CONVEGNO MACROREGIONALE
AME DAY
20/21
MAGGIO 2016

Come l'obesità può condizionare la terapia medica del Diabete

UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA

Firenze 20 Maggio 2016

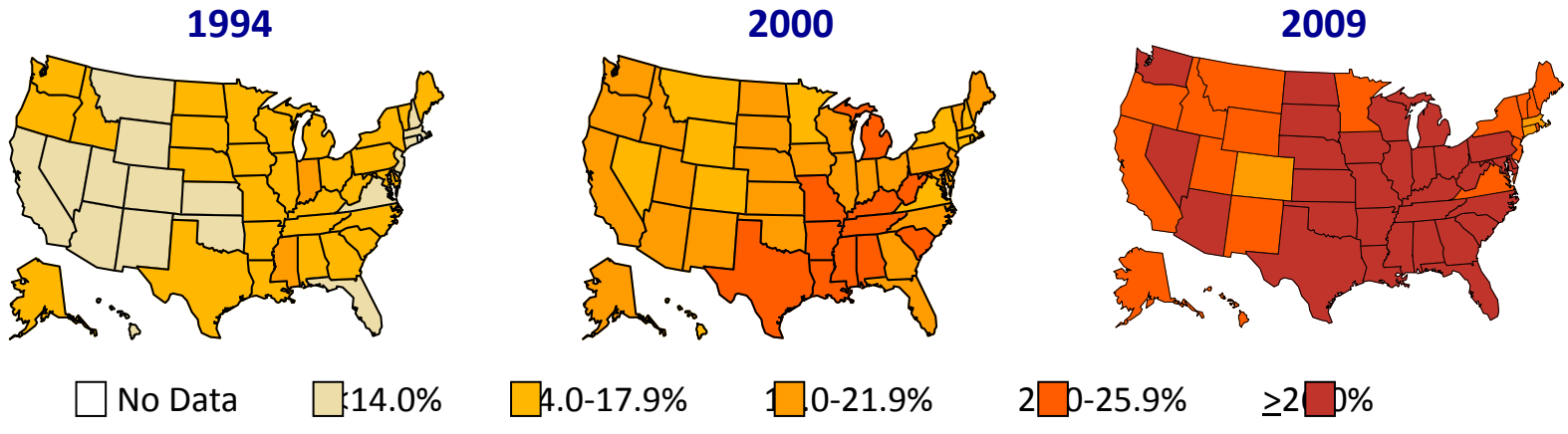
Dott.ssa Giusi Beretta Anguissola

Agenda

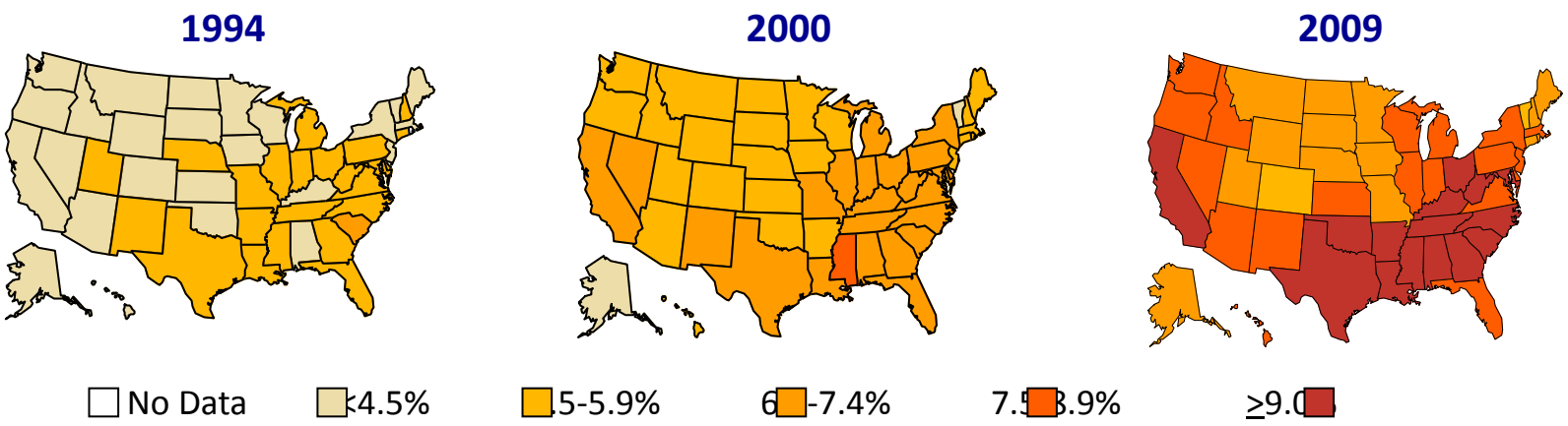
- ✓ Associazione di Diabete tipo 2 e Obesità
- ✓ Il paziente diabetico obeso
- ✓ Personalizzazione della terapia farmacologica nel Diabete tipo 2
- ✓ Farmaci ipoglicemizzanti efficaci sulla riduzione del peso corporeo :
  - Analoghi GLP1
  - Inibitori SGLT2

Aumento di prevalenza di Diabete e di Obesità

OBESITY

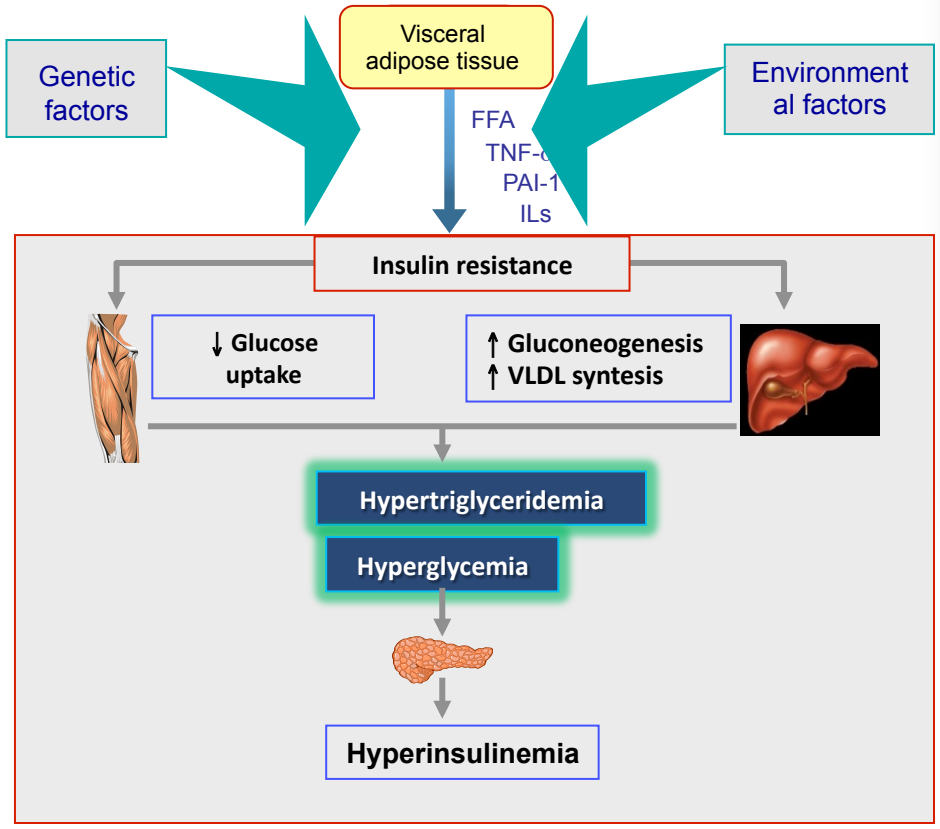


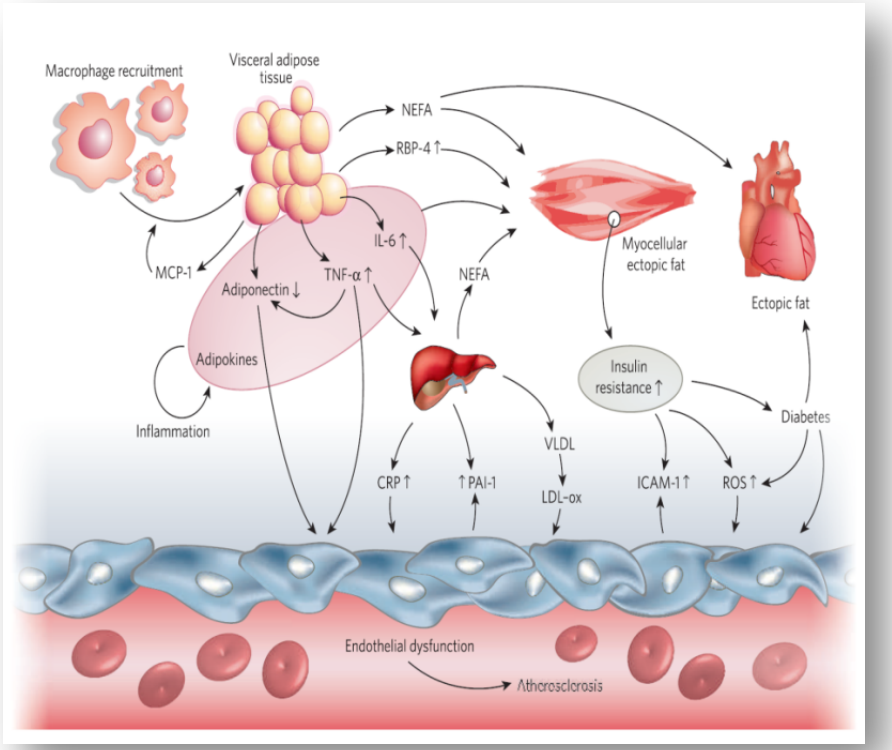
DIABETES



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Pattern fisiopatologici della insulino resistenza

