Università degli Studi di Firenze
Dipartimento di Scienze Biomediche, Sperimentali e Cliniche,
«Mario Serio»
SODc Diabetologia, Progetto Terapia del paziente Obeso.

# Il nuovo rottama sempre il vecchio?

**Firenze 3 dicembre 2016**

**Carlo Maria Rotella**

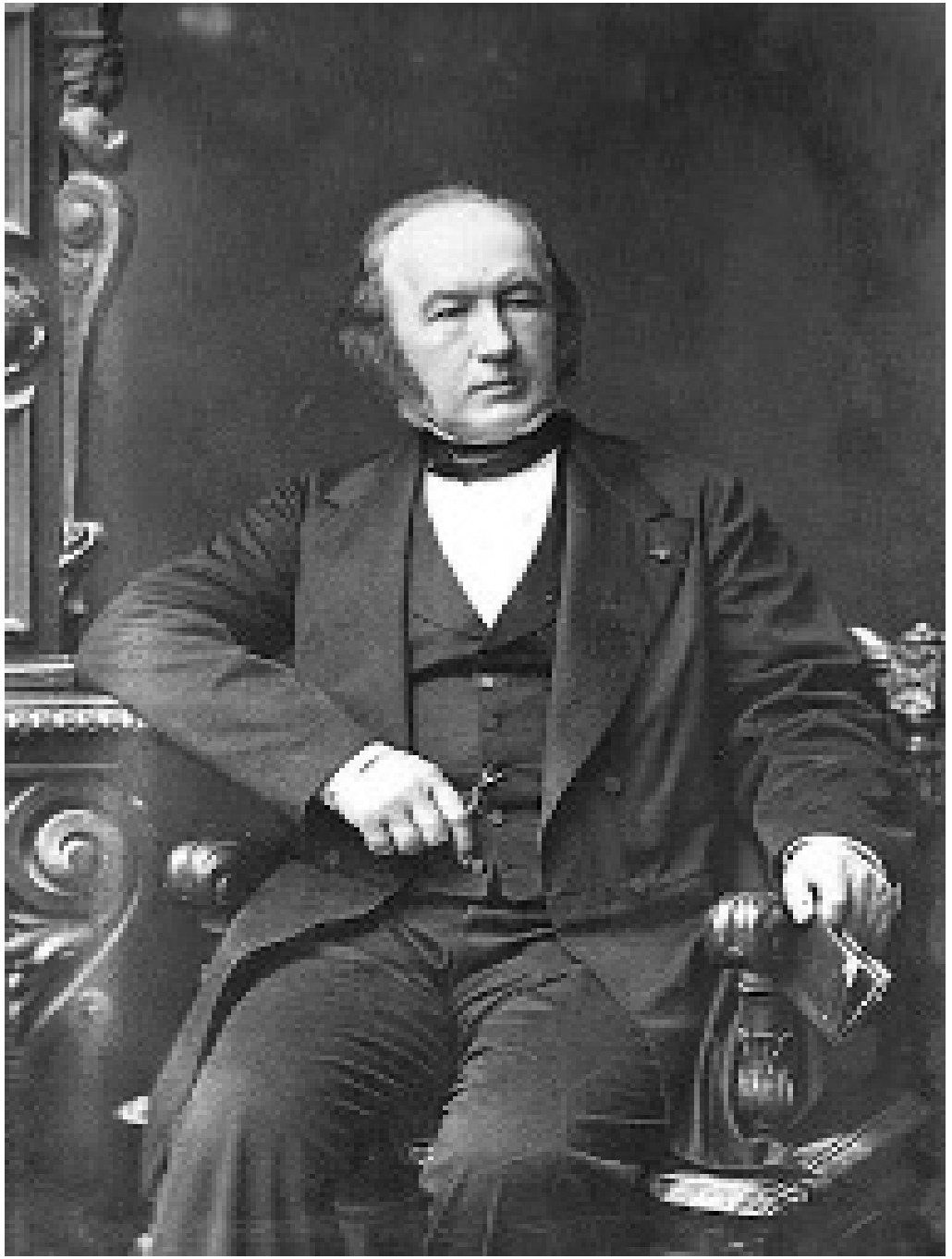
# DICHIARAZIONE POTENZIALI CONFLITTI DI INTERESSI

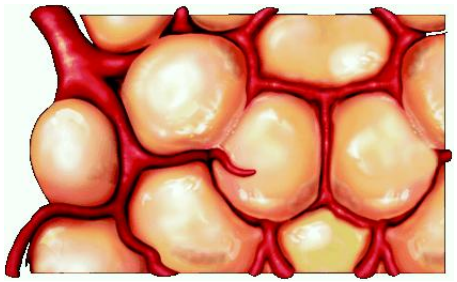
IL PROF. CARLO MARIA ROTELLA DICHIARA CHE NEL CORSO DEGLI ULTIMI DUE ANNI  DI AVER RICEVUTO COMPENSI O FINANZIAMENTI DALLE SEGUENTI AZIENDE FARMACEUTICHE 0 DIAGNOSTICHE:

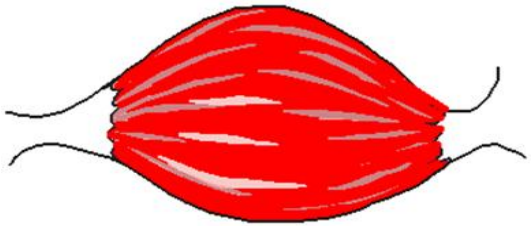
- NOVO NORDISK
- ABIOGEN
- GUNA
- ASTRA ZENECA

# Claude Bernard

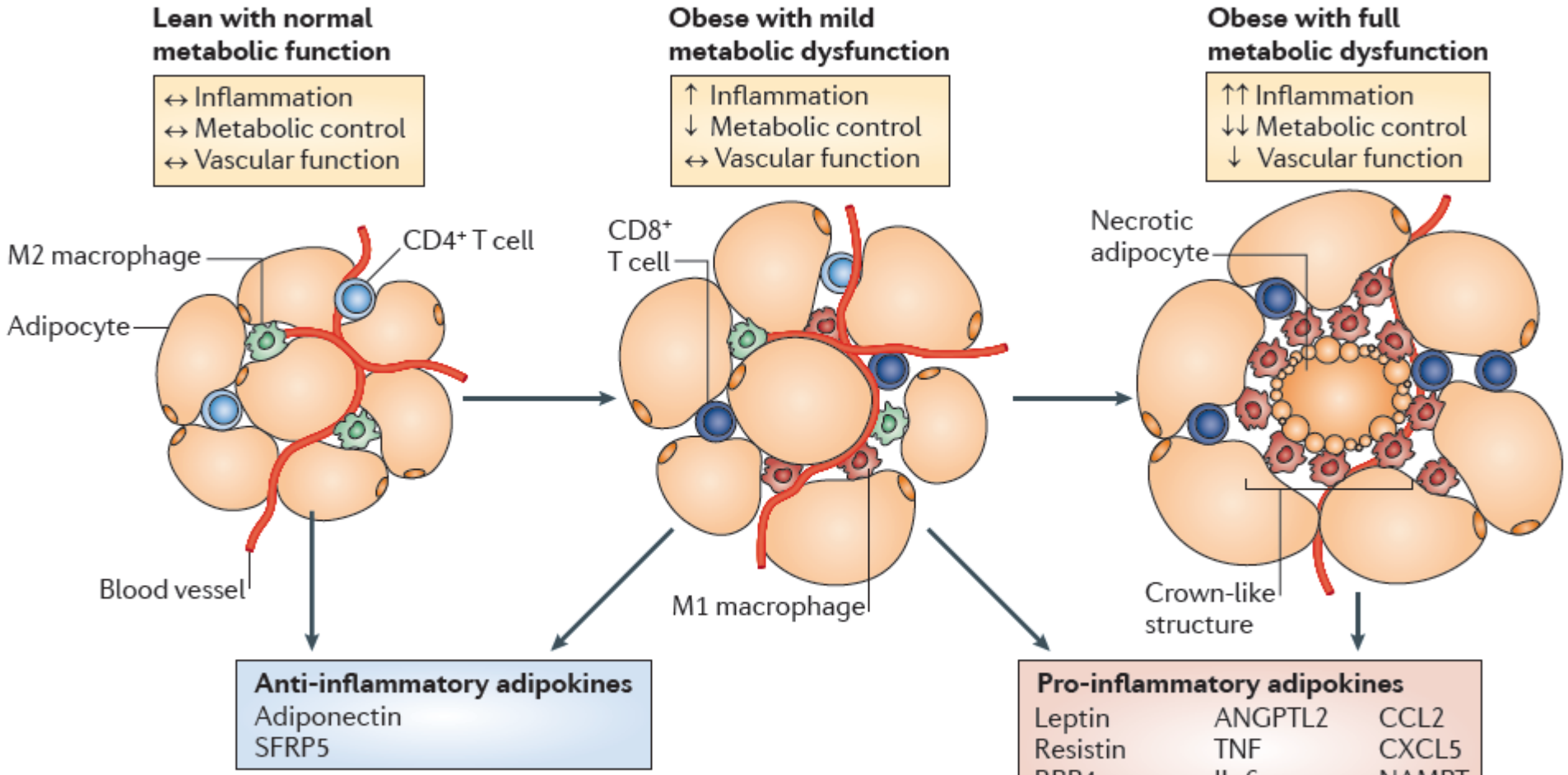
**1813 - 1878**





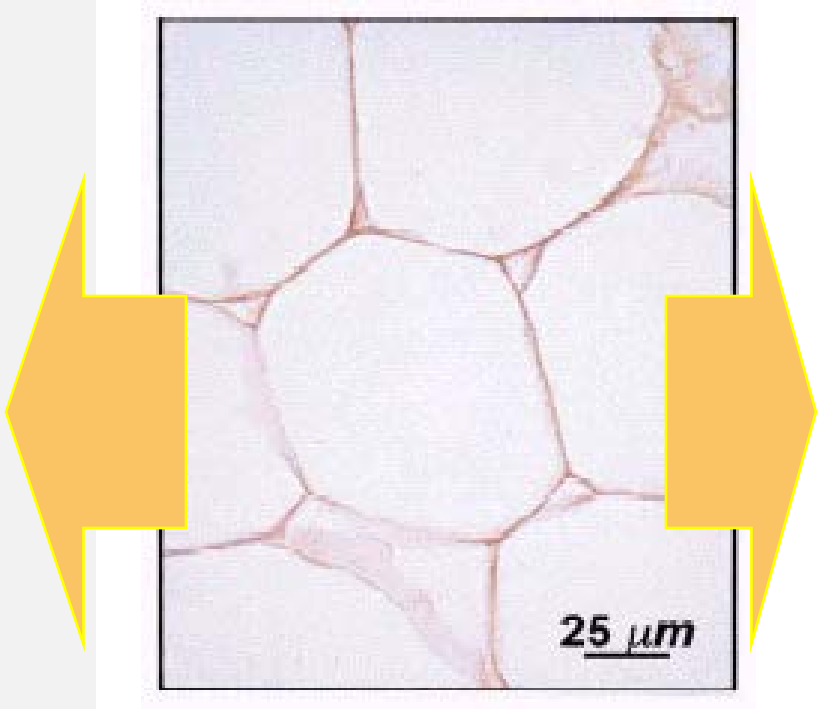


# Tessuto adiposo & disfunzione metabolica



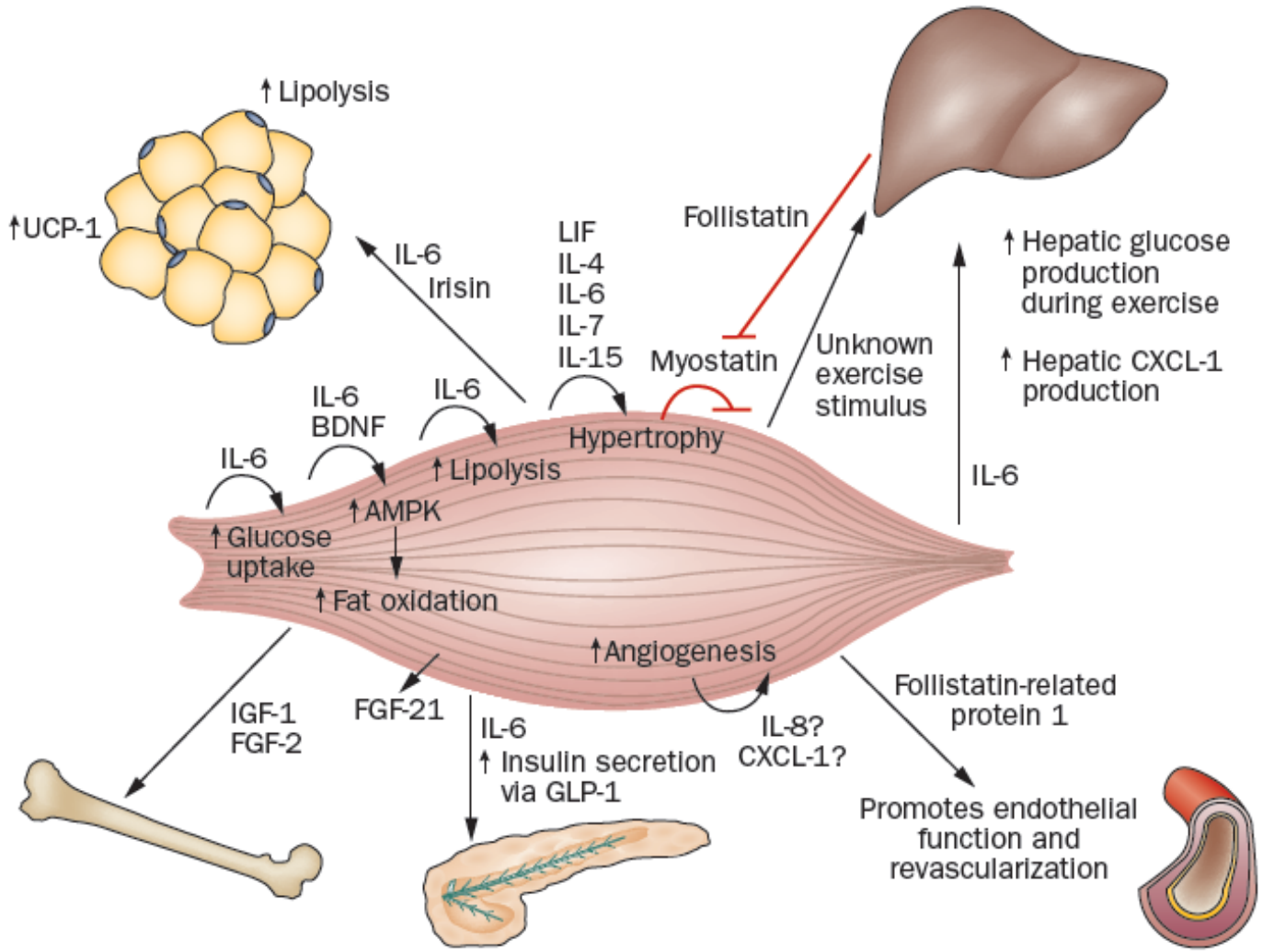
# Tessuto adiposo come organo endocrino

Adiponectina
Adipsina
Amiloide A
AGRP
ANGPTL2
Angiotensinogeno
Apelina
ApoE
CCL2
CETP
Chemerina
COX-pathway
CRP
CXCL5
Aptoglobina
HGF
ICAM-1
IGF-I
IL-6
IL-8
IL-10



