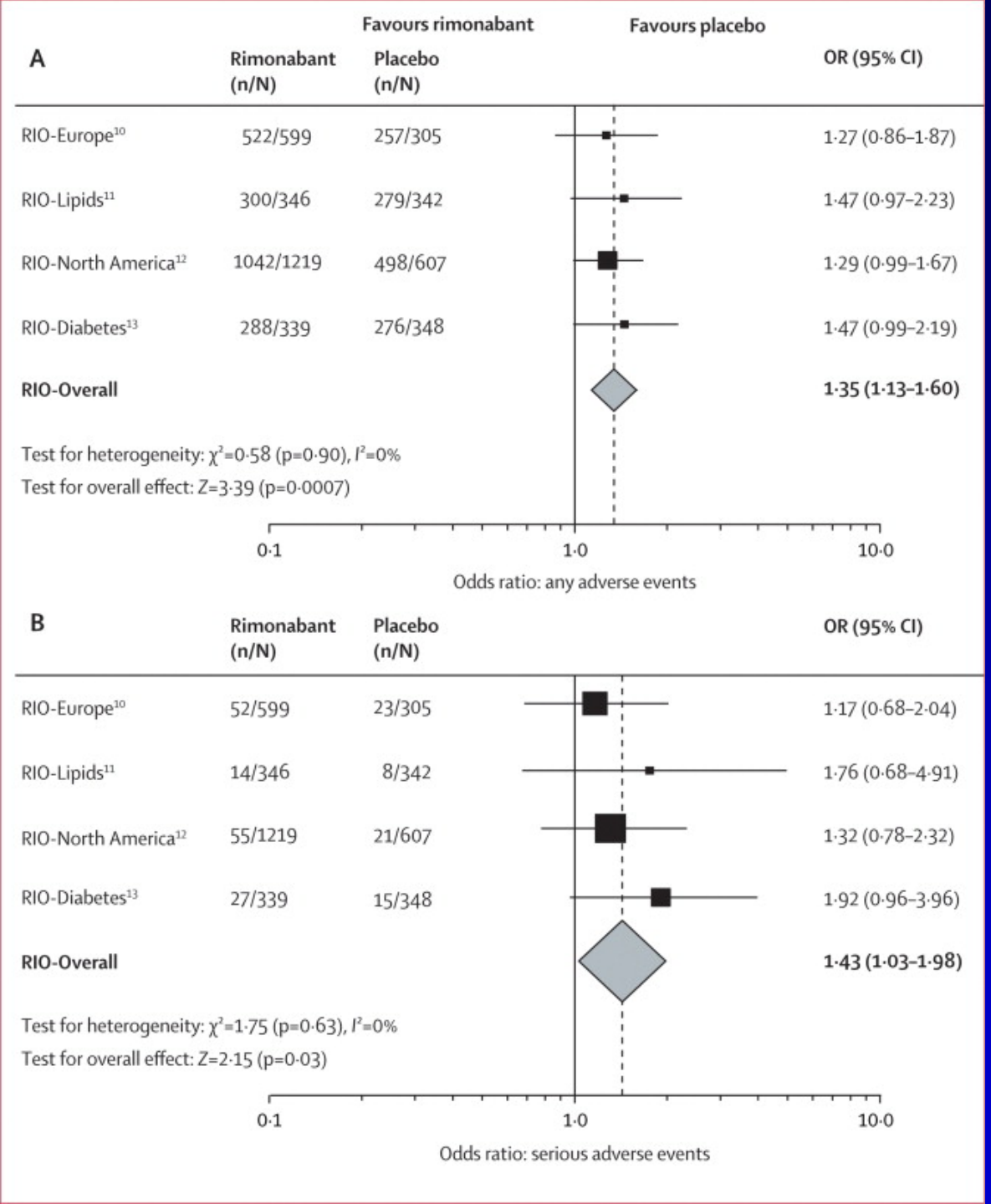
Pi-Sunyer FX et al, 2006; Després JP et al, 2005; Van Gaal L et al, 2005; Scheen A et al, unpublished

RIO~DIABETES: Change in HbA1c

ITT, LOCF

% (Mean ± SD)	Placebo n=317	Rimonabant 5 mg n=330	Rimonabant 20 mg n=315
Baseline	7.2 ± 0.9	7.3 ± 0.8	7.3 ± 0.8
Year 1	7.3 ± 1.1	7.2 ± 1.1	6.7 ±0.9
Change	0.1 ± 1.0	-0.1 ± 1.0	-0.6 ± 0.8
Difference rimonabant v. placebo (SEM)		-0.2 (0.1)*	-0.7 (0.1)**
		*p=0.034	**p< 0.001

Completers:
R5mg vs Placebo : -0.1% v. +0.1%, p=0.035
R20mg vs Placebo : -0.7% v. +0.1%, p<0.001



Christensen et al. Lancet 2007