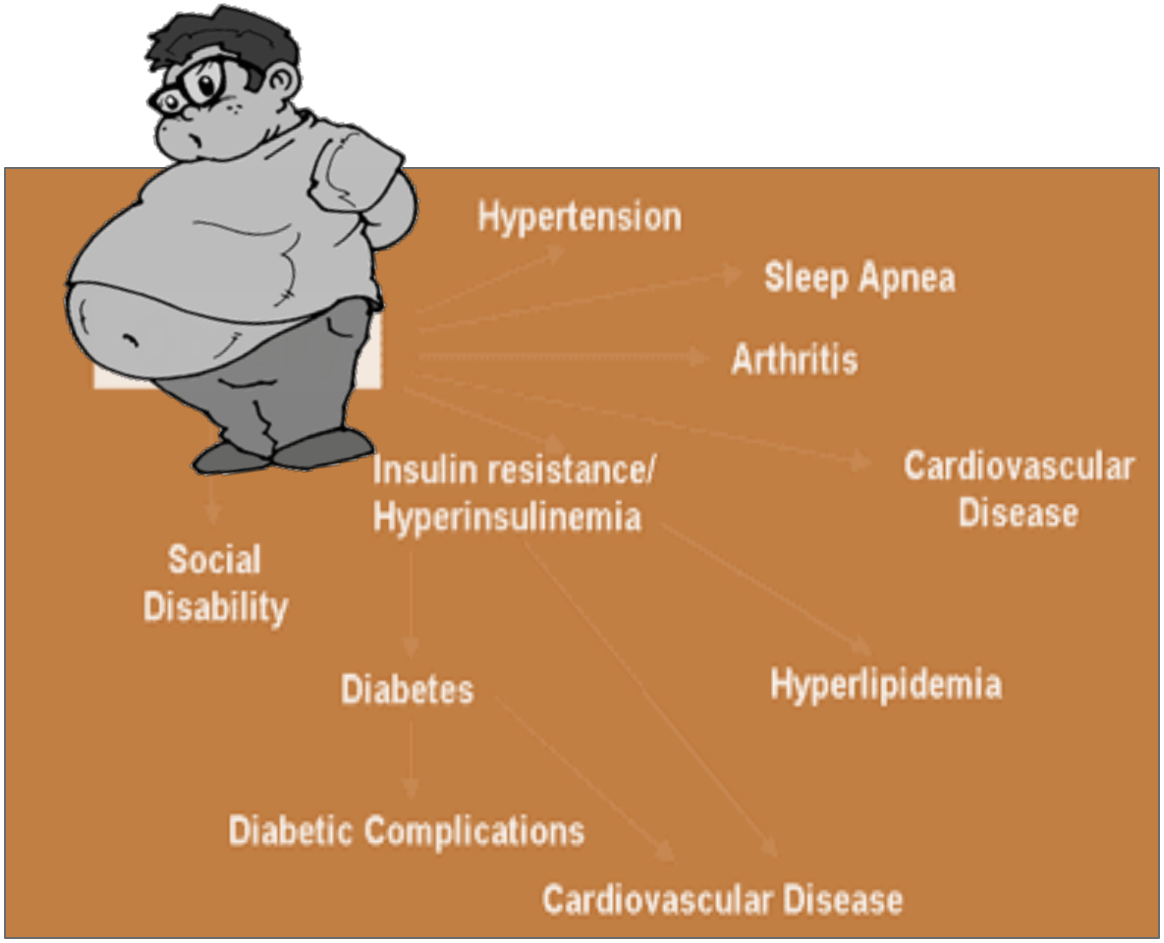




Il paziente diabetico obeso

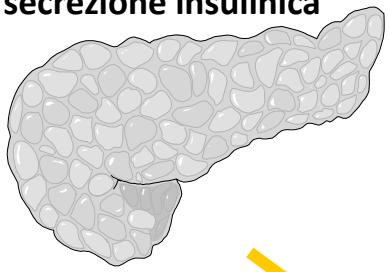
Più del 70% dei pazienti affetti da Diabete tipo 2 presenta sovrappeso o obesità

SOVRAPPESO BMI >25
OBESITA' I GRADO BMI > 30
OBESITA' II GRADO BMI >35
OBESITA' III GRADO BMI >40

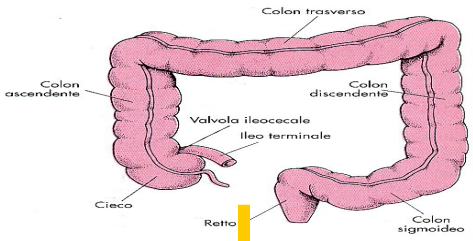


Diabete è una malattia complessa

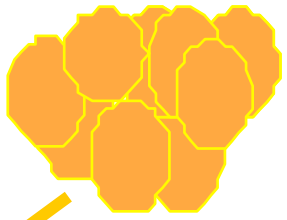
↓ secrezione insulinica



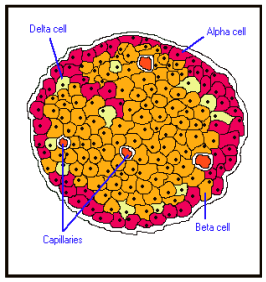
↓ effetto incretinico



↑ lipolisi

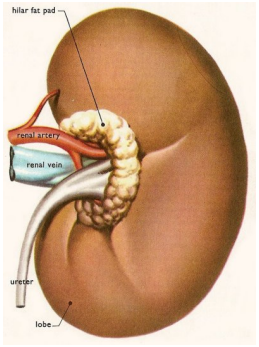


↑ secrezione glucagone

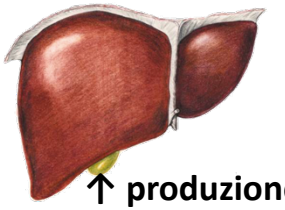


α-cellule

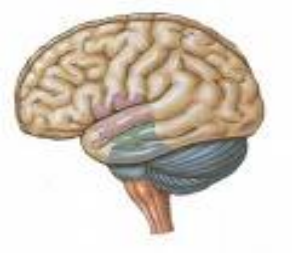
IPERGLICEMIA



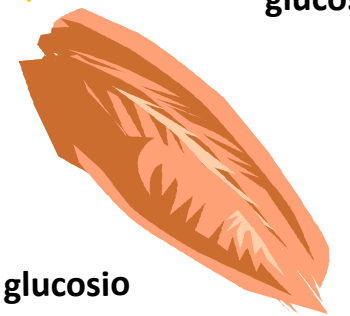
↑ riassorbimento glucosio



↑ produzione glucosio



Disfunzione trasmettitori



↓ uptake glucosio

Modificata da DeFronzo R.A, *Diabetes* 2009

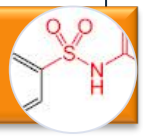
… terapia farmacologica complessa

- Detemir
- Glargine
- Degludec
- Lispro
- Aspart
- Glulisine
- Regular human

INSULINE

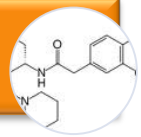
- Glicazide
- Glibenclamide
- Glimepiride
- Tolbutamide
- Chlorpropamide
- Gliburide

SULFANILUREE



- Nateglinide
- Repaglinide

GLINIDI

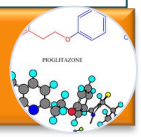


- Metformin
- Phenformin

BIGUANIDI

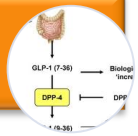
- Pioglitazone

TZD



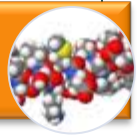
- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin

INIBITORI DPP-IV



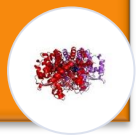
- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

ANALOGHI GLP1



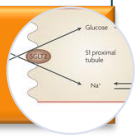
- Acarbose
- Miglitol

INIBITORI ALFA GLUCOSIDASI



- Dapagliflozin
- Empagliflozin
- Canagliflozin

INIBITORI SGLT2



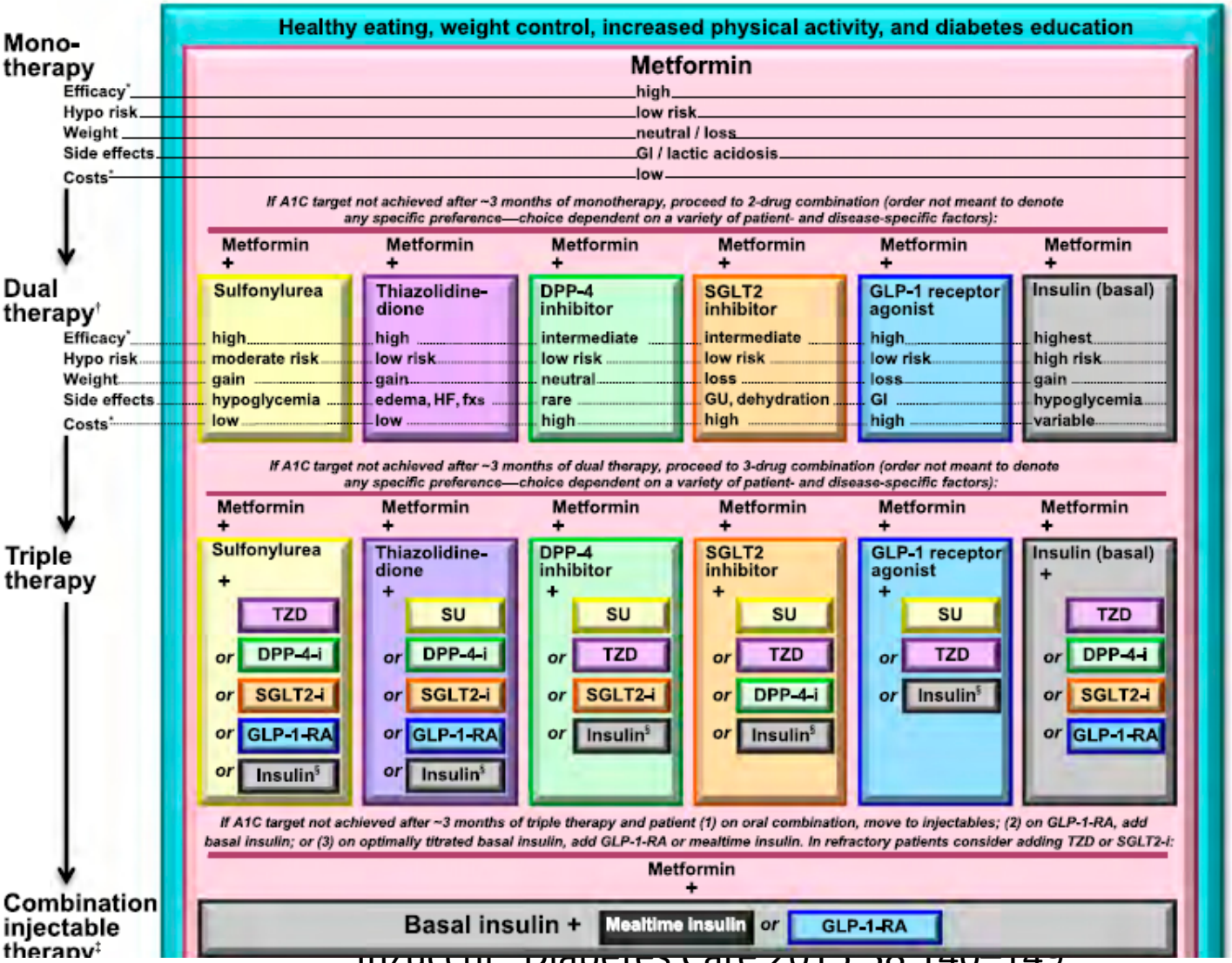
Personalizzazione della terapia

- ✓ Obiettivo glicemico
- ✓ Durata di malattia, funzione b cellulare residua
- ✓ Eta’
- ✓ Rischio CV
- ✓ Rischio di ipoglicemia
- ✓ Patologie concomitanti
- ✓ Sicurezza e tollerabilità
- ✓ Peso corporeo

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Silvio E. Inzucchi,[1] Richard M. Bergenstal,[2] John B. Buse,[3] Michaela Diamant,[4] Ele Ferrannini,[5] Michael Nauck,[6] Anne L. Peters,[7] Apostolos Tsapas,[8] Richard Wender,[9,10] and David R. Matthews[11,12,13]

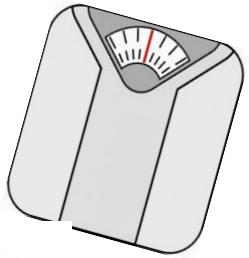
Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441