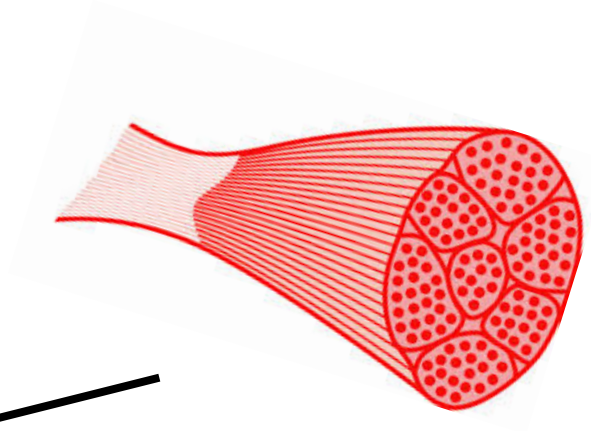

IL-18
Leptina
Lipocalina 2
LPL
MIF
Nesfatina
NGF
NO
Omentina
PAI-1
RANTES
RAS
RBP4
Resistina
SFRP5
TGF-ß
TNF-α
Vaspina
VCAM-1
VEGF
Visfatina

# Tessuto muscolare & cross-talk multiorgano



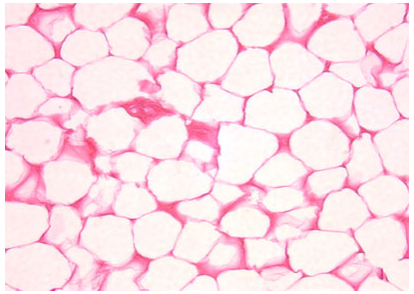

Pedersen, B. K. & Febbraio, M. A. *Nat. Rev. Endocrinol.* **8**, 457–465 (2012)

**L'esercizio fisico aumenta l'espressione intramuscolare di FDNC5 (membrane protein fibronectin type III domain containing 5), da cui deriva mediante clivaggio la miochina IRISINA, che stimola la trasformazione di adipociti bianchi in Brite con un'aumentata espressione di UCP-1 (uncoupling protein 1).**

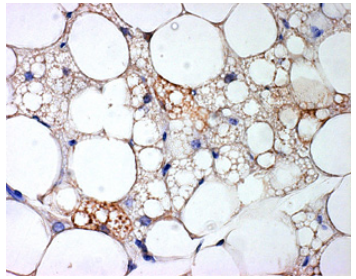


**IRISIN**

White adipocyte



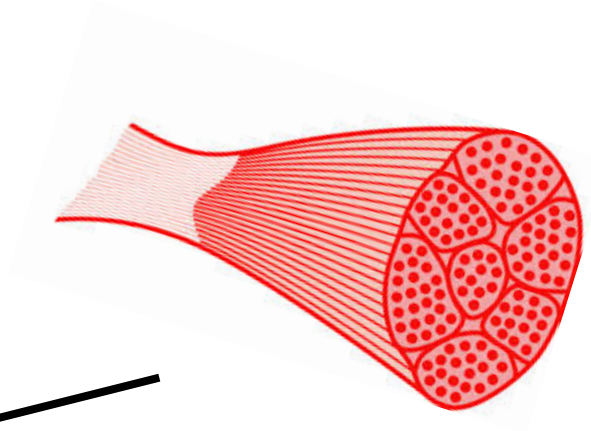
Brite adipocyte



**UCP1**

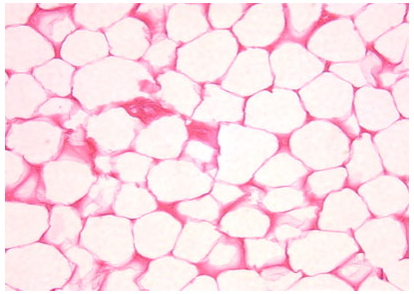
Rotella C & Dicembrini; World International J of Methodology, 2015

**L'esercizio fisico aumenta l'espressione intramuscolare di FDNC5 (membrane protein fibronectin type III domain containing 5), da cui deriva mediante clivaggio la miochina IRISINA, che stimola la trasformazione di adipociti bianchi in Brite con un'aumentata espressione di UCP-1 (uncoupling protein 1).**

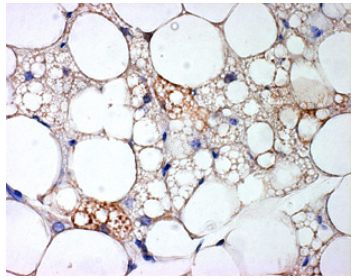


**IRISIN**

White adipocyte



Brite adipocyte



**UCP1**

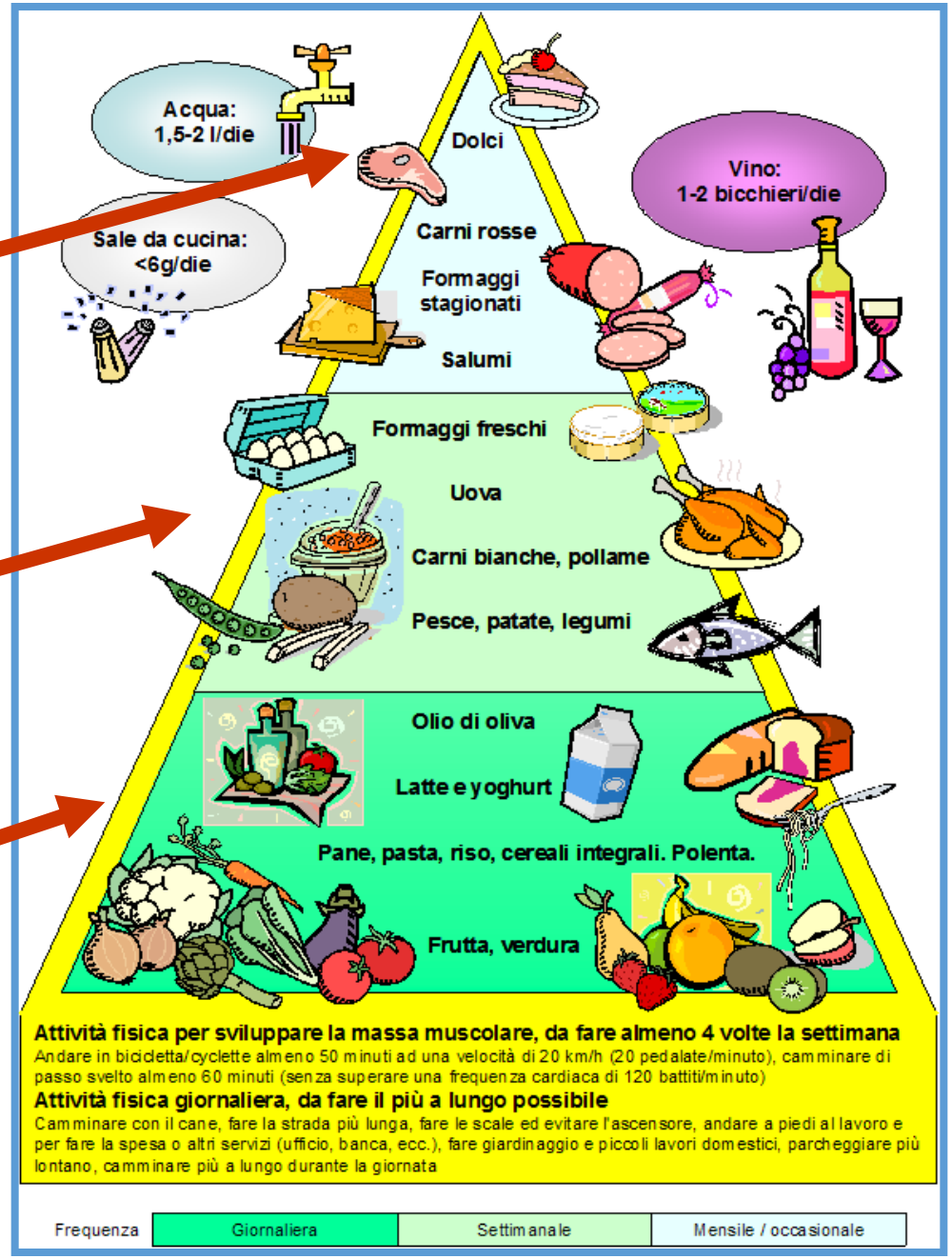
Rotella C & Dicembrini; World International J of Methodology, 2015