Inzucchi, Diabetes Care 2015;38:140–149

Modifiche dello stile di vita

Ottimizzazione del peso

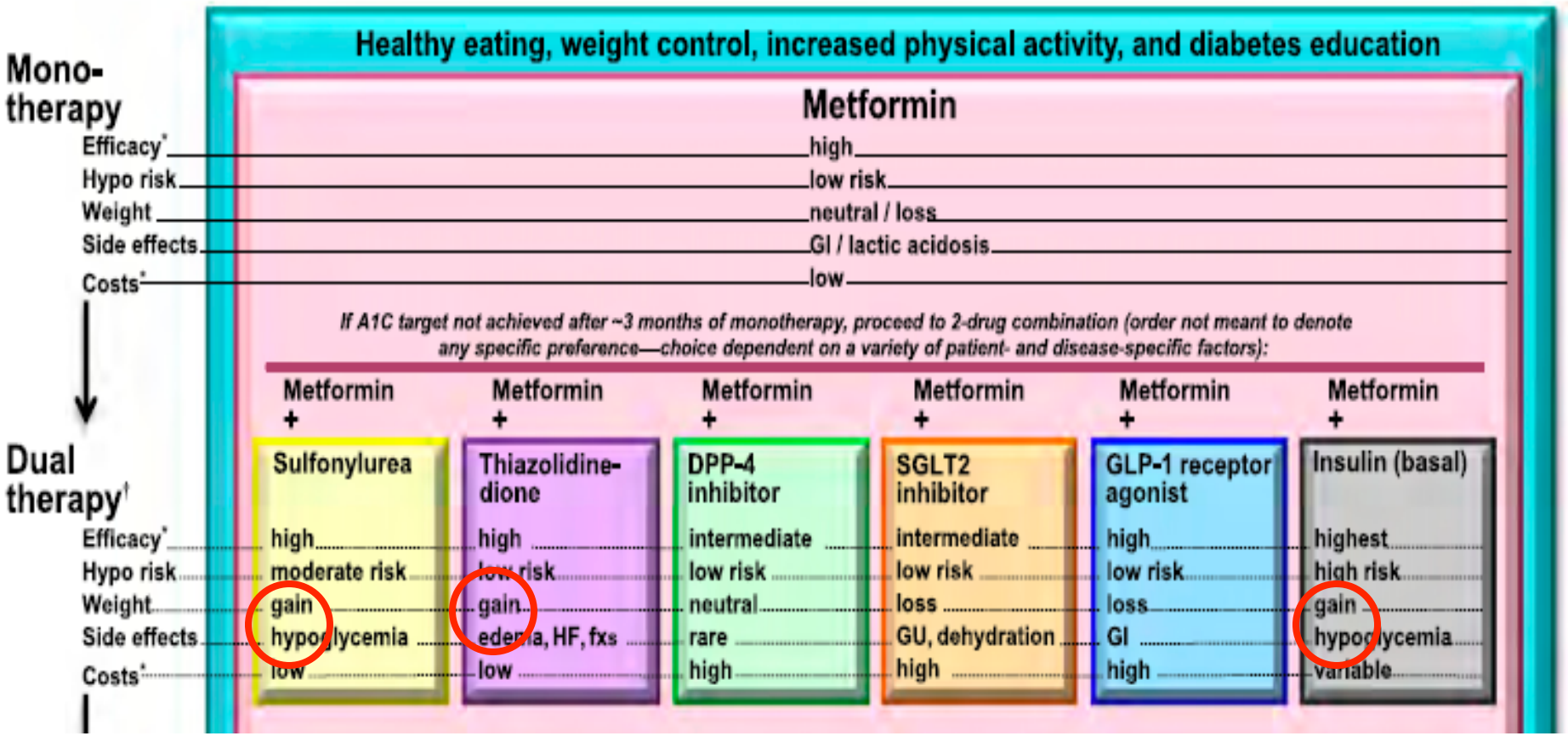


Dieta ipocalorica

Incremento attività fisica

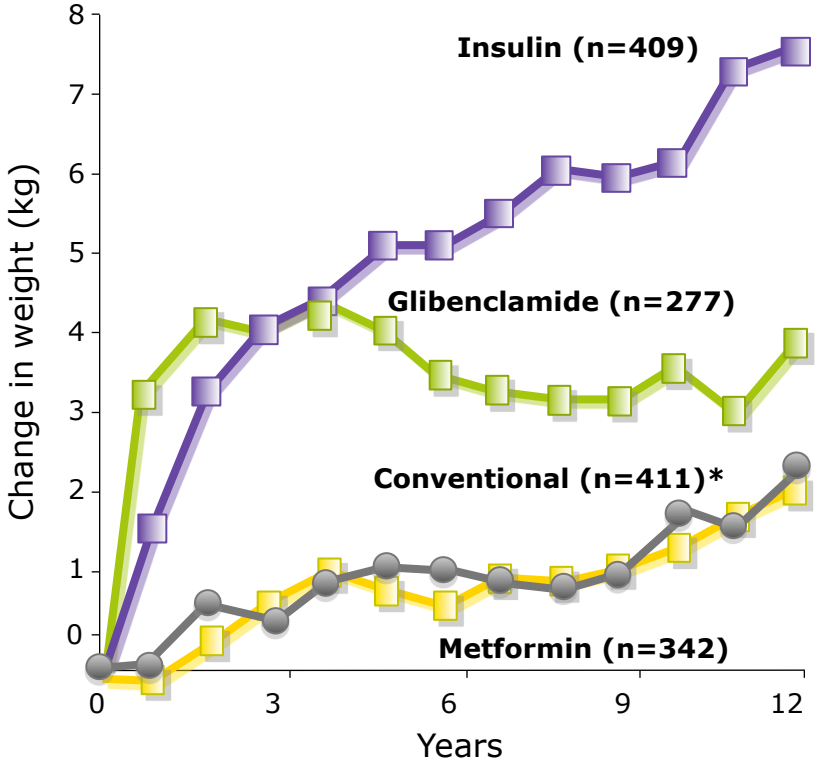
Diabetes Care, *Diabetologia*. **19 April 2012**

Farmaci ipoglicemizzanti che determinano incremento del peso corporeo

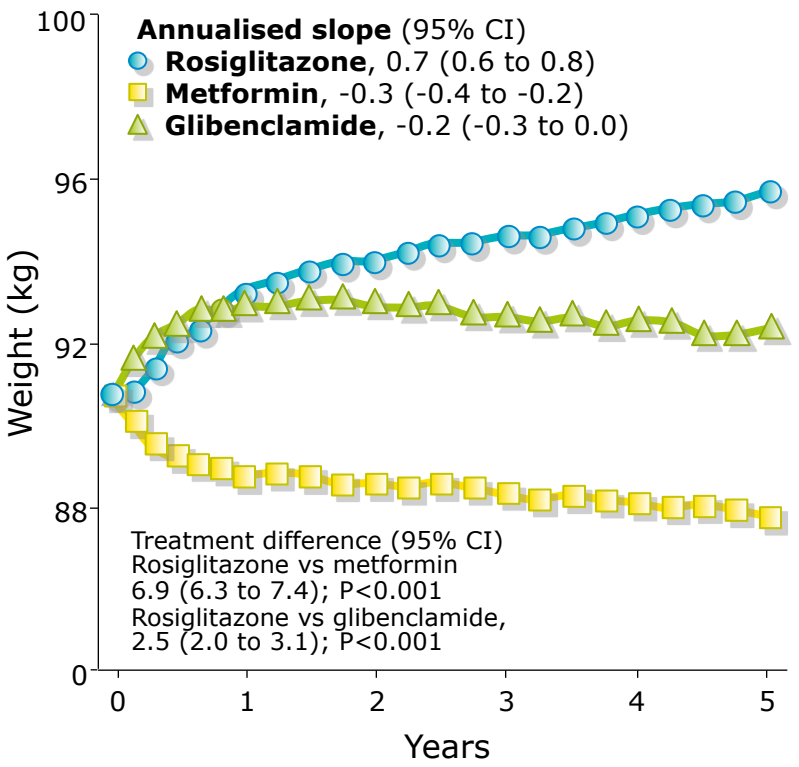


Inzucchi , Diabetes Care 2015;38:140–149

UKPDS: fino a 8 kg in 12 anni[1]



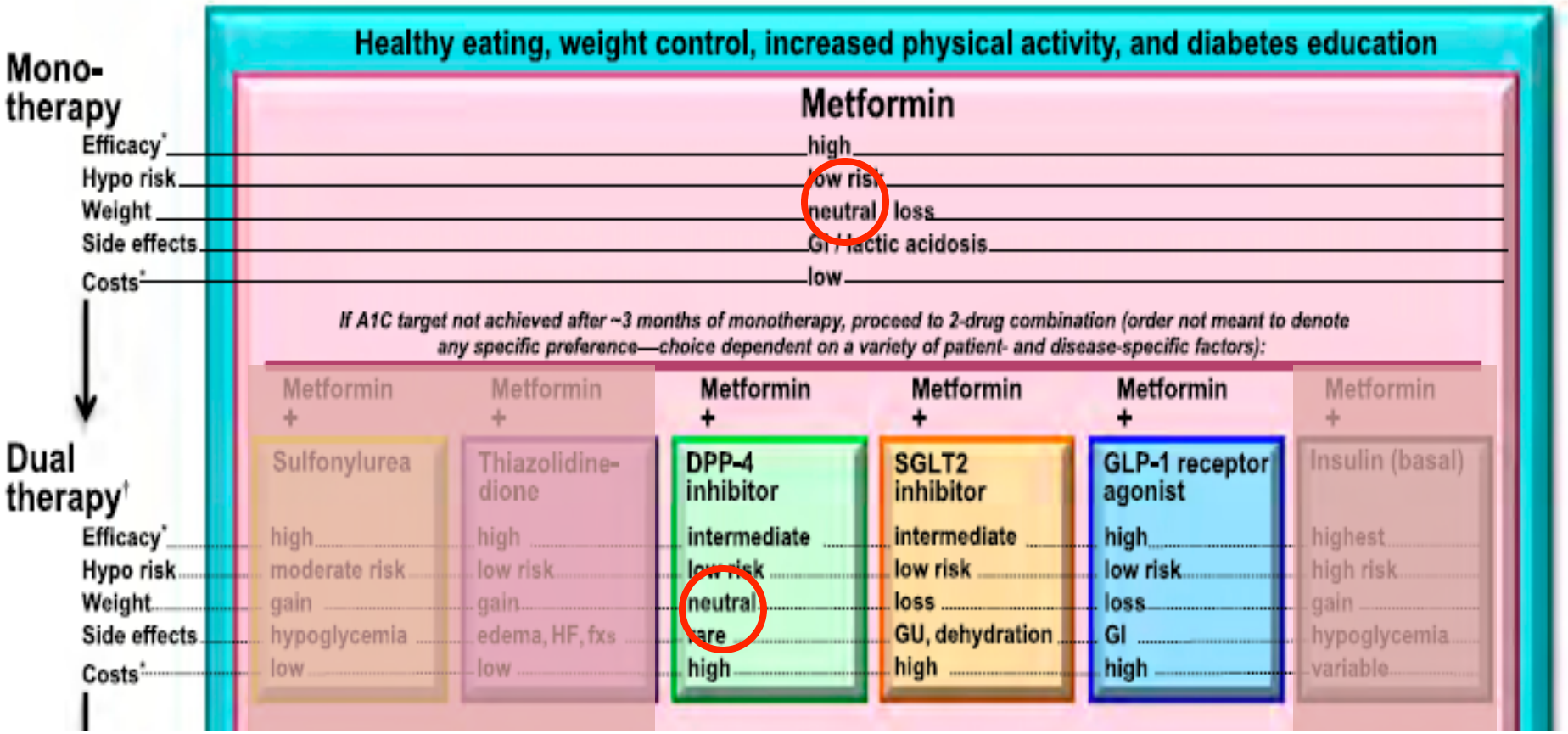
ADOPT: fino a 4.8 kg in 5 anni[2]



* Conventional treatment; diet initially then sulphonylureas, insulin and/or metformin if FPG >15 mmol/L (>270 mg/dL)
n=at baseline