# *LA PIRAMIDE ALIMENTARE*

**MENSILE / OCCASIONALE**

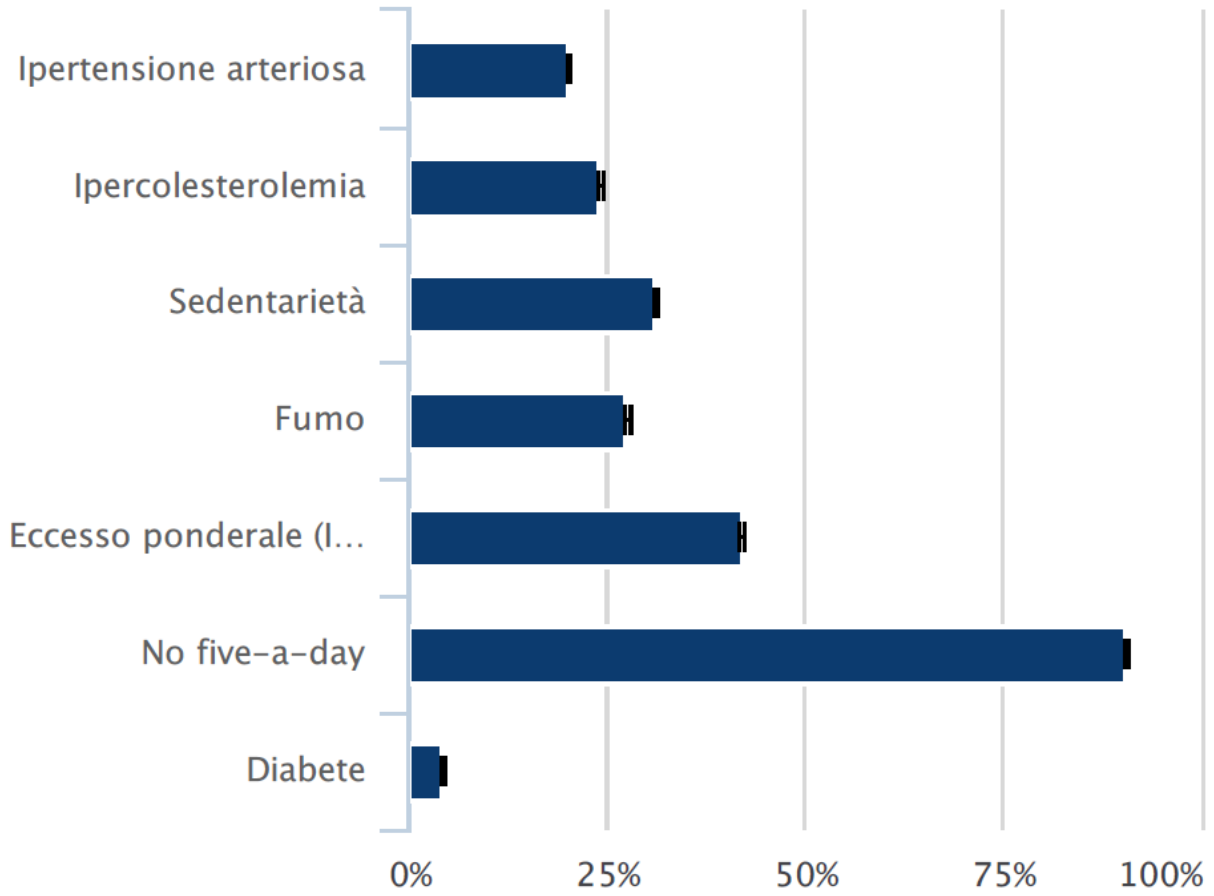
**SETTIMANALE**

**GIORNALIERA**



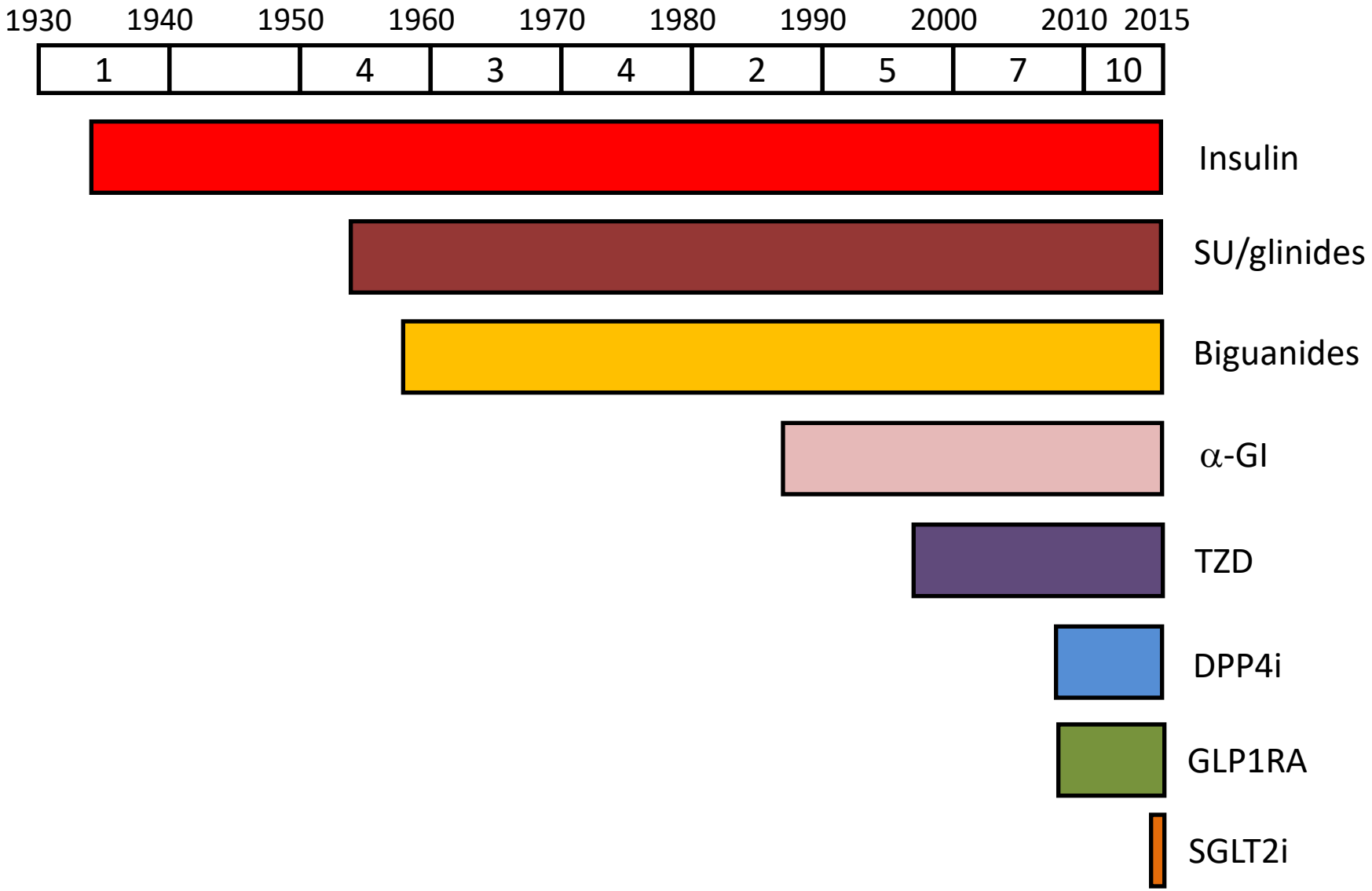

**Lippi & Rotella, 2007**

# Fattori di rischio cardiovascolare nella popolazione 18-69 anni - Pool di Asl 2011-2014



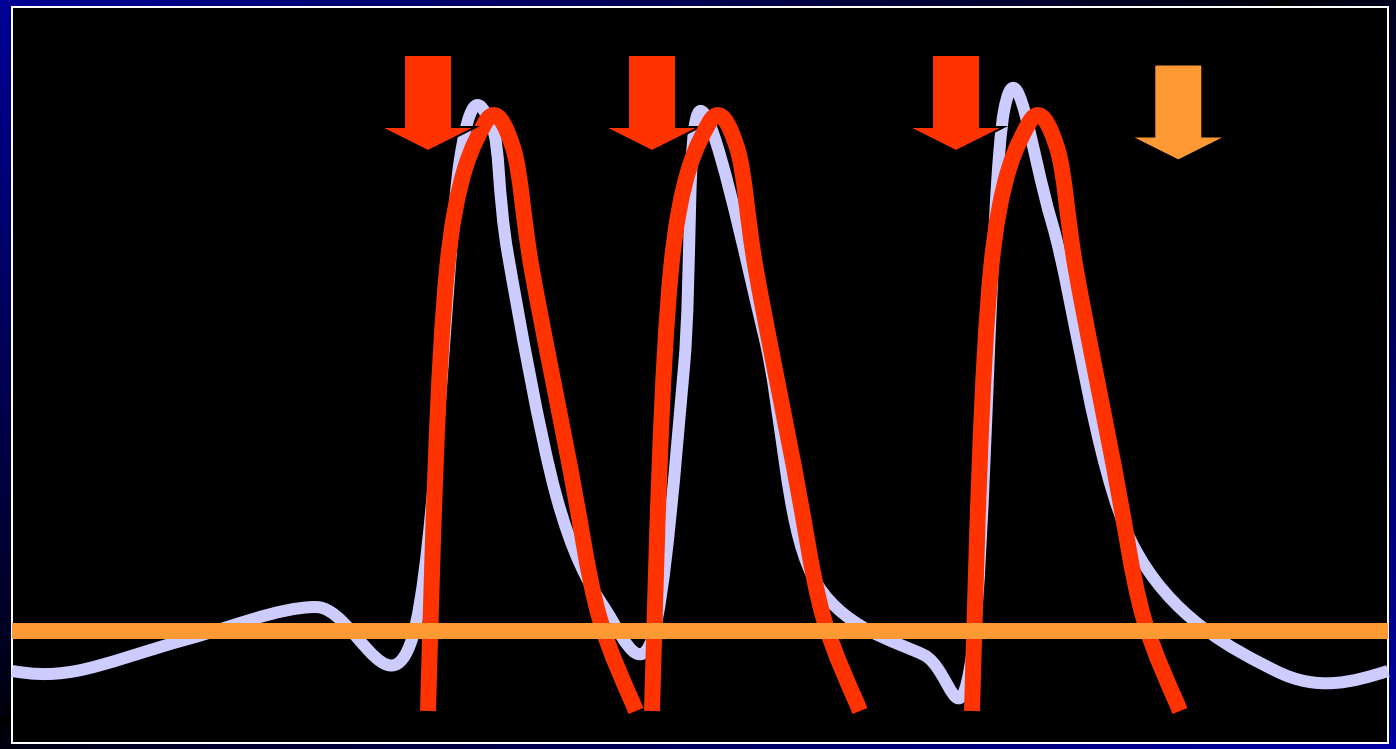

2014, Sperimentazione del Sistema di Sorveglianza della popolazione italiana PASSI
(Progressi delle Aziende Sanitarie per la Salute in Italia )
No five-a-day=Meno di 5 porzioni di frutta e verdura al giorno

# Drugs for T2DM



# *Insulina*

Terapia intensiva con LysPro e Glargine

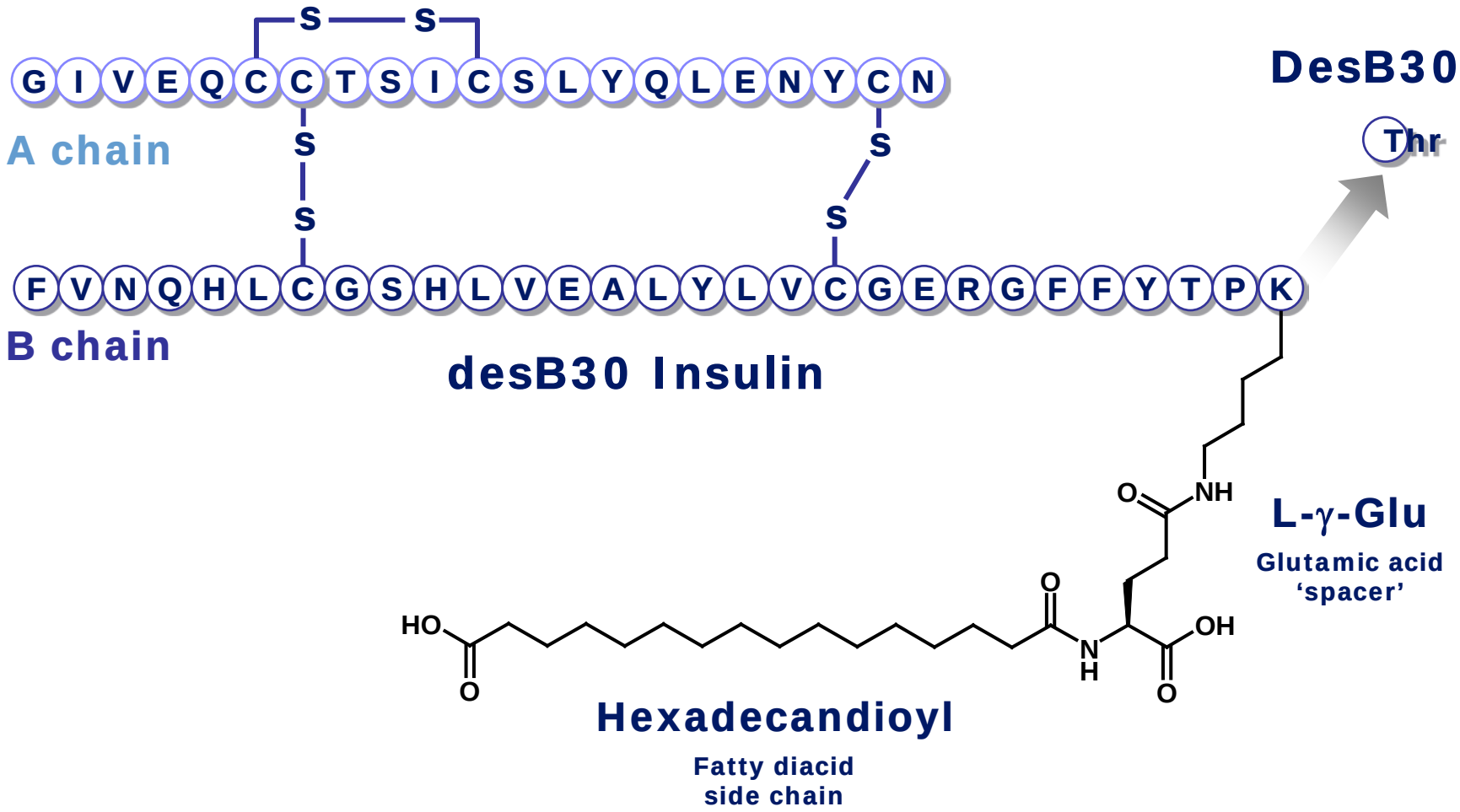


6 13 20

# Insulin degludec structure

ADA/EASD 2010

***LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human ins***





I Jonassen et al. Diabetes 59 (Suppl. 1): A11, 2010

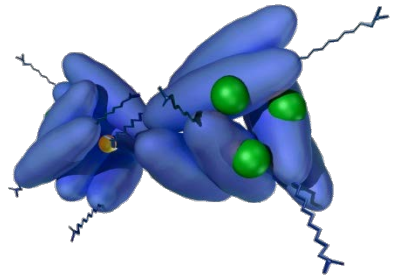
I Jonassen et al. Diabetologia 2010;53(Suppl.1):S388 972-P

# Insulin degludec association

## From injection to absorption

Multi-hexamer formation key to protraction mechan

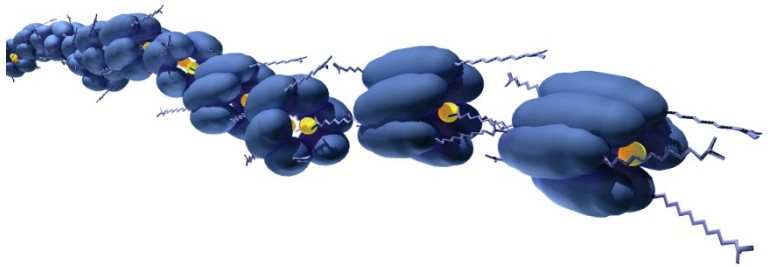
ADA/EASD 2010



Insulin degludec di-hexamers

Injected formulation

-Phenol



Insulin degludec multi-hexamers

S.c. depot formation

$-Zn^{2+}$

[Phenol; $Zn^{2+}$]

Insulin degludec monomers

Absorption

I Jonassen et al. Diabetes 59 (Suppl. 1): A11, 2010

I Jonassen et al. Diabetologia 2010;53(Suppl.1):S388 972-P

# Insulina biosimilare Glargine/Lantus

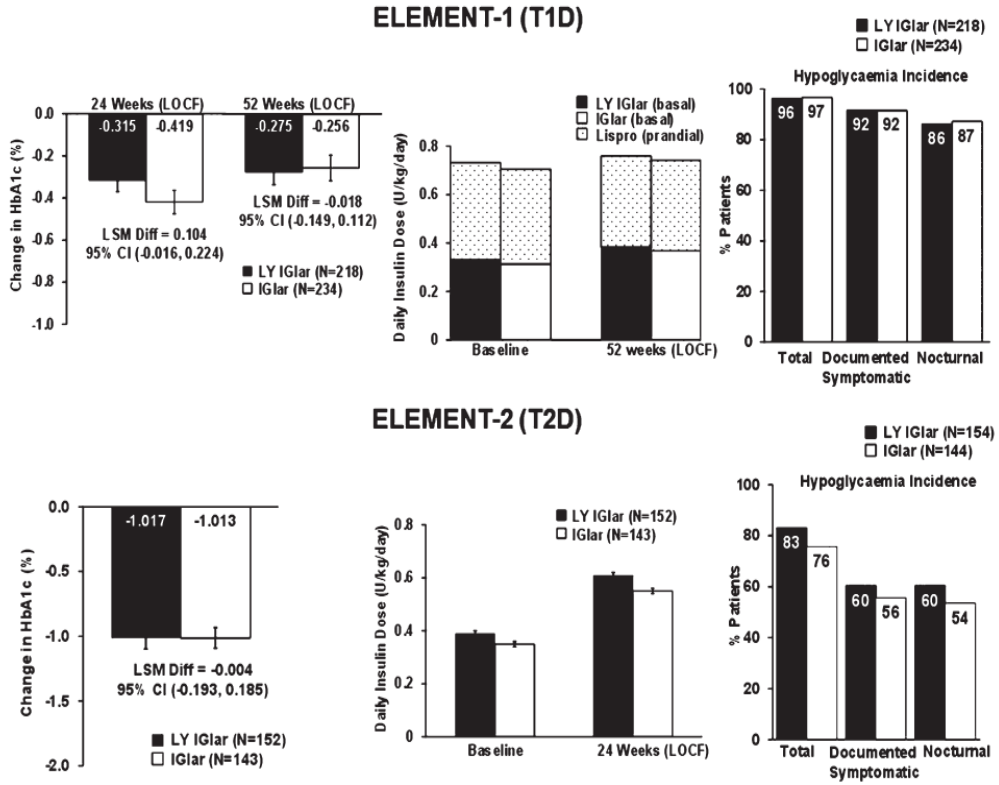
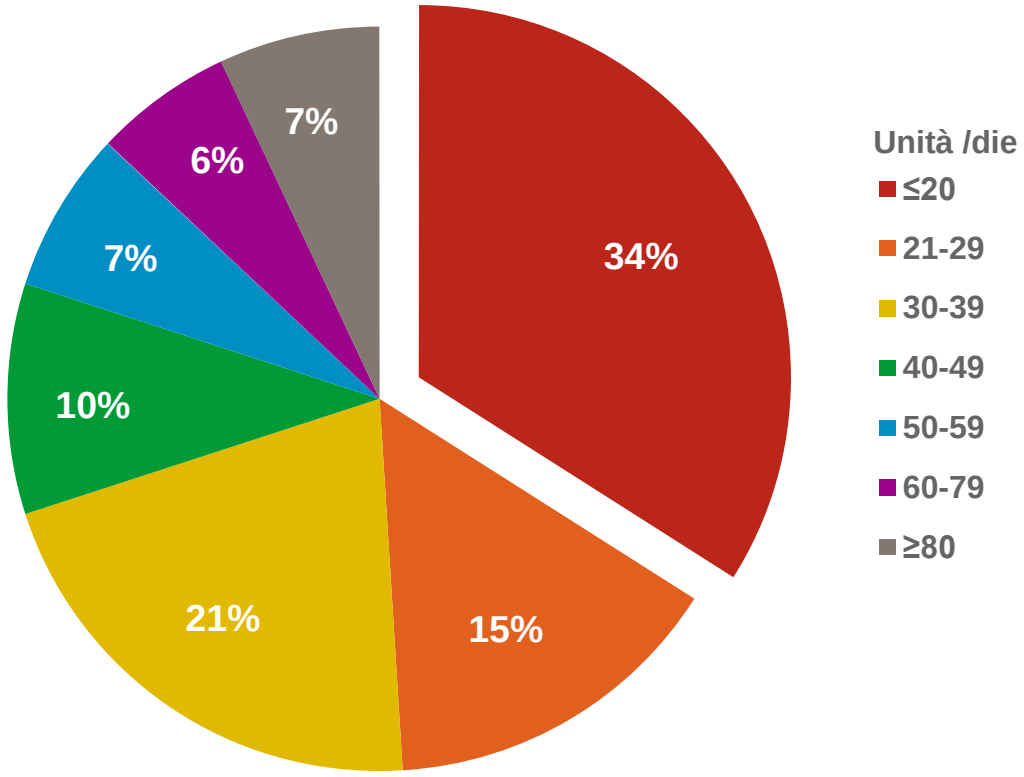



Figure 1. Efficacy and safety outcomes in the prior IGlar subgroup of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). All p values >0.05.

*Diabetes, Obesity and Metabolism* 2016.

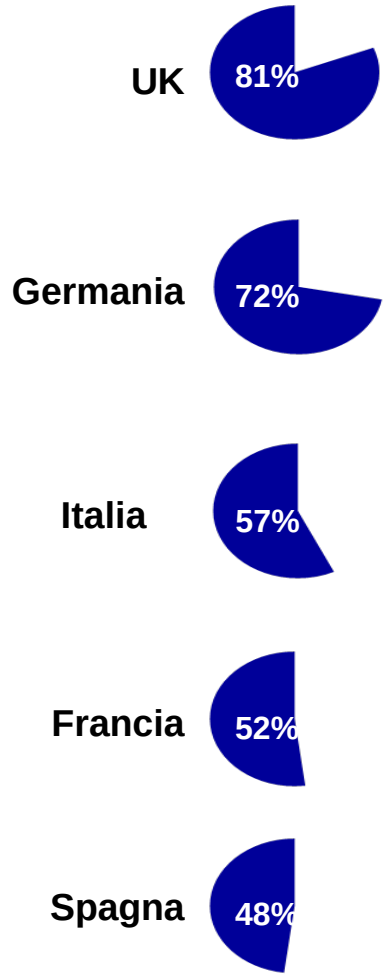
# T2DM: 66% dei pazienti che utilizzano insulina ai pasti in Europa, assumono più di 20 U/Die

**% di pazienti per dose di insulina prandiale**



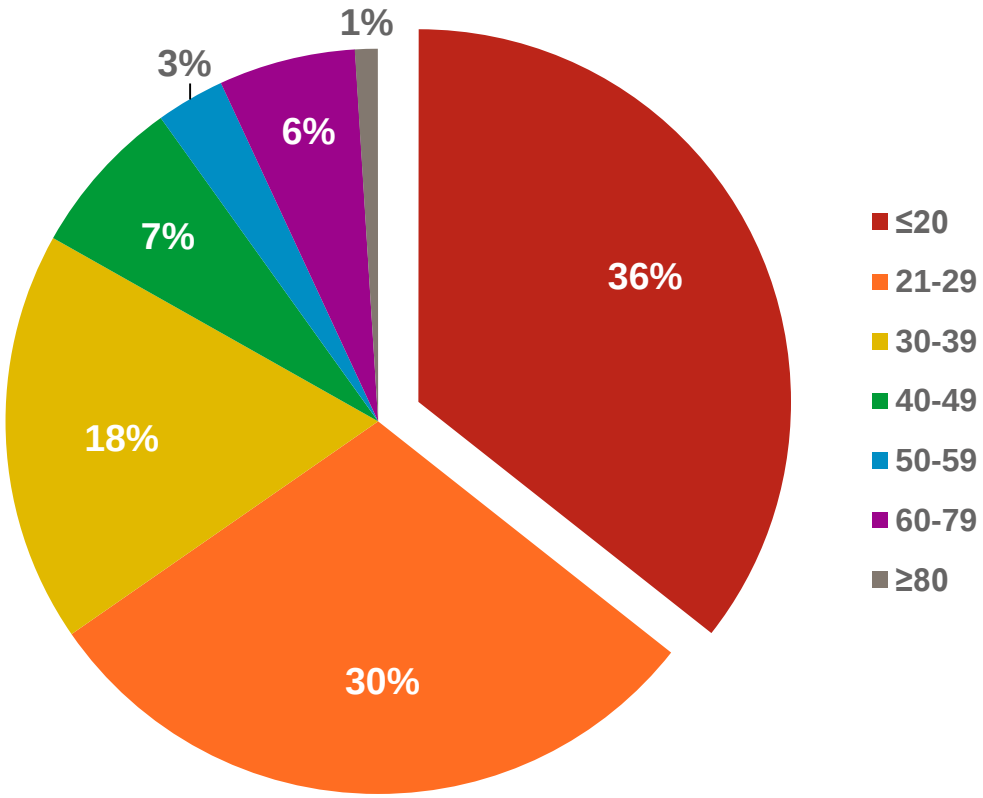

Data on file, Eli Lilly and Company

**% di pazienti che usano >20 U/Die**



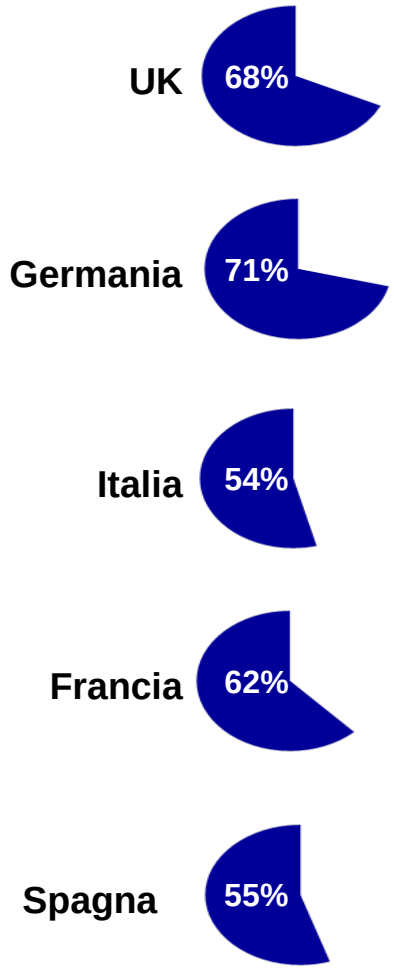
# T1DM: 64% dei pazienti che utlizzano insulina ai pasti in Europa assumono più di of 20 U/Die

**% di pazienti per dose di insulina prandiale**




Data on file, Eli Lilly and Company

**% di pazienti che usano >20 U/Die**



# Il panorama delle insuline concentrate

- Aumento costante prevalenza sovrappeso-obesità e diabete
- Necessità di ricorrere alla terapia insulinica in pazienti gravemente insulino-resistenti
- Percentuale significativa di pazienti con elevati dosaggi insulinici giornalieri

Insuline Concentrate

# Insulina Lispro 100 U/ml vs. 200 U/ml

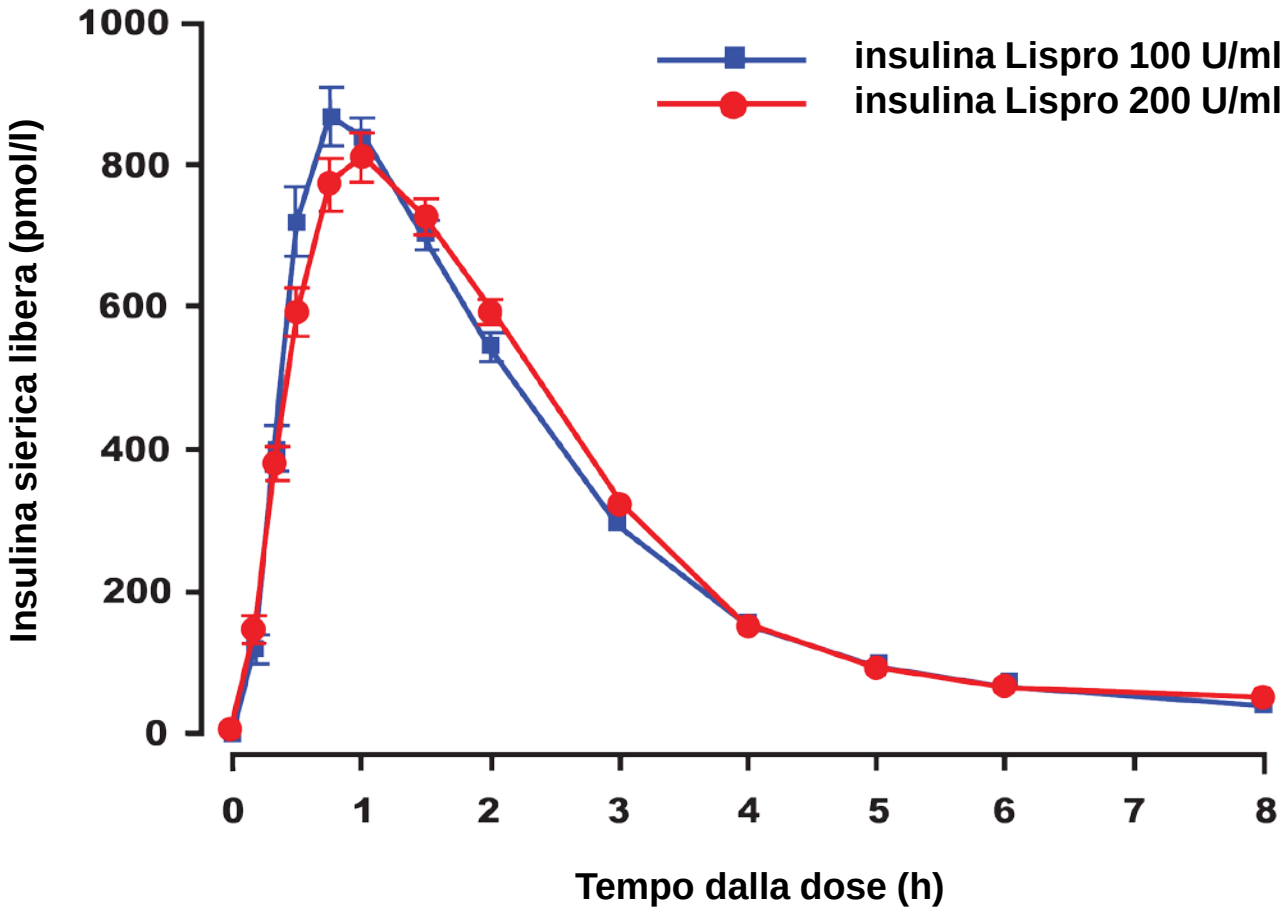
**Ingredienti per ml:**

| Insulina Lispro 100 U/ml[1] | Insulina Lispro 200 U/ml[2] |
|---|---|
| Principio attivo: 100 unità insulina lispro | Principio attivo: 200 unità insulina lispro |
| Tampone: 1.88 mg fosfato di sodio dibasico | tampone: 5 mg trometamolo |
| Zinco: 0.0197 mg/100 unità | Zinco: 0.023 mg/100 unità |