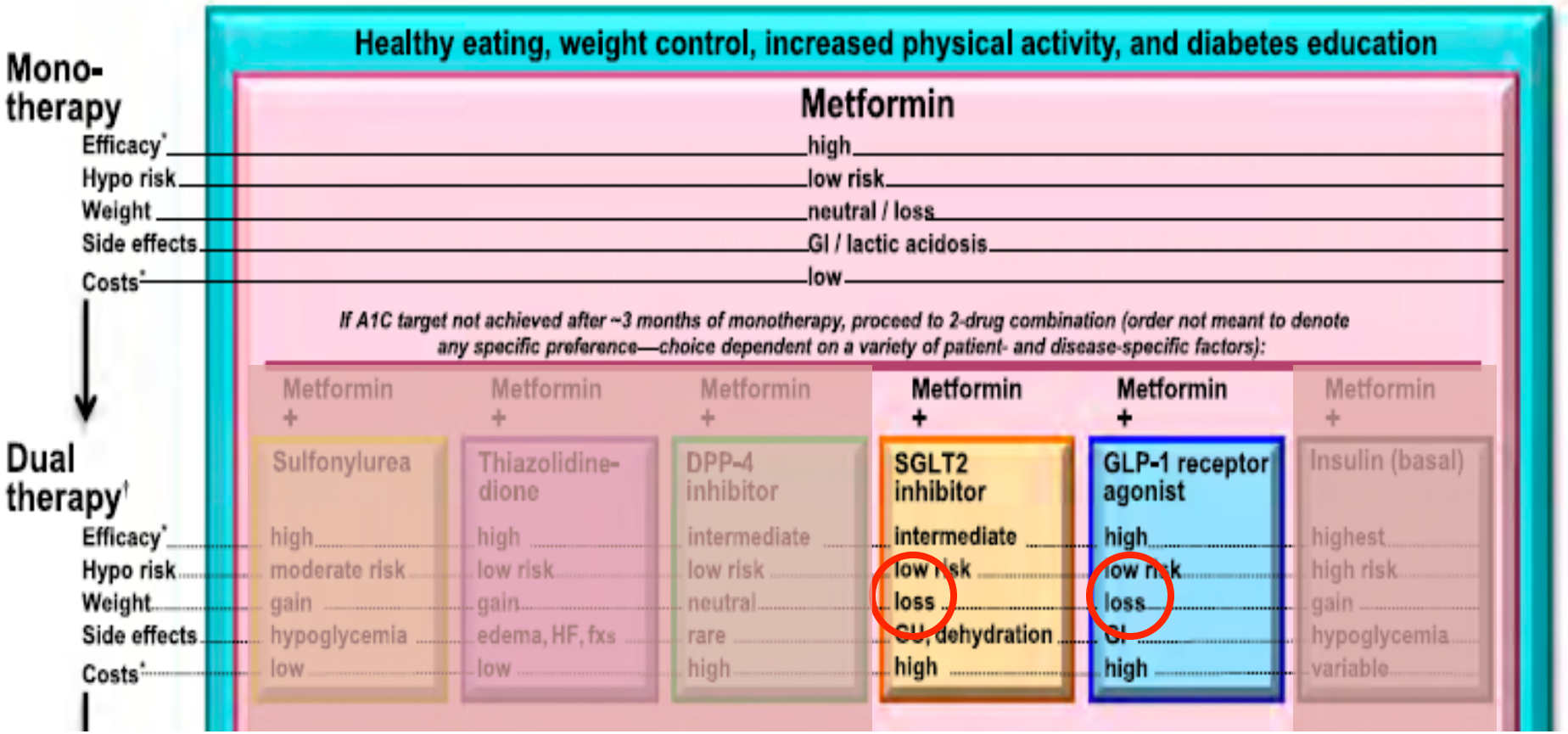
1. UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-65. 2. Kahn SE, et al (ADOPT). N Engl J Med. 2006;355:2427-43.

Farmaci ipoglicemizzanti che determinano stabilità del peso corporeo



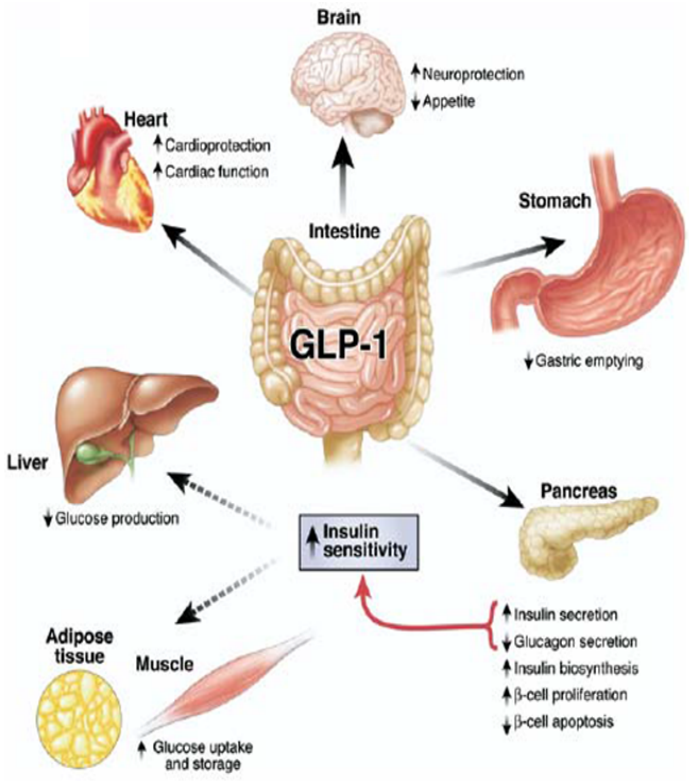
Inzucchi , Diabetes Care 2015;38:140–149

Farmaci ipoglicemizzanti che determinano riduzione del peso corporeo

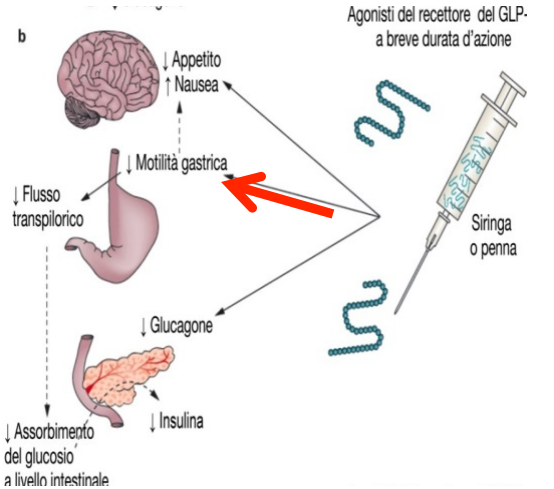


Inzucchi , Diabetes Care 2015;38:140–149

Analoghi GPL-1

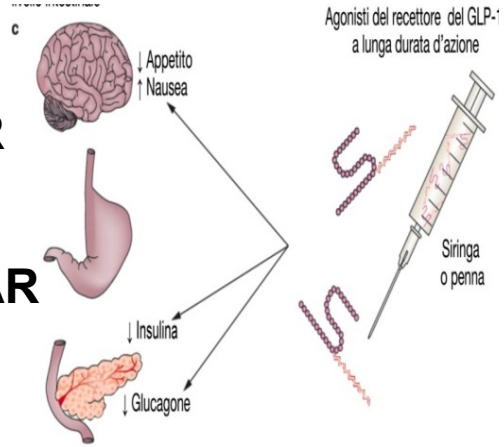


- **Exenatide**
- **Lixisenatide**



Riduzione glicemia postprandiale

- **Exenatide LAR**
- **Liraglutide**
- **Dulaglutide LAR**



Riduzione glicemia preprandiale

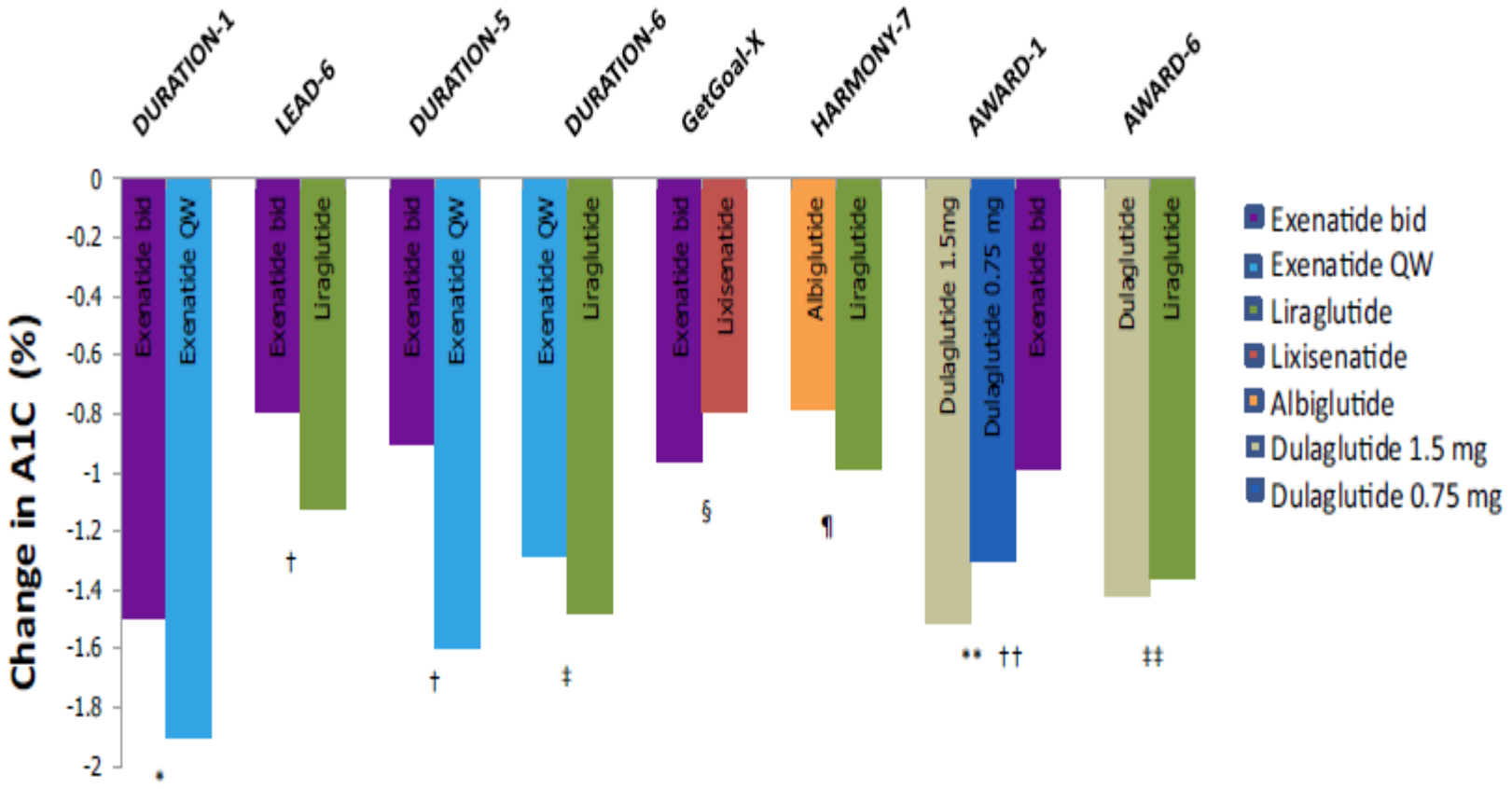
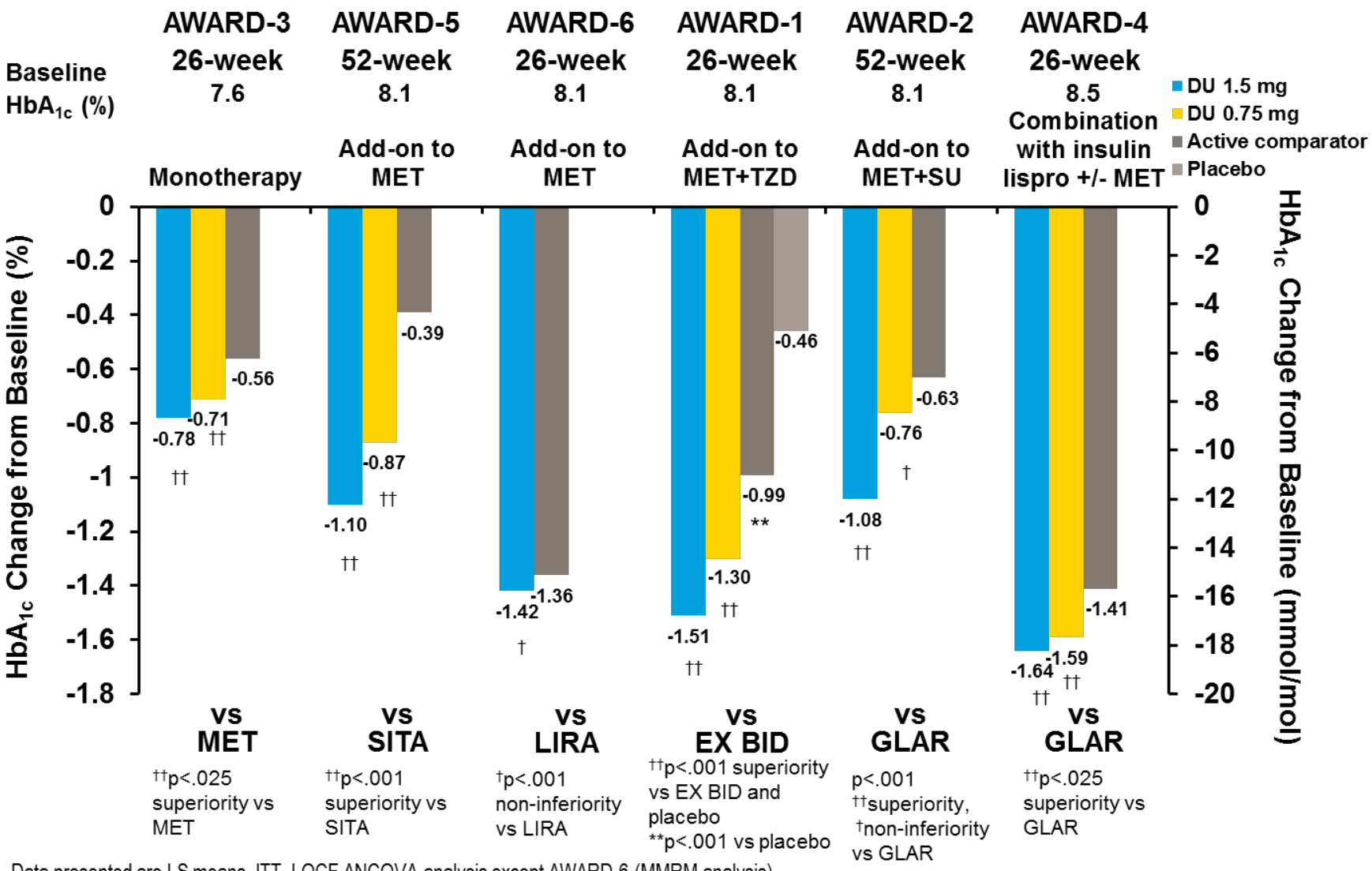


Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority unless otherwise noted as noninferiority; *$p < 0.0025$, †$p < 0.0001$, ‡$p = 0.02$, §p = not significant, noninferiority *p*-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority *p*-value = 0.846 (not meeting predefined noninferiority margin), **$p < 0.001$ for both doses of dulaglutide *versus* exenatide bid, ††p = not significant, noninferiority *p*-value < 0.0001 (meeting predefined noninferiority margin).

Trujillo 2015, *Ther Adv Endoc Metab*



Data presented are LS means, ITT, LOCF ANCOVA analysis except AWARD-6 (MMRM analysis)

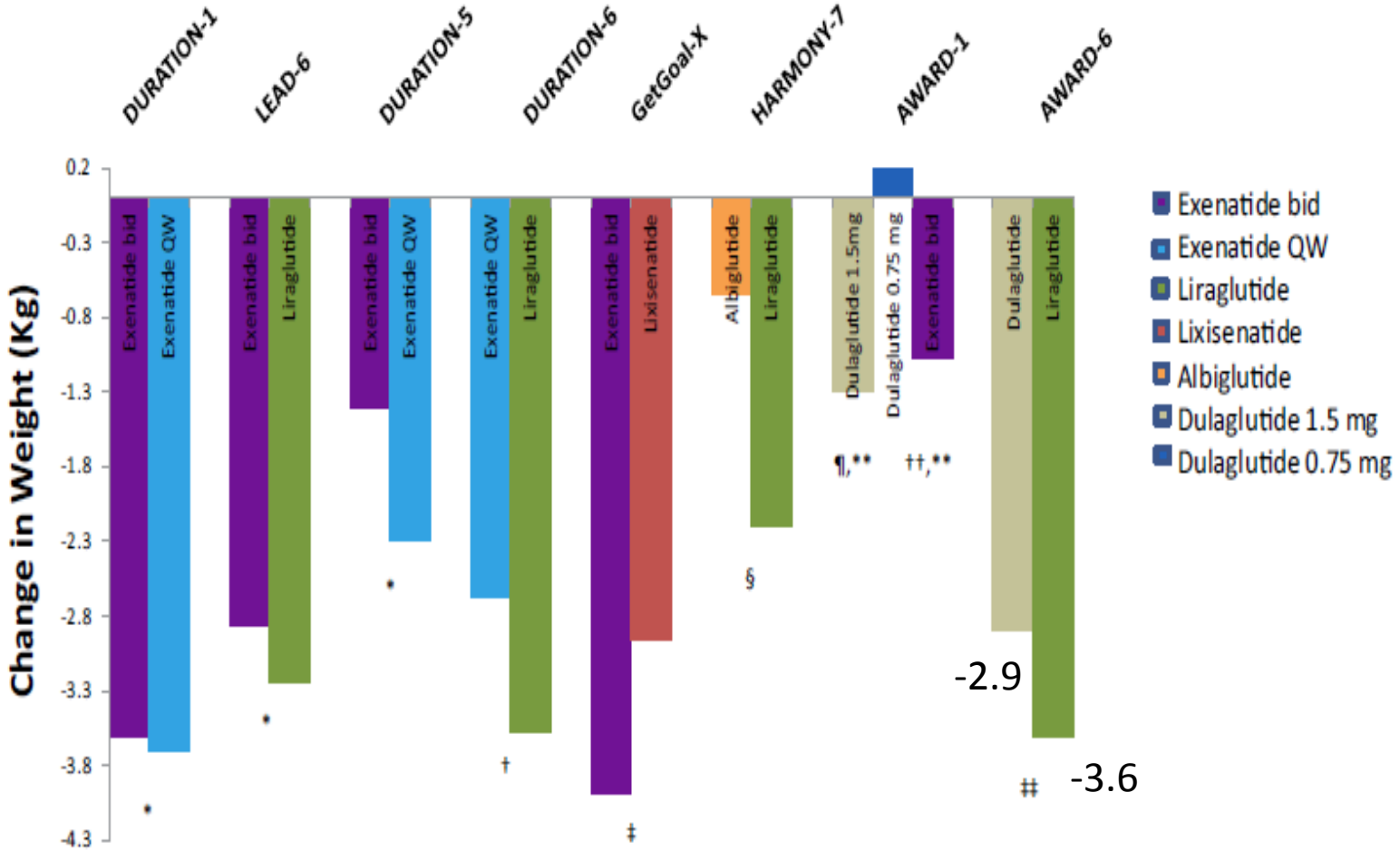


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority (unless noted for noninferiority); **p* = not significant, †*p* = 0.0005, ‡*p*-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §*p* < 0.0001, ¶ *p* < 0.001 *versus* dulaglutide 0.75 mg, ***p* = not significant between dulaglutide 1.5 mg *versus* exenatide bid, ‡‡*p* = 0.011.

Trujillo 2015, *Ther Adv Endoc Metab*

Analoghi GLP-1 nella pratica clinica

Criteri prescrivibilità

- Prescrivibili con piano terapeutico
- HbA1c tra 7.5-8.5 %
  (paziente fragile 9%)

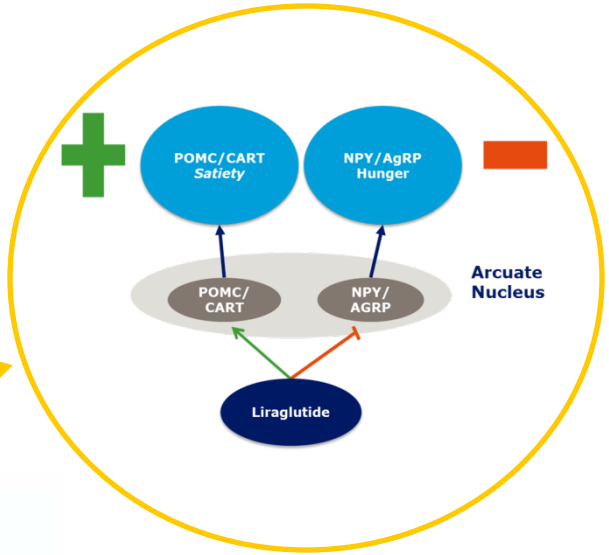
- Duplice o triplice terapia
- Add on con insulina basale (Liraglutide)

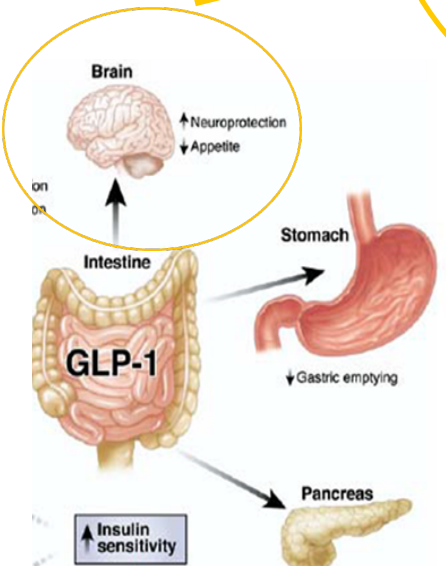
Effetti collaterali

- Sintomi gastrointestinali
- Rischio di pancreatiti

Terapia iniettiva

Liraglutide 3 mg /die per il trattamento del paziente obeso: Azione sui nuclei ipotalamici coinvolti nella regolazione dell' appetito





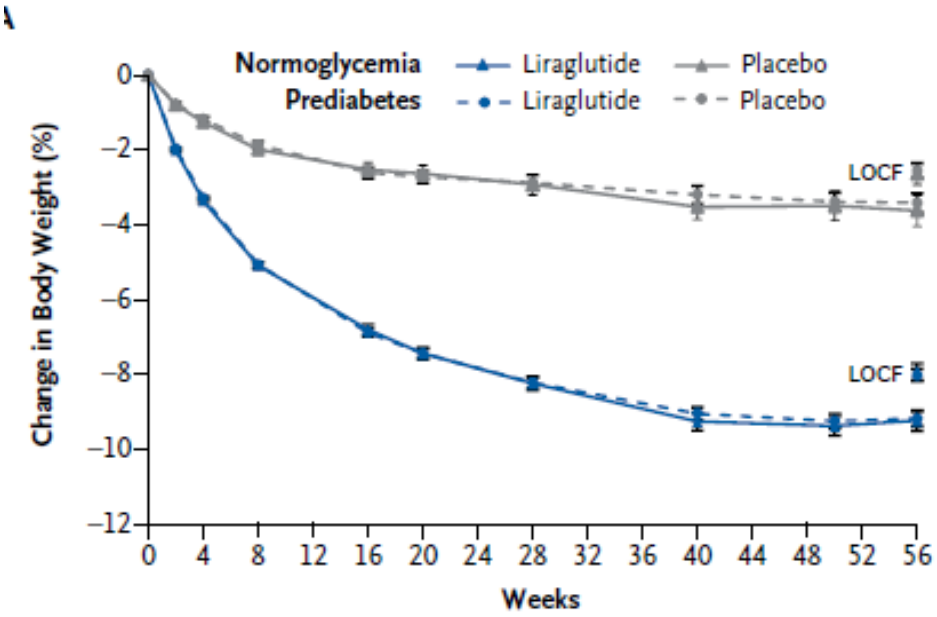
Energy metabolism[1]

- Satiety
- Fullness
- Hunger
- Prospective food consumption
- Energy intake

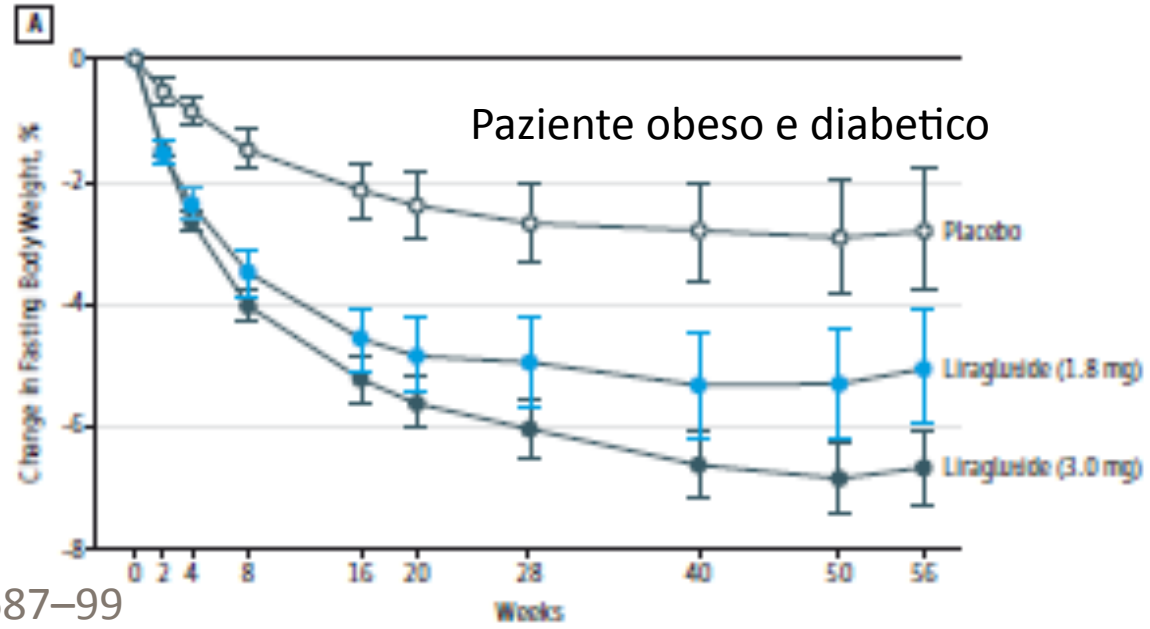
Glucose metabolism[1,2]

- Insulin secretion (glucose-dependent)
- Glucagon secretion (glucose-dependent)

1. van Can *et al. Int J Obes* 2014;38:784–93; 2. Flint *et al. Adv Ther* 2011;28:213–26



Pi-Sunyer *et al. NEJM* 2015;373:11–22



Davies *et al*. *JAMA* 2015;314:687–99

Liraglutide 3 mg/die per il trattamento dell'obesità

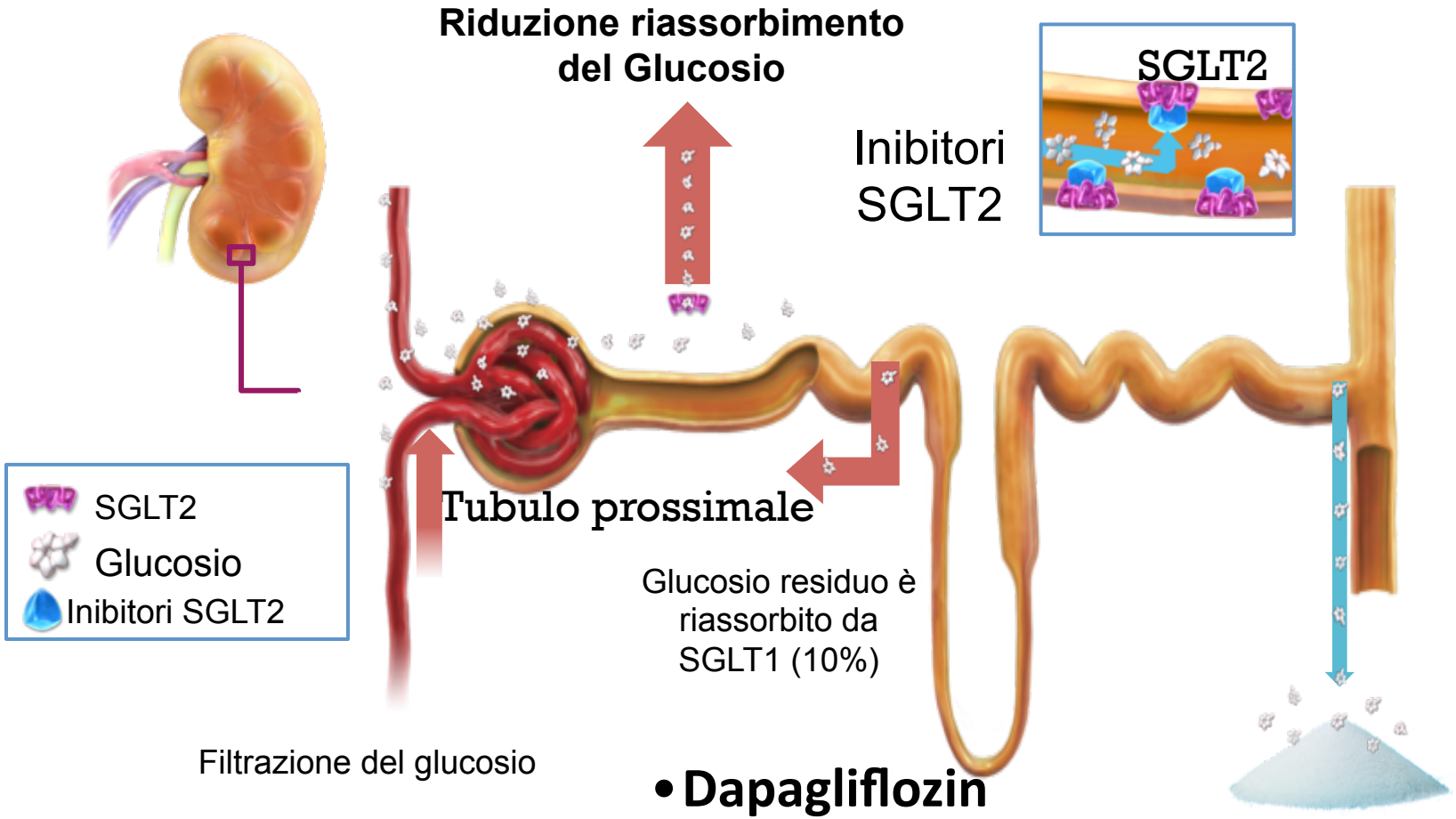
Non indicato nella terapia del paziente con Diabete al dosaggio 3 mg/die

- **BMI >30 Kg/m2**
- **BMI >27 e < 30 Kg/m2 con una co-morbidità (Diabete tipo 2, prediabete, ipertensione, dislipidemia, apnea ostruttiva sonno)**

Dose iniziale 0.6 mg da aumentare settimanalmente fino a 3 mg/die

- Effetti collaterali: nausea vomito diarrea stipsi insonnia
- Sospendere dopo 12 settimane se calo ponderale inferiore < 5%
- Considerare riduzione della terapia insulinica o sulfaniluree nel paziente diabetico

Inibitori SGLT2
Aumentata escrezione urinaria di glucosio

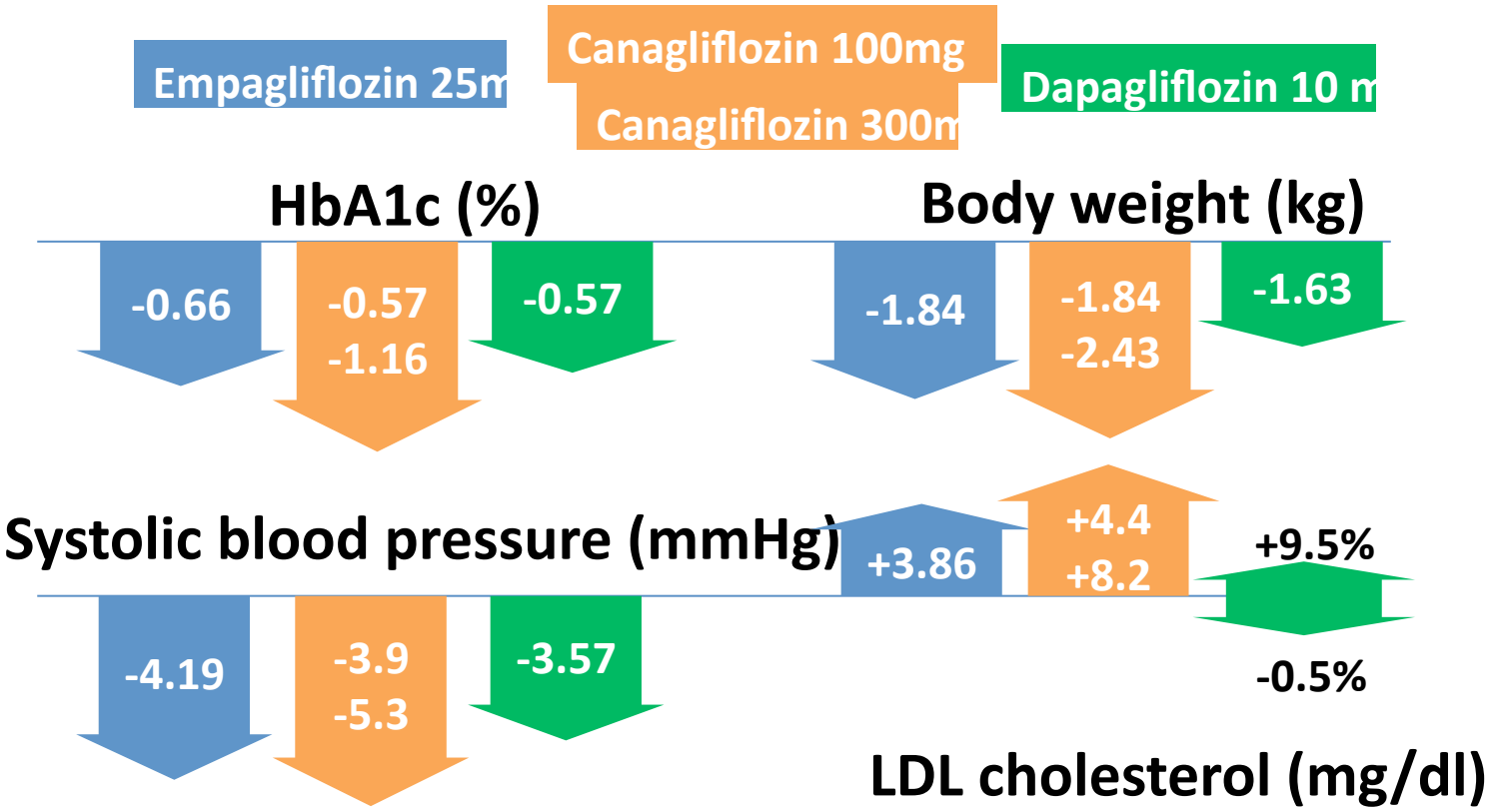


- **Dapagliflozin**
- **Canagliflozin**
- **Empagliflozin**

Aumentata escrezione urinaria di glucosio (~70 g/giorno, 280 kcal/day[2])