1. Humalog [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2013
2. EMA. Humalog Assessment Report #EMEA/H/C/000088/X/0125. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000088/WC500176634.pdf

# Profili farmacocinetici (media ± SE)

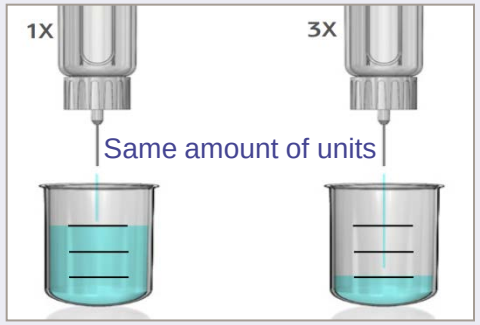
SE=Standard Error




Adattato da: de la Pena A. et al. Clinical Pharmacology in Drug Development, Wiley online, DOI 10.1002/cpdd.221 – August 2015

# U300 is a new long-acting basal insulin with a more even and prolonged PK/PD profile vs Lantus®

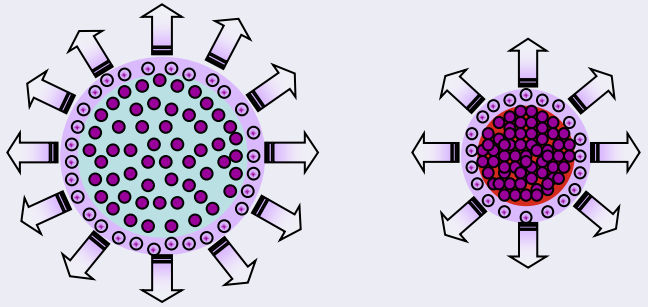
**Reduction of volume by 2/3**




Lantus® U300

**Stesse unità di insulina in 1/3 di volume**

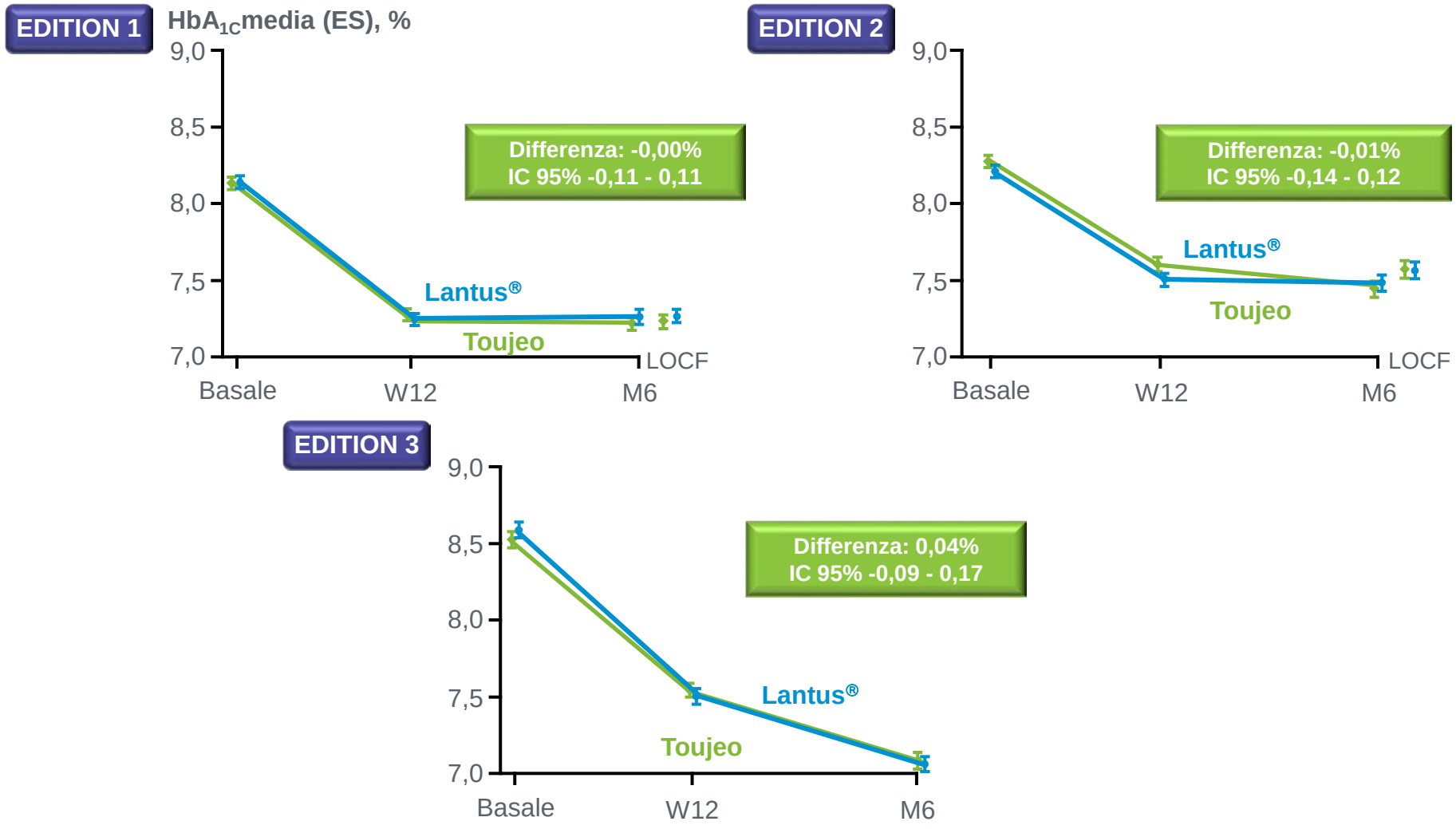
**Reduction of depot surface by 1/2**



Lantus® U300

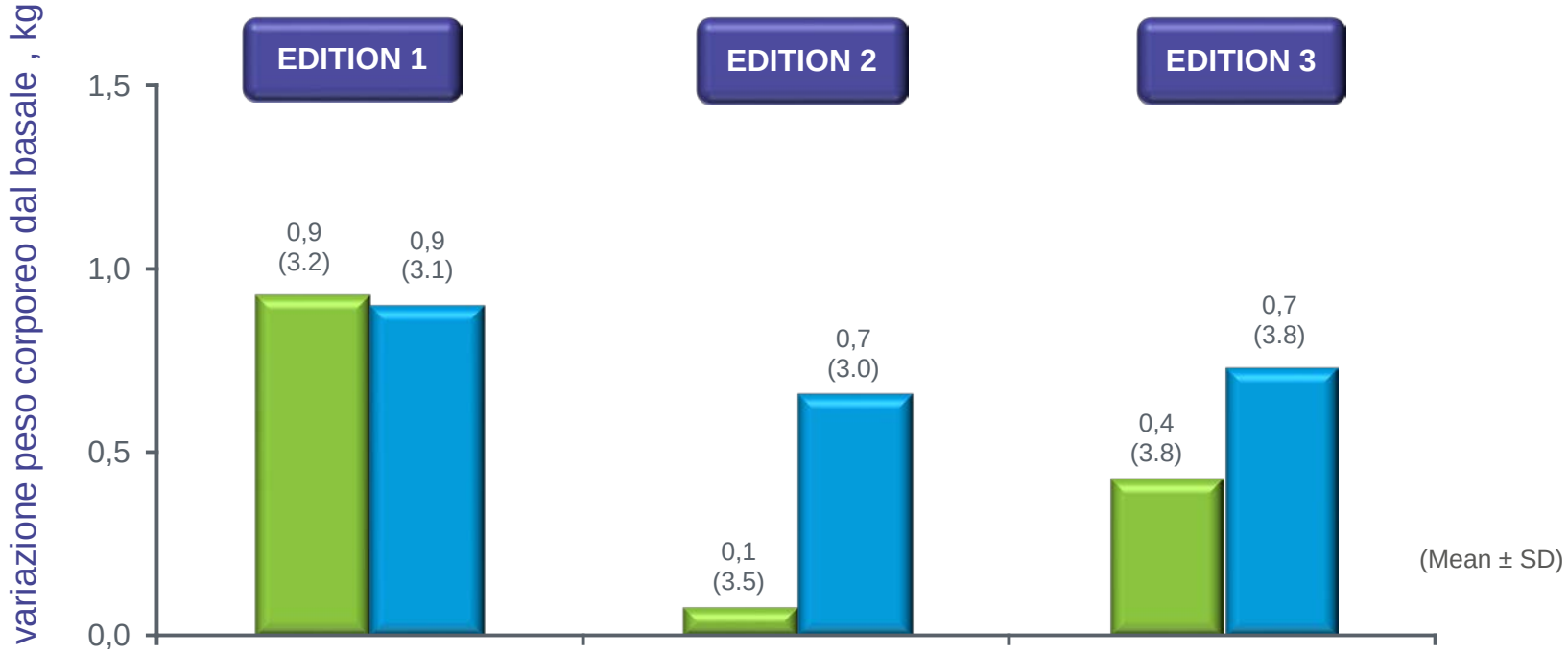
Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

# Endpoint primario di non inferiorità valore di $HbA_{1C}$ al mese 6




Riddle MC et al. Diabetes Care. 2014 Yki-Järvinen H et al. Diabetes Care. 2014 Bolli GB et al. Diabet Obes Metab 2015

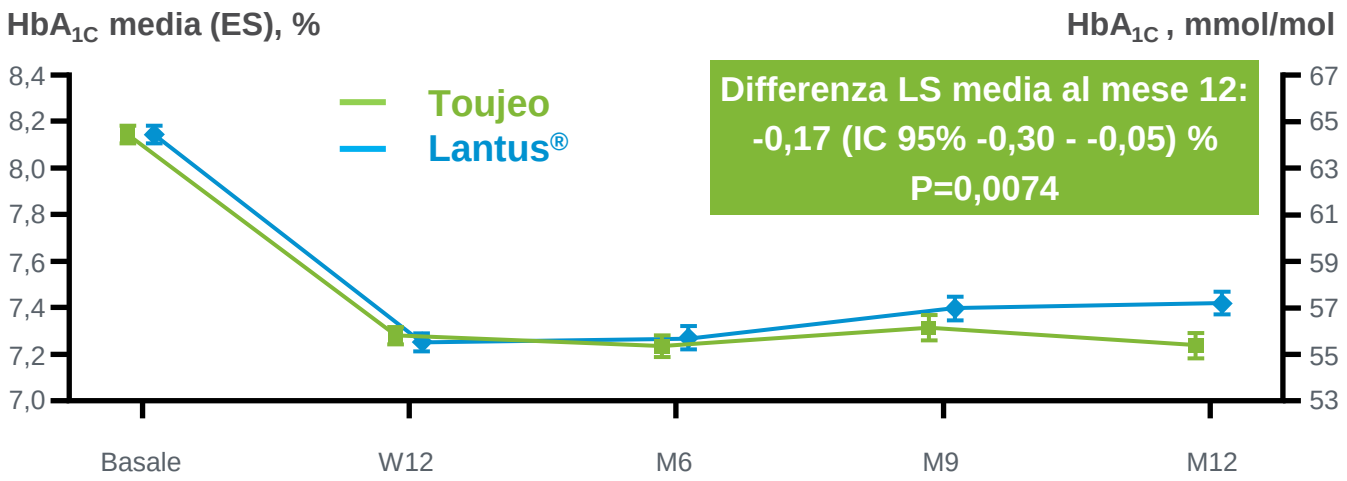
# Variazione del peso corporeo e dosi di insulina




| Insulina basale, dose U/kg | EDITION 1 | EDITION 2 | EDITION 3 |
|---|---|---|---|
| Toujeo | 0.97 | 0.92 | 0.62 |
| Lantus | 0.88 | 0.84 | 0.53 |
| **% differenza per Toujeo** | **+10%** | **+10%** | **+17%** |

Riddle MC et al. Diabetes Care. 2014 Yki-Järvinen H et al. Diabetes Care. 2014 Bolli GB et al. Diabet Obes Metab 2015