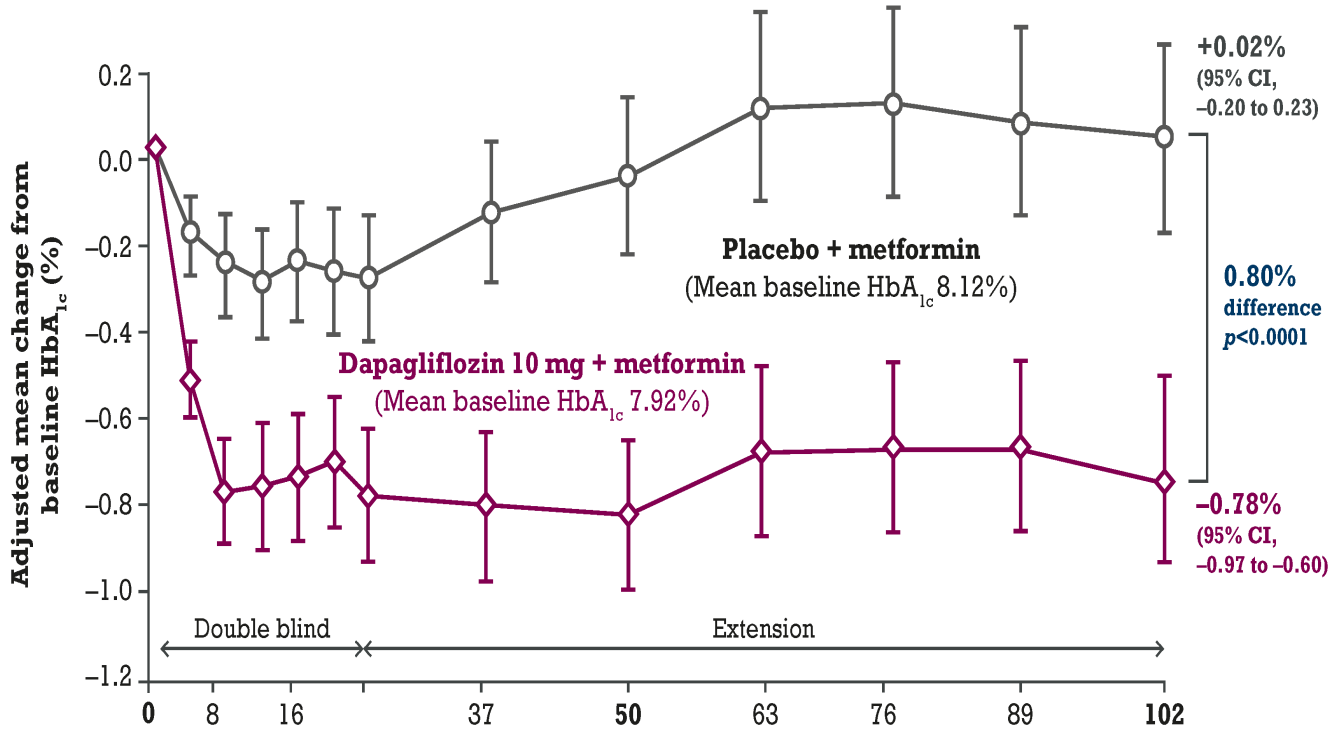
1. Marsenic O. *Am J Kidney Dis* 2009;**53**:875–85; 2.

Effetti metabolici degli inibitori SGLT2



Liakos et al. DOM Nov.2014; Zhang et al. DMRR 2014; Haas et al. Nutrition&Diabetes 2014; Hach et al. Diabetes. 2013;62(Suppl 1):Abstract 69-LB ; Nauck Drug Des Dev Ther 2014.

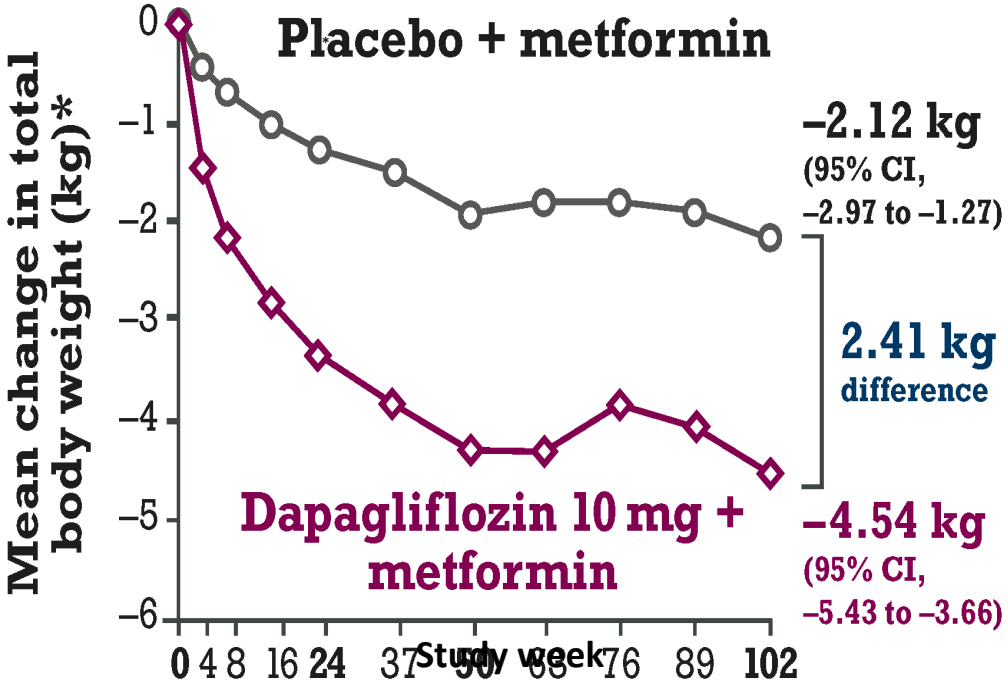
Riduzione significativa HbA_{1c} persistente in 2 anni Dapagliflozin add-on metformina verso placebo

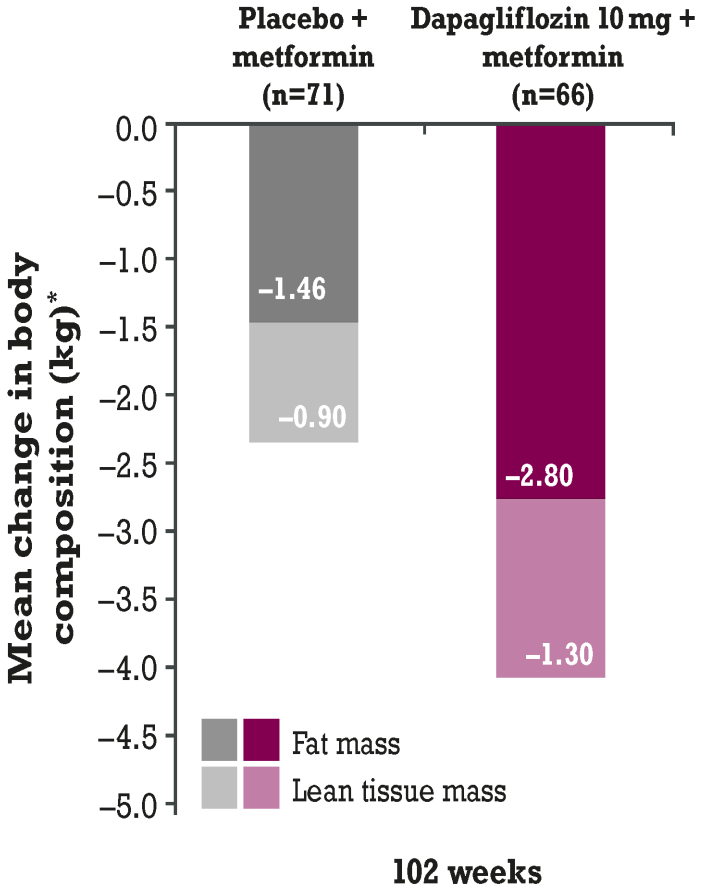


At the 24-week primary endpoint, dapagliflozin 10 mg delivered HbA_{1c} reductions of –0.8% versus –0.3% with placebo ($p<0.0001$)[2]

1. Bailey CJ, *et al. BMC Med* 2013;**11:**43; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

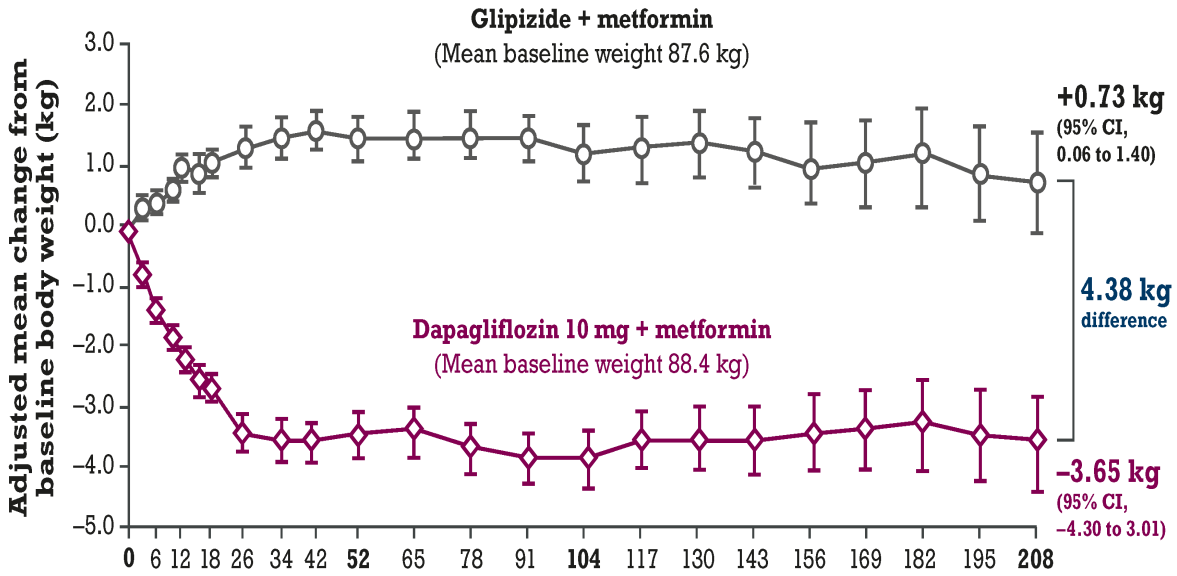
Dapagliflozin add-on con metformina : effetto sulla riduzione del peso