# Riduzione della $HbA_{1C}$ a 1 anno maggiore con Toujeo vs Lantus



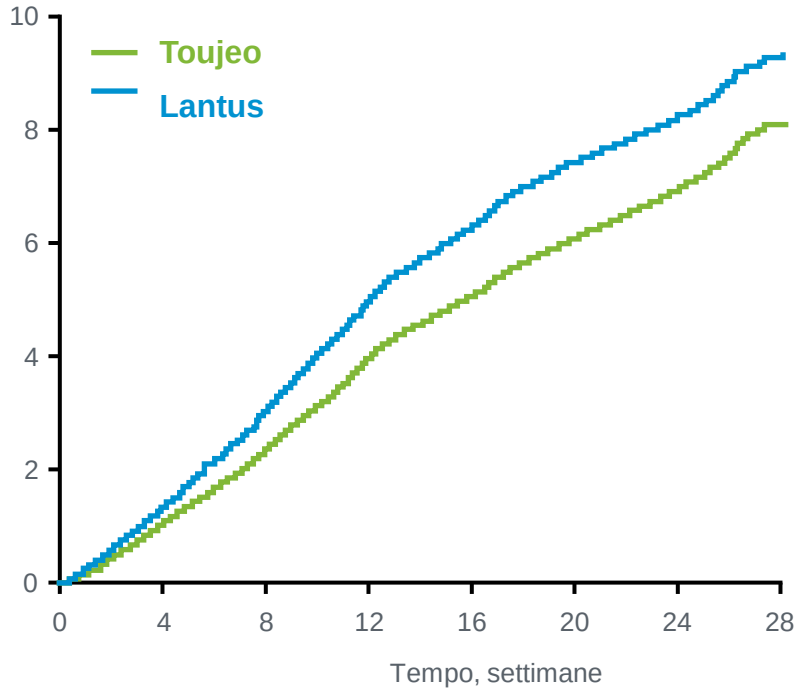

- Con l'aumento della durata del trattamento, il vantaggio di Toujeo® in termini di rischio ipoglicemico, può aver migliorato la capacità dei pazienti di aggiustare in modo adeguato la dose e il timing delle iniezioni di insulina[1]

Riddle MC et al. Diabetes Obesity and Metabolism 2015

# Ipoglicemia confermata e/o grave a qualsiasi ora (24 h) e notturna

**EDITION 1-2-3 T2DM**
**Pooled analisi**

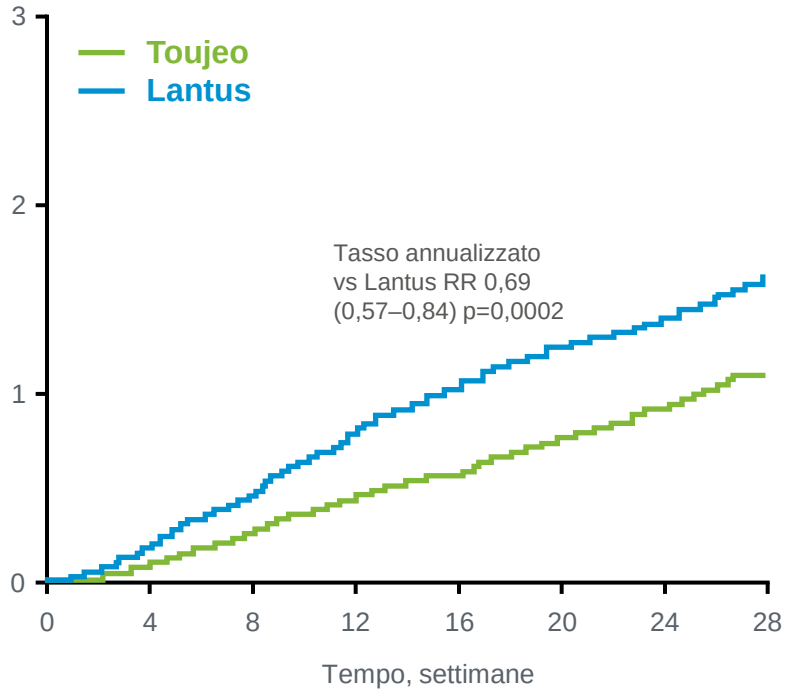
**Ipoglicemia a qualsiasi ora (24 h)**
Numero medio complessivo di eventi confermati* e/o gravi




Tasso annualizzato vs Lantus
RR: 0,86 (0,77–0,97) p=0,0116

14%

**Ipoglicemia notturna (00:00–05:59 h)**
Numero medio complessivo di eventi confermati* e/o gravi




Tasso annualizzato vs Lantus
RR 0,69 (0,57–0,84) p=0,0002

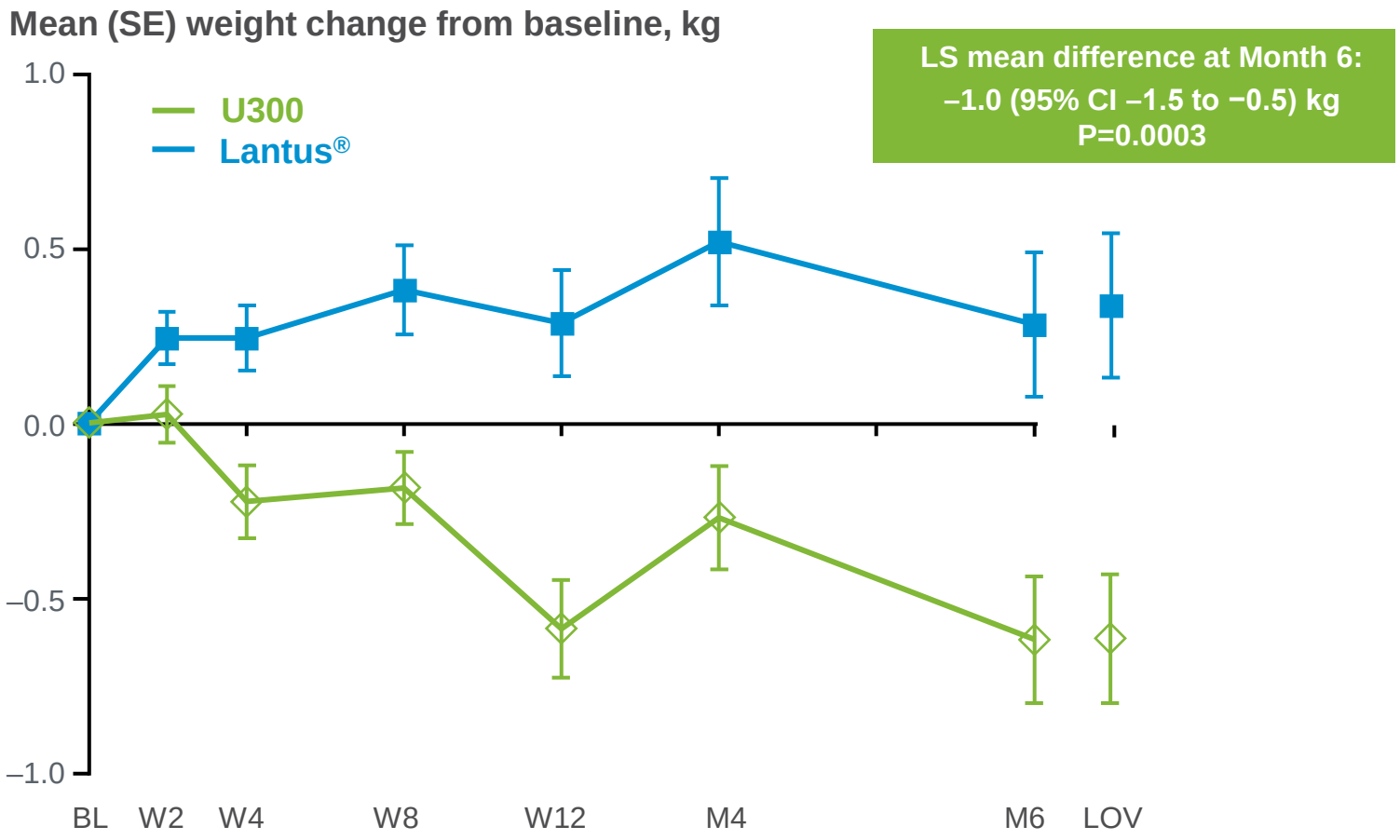
31%

*Eventi confermati sulla base del glucosio plasmatico ≤70 mg/dl (3,9 mmol/l)

Ritzel R et al. Diabetes Obes Metab. 2015

EDITION JP 2

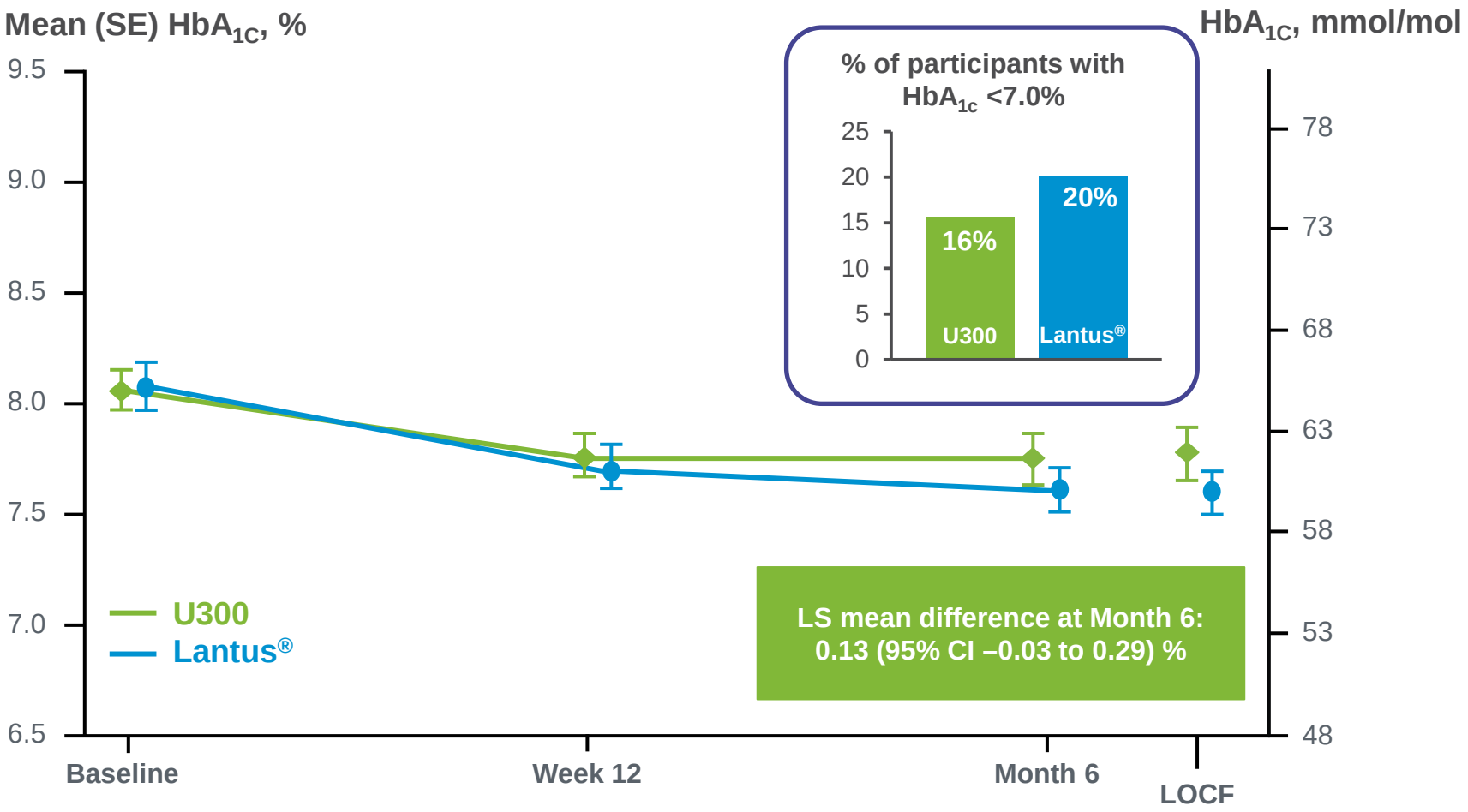
# Less weight gain with U300 vs Lantus®




Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976 Available at: http://www.easdvirtualmeeting.org/resources/19078 Accessed September 2014

EDITION JP 1

# U300 met the primary endpoint of non-inferiority to Lantus® for reduction in $HbA_{1C}$ at Month 6



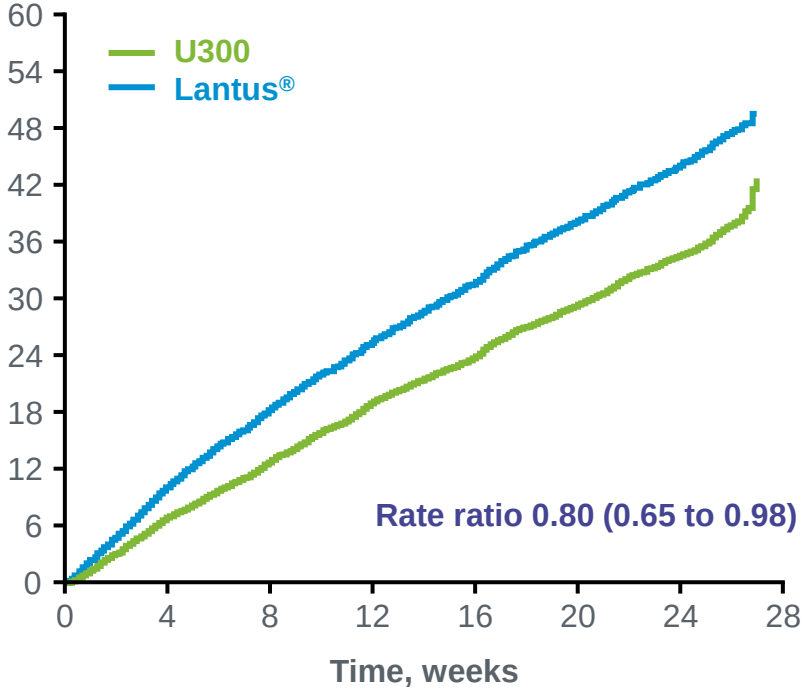

mITT population

Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975 Available at: http://www.easdvirtualmeeting.org/resources/18532 Accessed September 2014

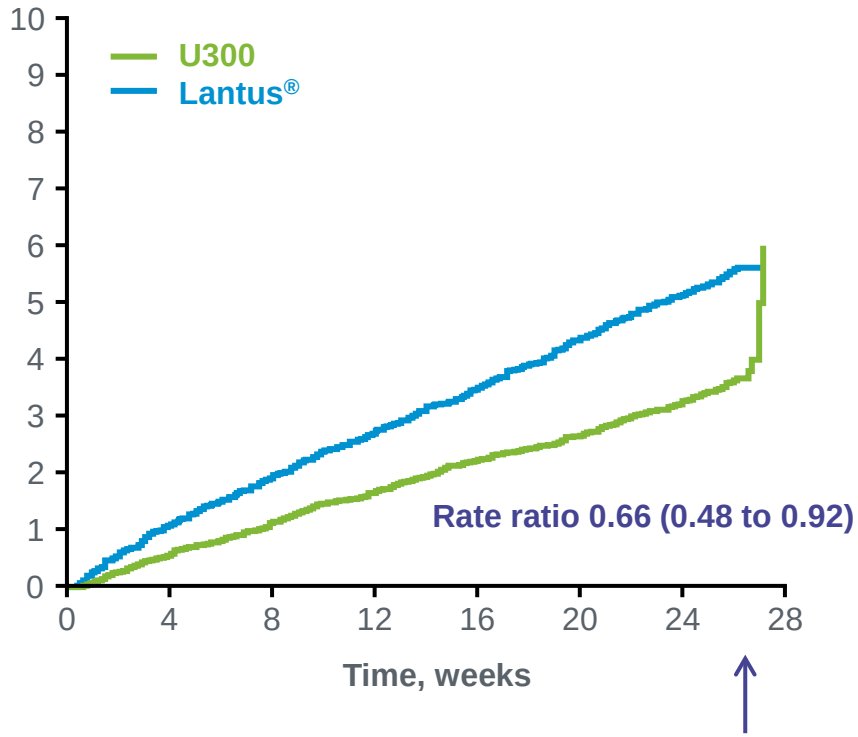
Data on file, EDITION JP 1 CSR, pg 85

# Lower confirmed and/or severe hypoglycemia at night and at any time (24 h)

**Hypoglycemia at any time (24 h)**
Cumulative mean number of confirmed* and/or severe events




**Nocturnal hypoglycemia (00:00–05:59 h)**
Cumulative mean number of confirmed* and/or severe events



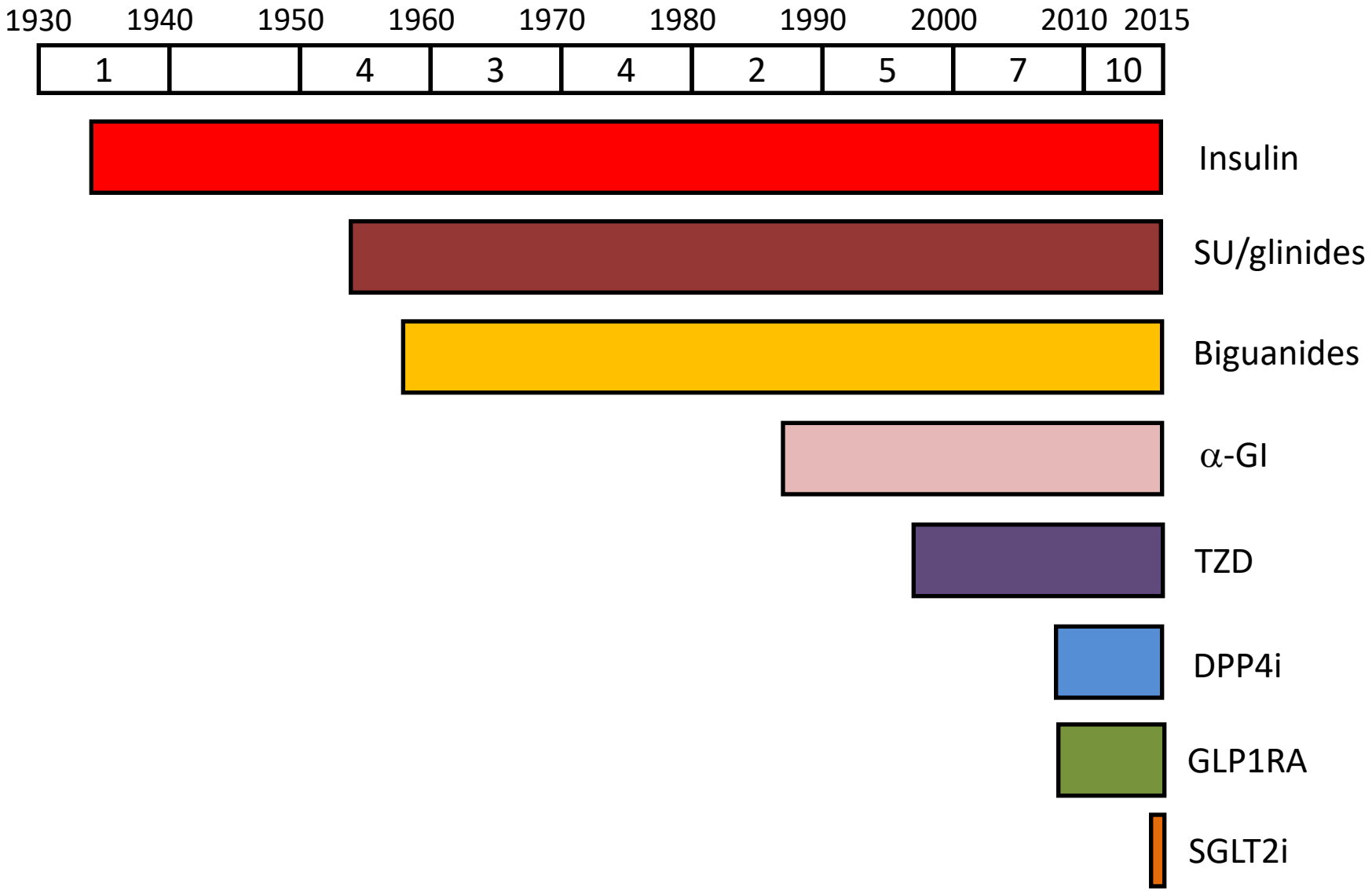

The steep increase in the U300 group during the last 8 days of the main 6-month treatment period is explained by the very low number of patients exposed to treatment during this time who experienced only 1 event on each of Day 187, Day 189 and Day 190

*Confirmed events based on plasma glucose ≤70 mg/dL (3.9 mmol/L)

Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975
Available at: http://www.easdvirtualmeeting.org/resources/18532
Accessed September 2014

| Day of study | 182 | 183 | 184 | 185 | 186 | 187 | 188 | 189 | 190 |
|---|---|---|---|---|---|---|---|---|---|
| Participants at risk U300 | 101 | 88 | 25 | 16 | 8 | 4 | 3 | 1 | 1 |
| Participants at risk Lantus | 103 | 92 | 28 | 22 | 19 | 11 | 4 | 1 | 1 |

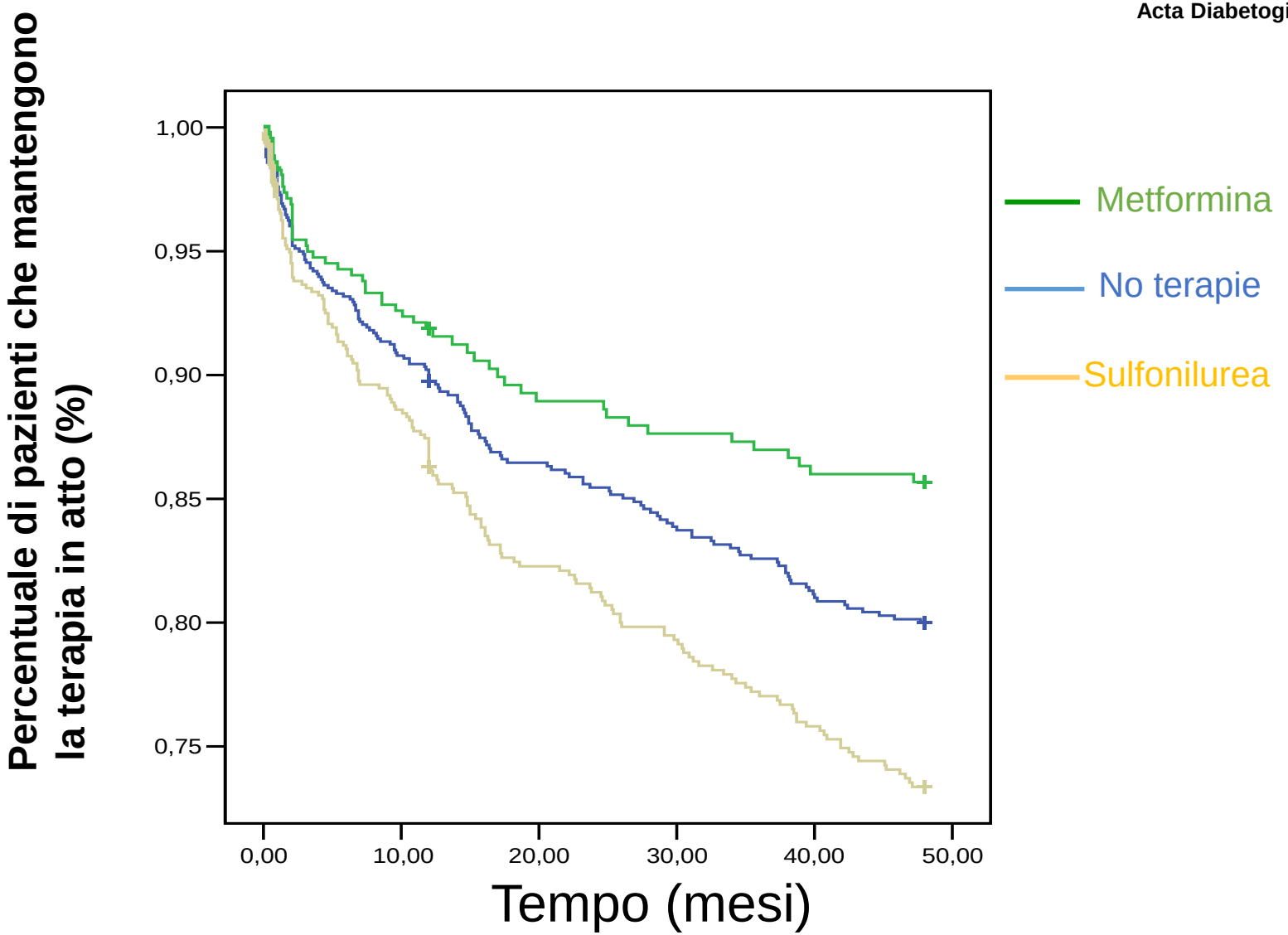
# Drugs for T2DM



# Failure to metformin and insulin secretagogue monotherapy: an observational cohort study

Laura Pala · Matteo Monami · Caterina Lamanna · Barbara Cresci · Claudia Colombi · Gianluca Bardini · Jolanda Sposato · Niccolò Marchionni · Carlo M. Rotella · Edoardo Mannucci

Acta Diabetogica 2009 Mar 17



The NEW ENGLAND JOURNAL of MEDICINE

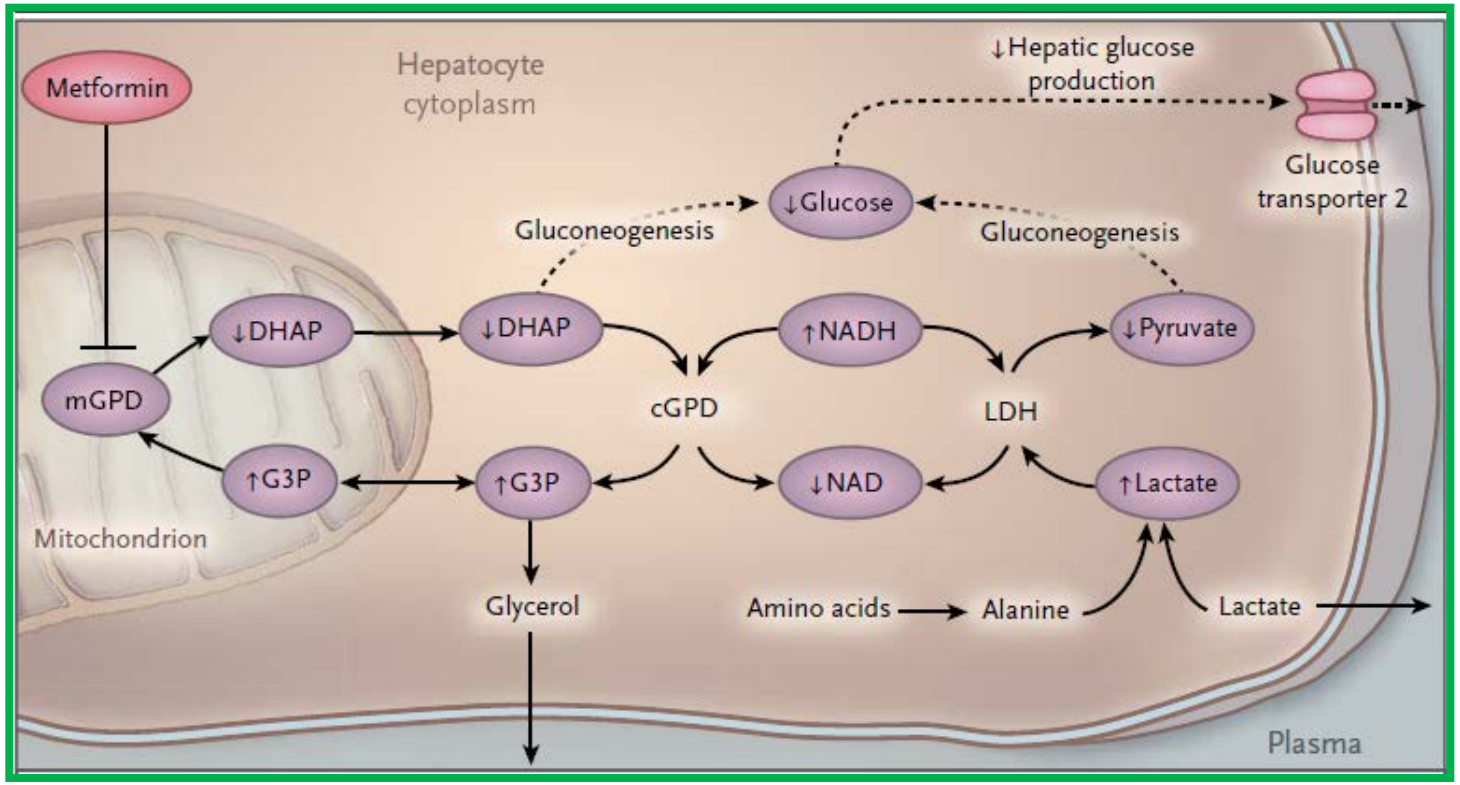
CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

# The Target of Metformin in Type 2 Diabetes

Ele Ferrannini, M.D.