Significativa riduzione della massa grassa rispetto a massa magra e alla perdita di fluidi persistente a 102 settimane

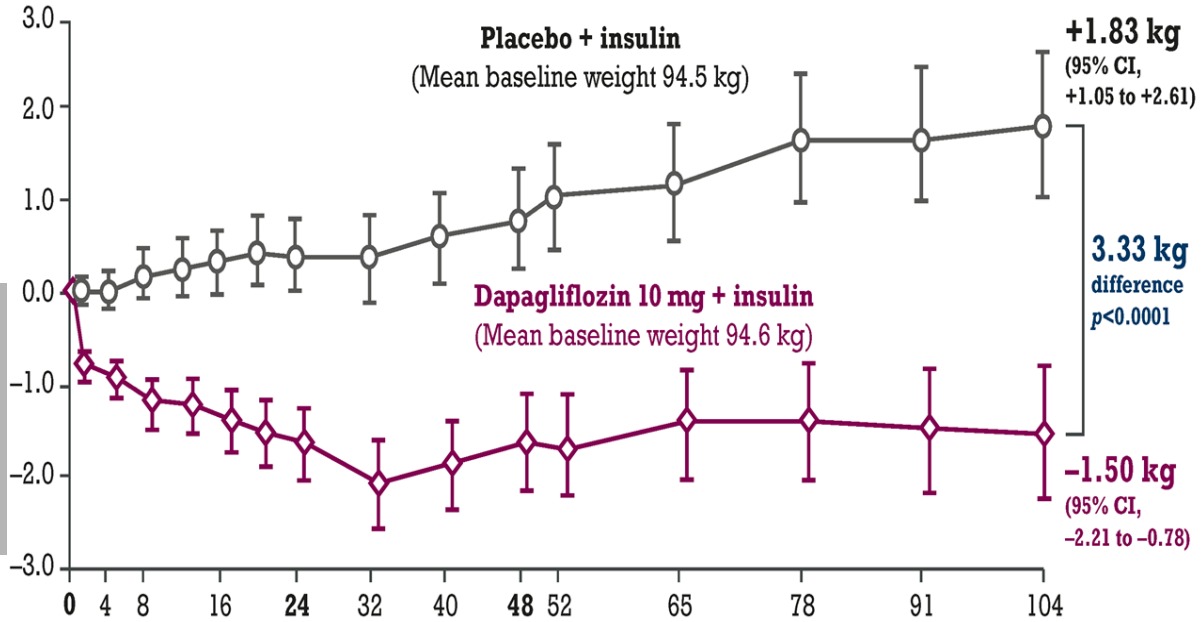
1. Bolinder J, *et al. Diabetes Obes Metab* 2014;**16**:159–69.



Dapagliflozin add-on metformina verso SU:
Perdita di peso mantenuta in 4 anni

1. Del Prato S, *et al. Diabetes Obes Metab* 2015;**17**:581–90;
2. 2. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22.

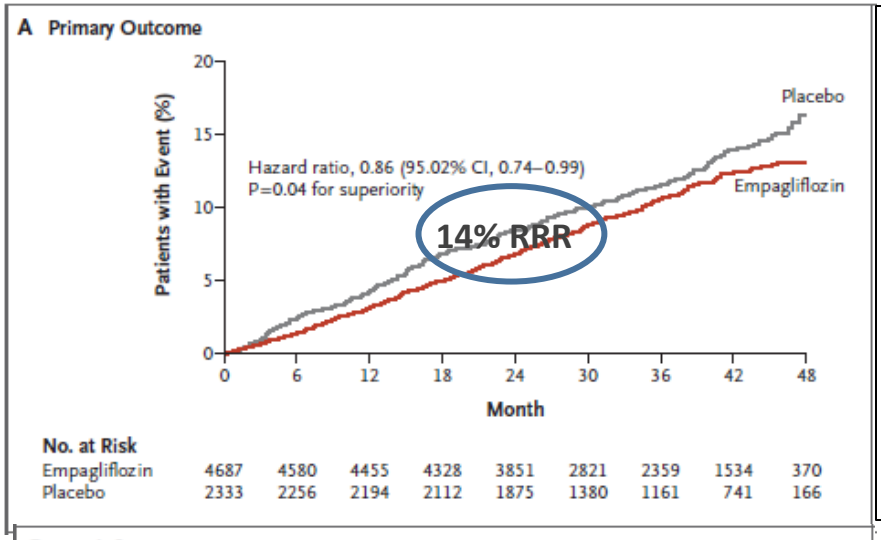
Dapagliflozin add-on insulina (± IGO): perdita di peso significativa mantenuta in 2 anni

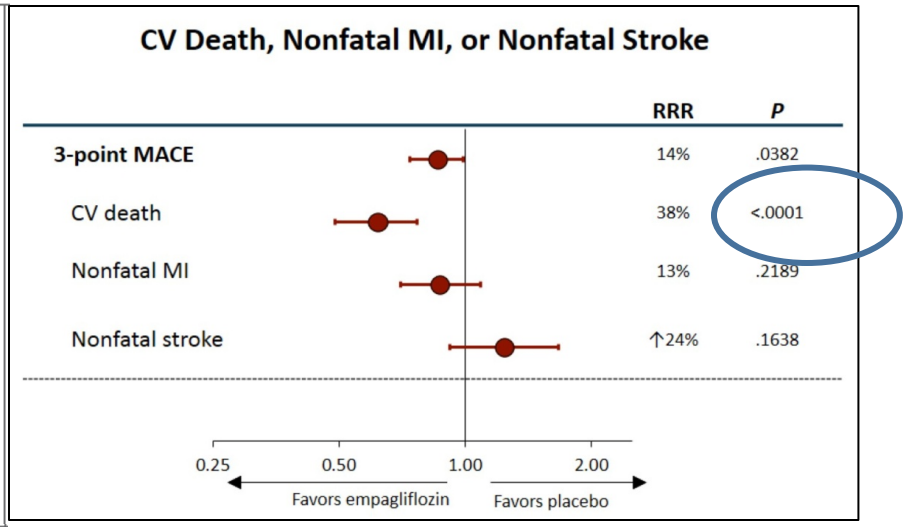


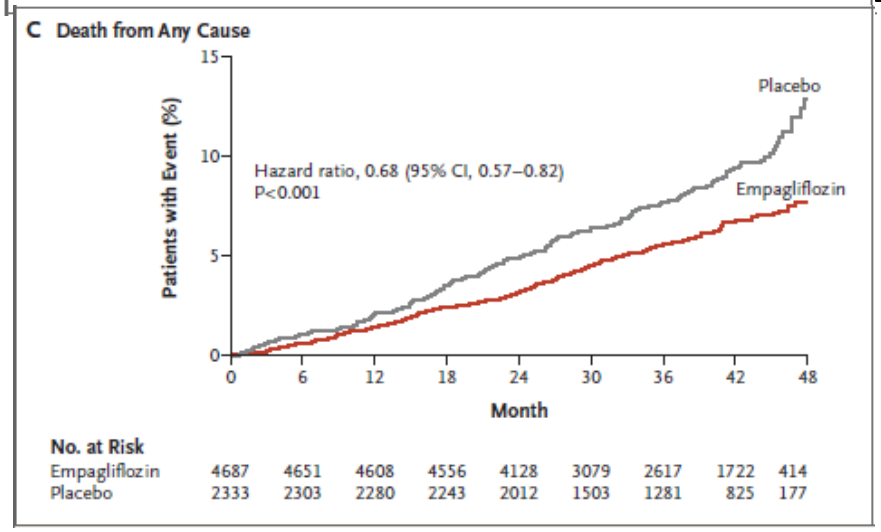
1. Wilding JP, et al. Diabetes Obes Metab 2014;16:124–36.

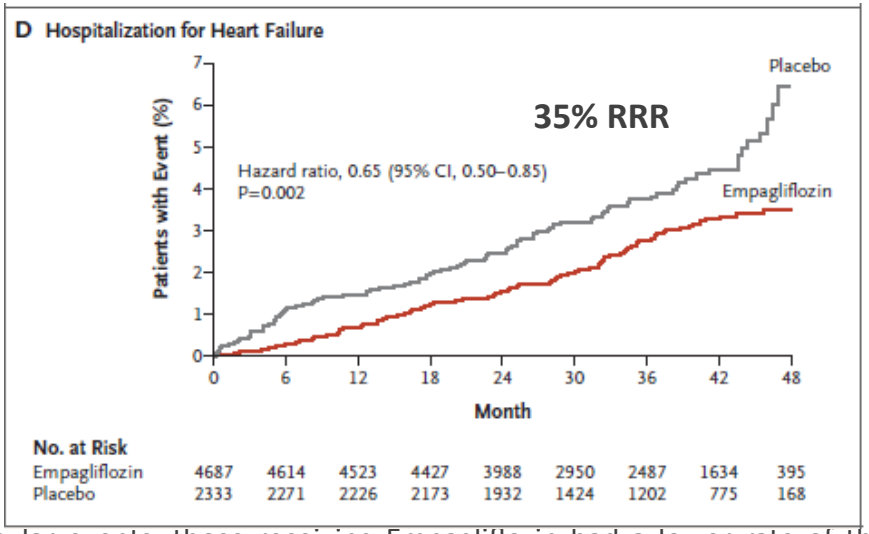
EMPA-REG OUTCOME

Zinman B, et al; EMPA-REG OUTCOME Investigators. N Engl J Med. 2015 Nov 26;373(22):2117-28









- ✓ Among patients with type 2 diabetes at high risk for cardiovascular events, those receiving Empagliflozin had a lower rate of the primary composite outcome.
- ✓ The difference between Empagliflozin and placebo was driven by a significant reduction in death from cardiovascular causes, with no significant between-group difference in the risk of myocardial infarction or stroke.

Inibitori SGLT2 nella pratica clinica

Criteri prescrivibilità

- Prescrivibili su piano terapeutico
- HbA1c non vincolante
- Non associati a diuretici dell' ansa

- GFR >60

- Duplice terapia con metformina
- Duplice terapia con insulina
- Triplice terapia con metformina e insulina

- Monoterapia solo se intolleranza alla metformina

Effetti collaterali

- Rischio di infezioni genitourinarie
- Incremento LDL (?)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Febbraio 2016

EMA ha confermato le raccomandazioni per minimizzare il rischio di chetoacidosi con gli inibitori SGLT2 usati per il diabete di tipo 2 – Alert su possibili casi atipici

Aprile 2016

EMA ha iniziato una revisione del farmaco Canaglifoxin dopo un **incremento di amputazioni , prevalentemente arti inferiori,** osservato durante uno studio clinico

Take home messages

- ✓ Personalizzazione della terapia ipoglicemizzante in base al fenotipo del paziente
- ✓ La presenza di obesità peggiora il controllo glicemico cosi come i parametri metabolici e di rischio cardiovascolare nel paziente diabetico
- ✓ Considerare i farmaci ipoglicemizzanti che hanno anche un azione di riduzione del peso
- ✓ Tra questi i più recenti farmaci Analoghi GLP1 e Inibitori SGLT2 hanno mostrato risultati efficaci