## La metformina sopprime la gluconeogenesi epatica



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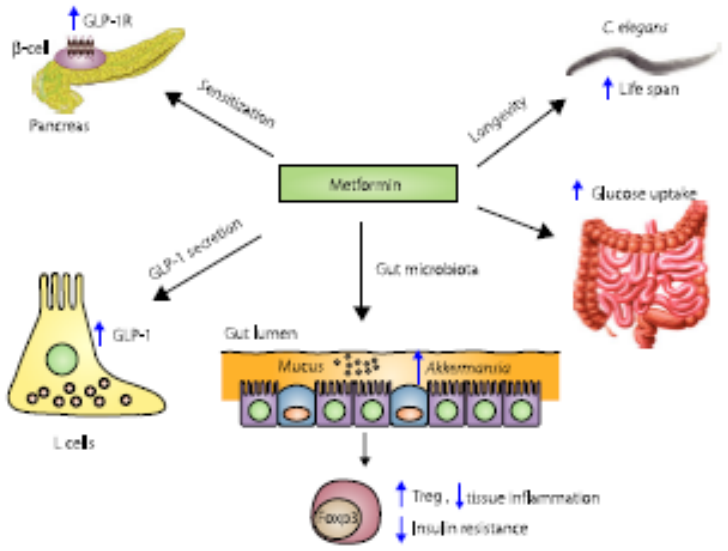
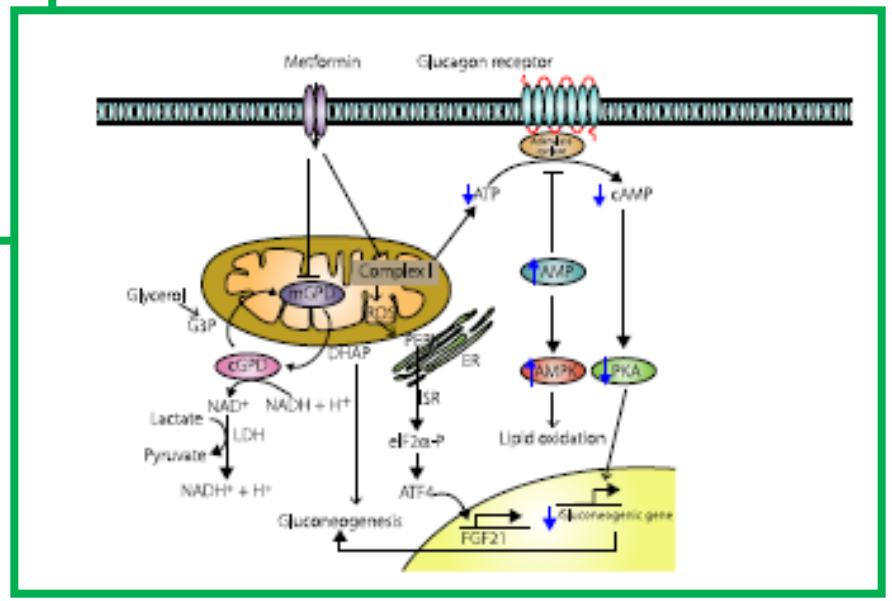
REVIEW ARTICLE

# New mechanisms of metformin action: Focusing on mitochondria and the gut

Kyu Yeon Hur, Myung-Shik Lee*




La metformina stimola il rilascio di GLP-1 nelle cellule L dell'intestino e anche l'espressione dei recettori per il GLP-1 a livello pancreatico



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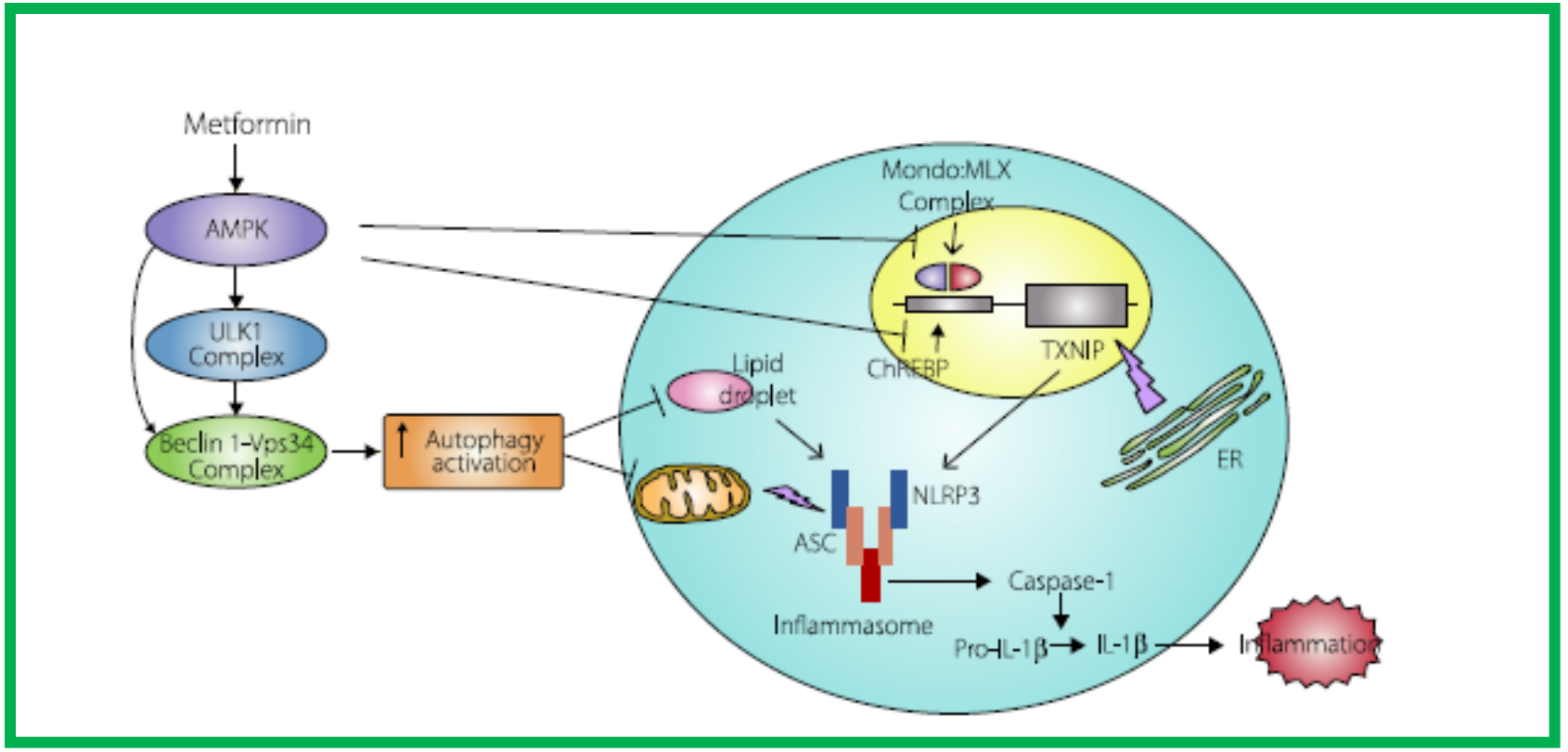


J Endocrinol Invest (2014) 37:497–498
DOI 10.1007/s40618-014-0065-x

OPINION

# The "slower" the better

L. Pala · C. M. Rotella

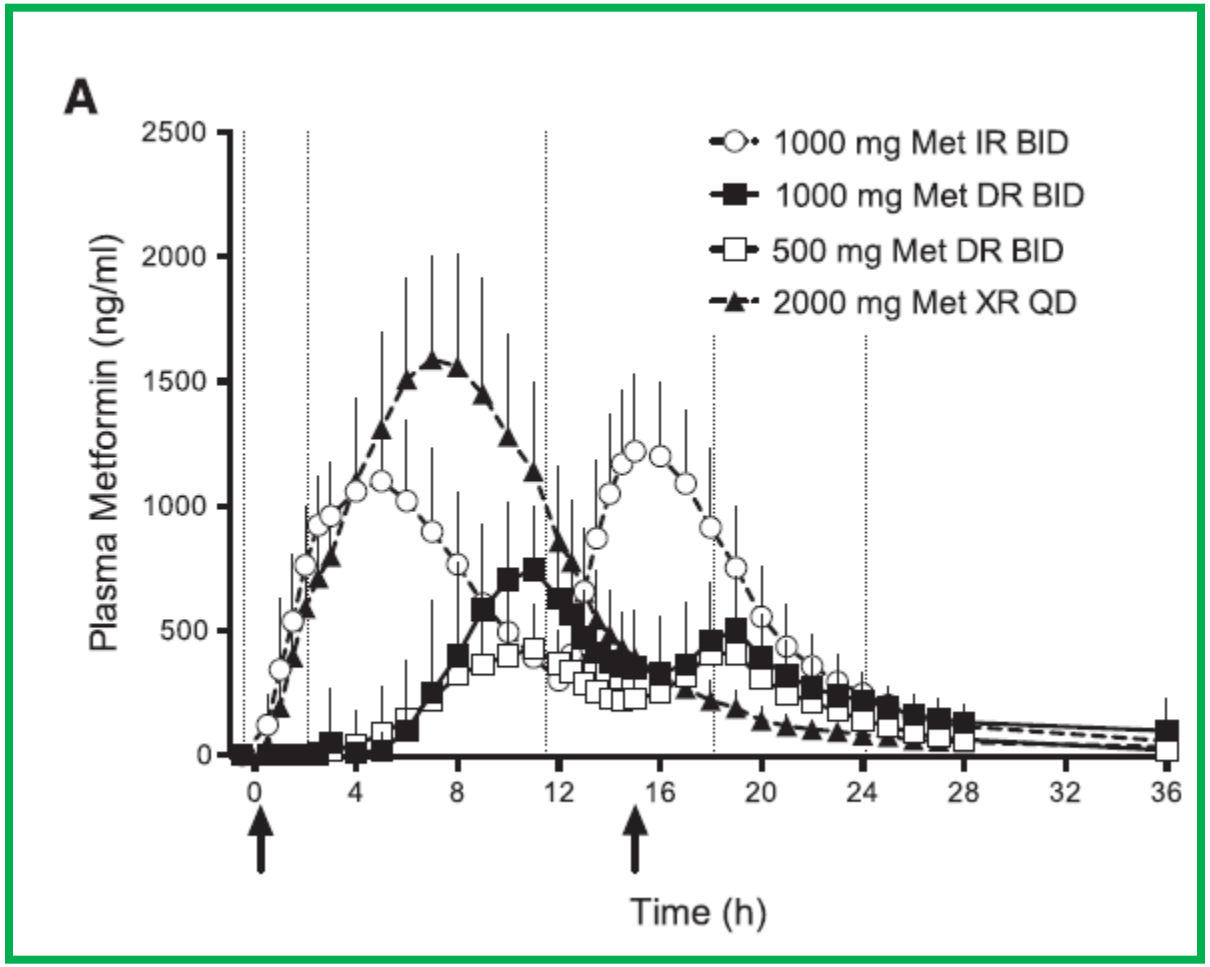
**Table 1** Comparison between metformin ER and metformin IR

| | Metformin ER | Metformin IR |
|---|---|---|
| Administration | Oral | Oral |
| Duration (hours) | 12 | 6 |
| Daily times dosing | 2 | 3 |
| Maximum plasma concentration (hours) | 7 | 3 |
| GI side effects | − | + |
| HbA1c Reduction (%) | 0.6–1 | 0.6–1 |

# The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies

John B. Buse,[1] Ralph A. DeFronzo,[2] Julio Rosenstock,[3] Terri Kim,[4] Colleen Burns,[4] Sharon Skare,[4] Alain Baron,[4] and Mark Fineman[4]

Diabetes Care 2016;39:198–205 | DOI: 10.2337/dc15-0488




Grazie