Il blocco del co-trasportatore sodio-glucosio come target della terapia anti-iperglicemica

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TEAM DIABETE
Gemelli

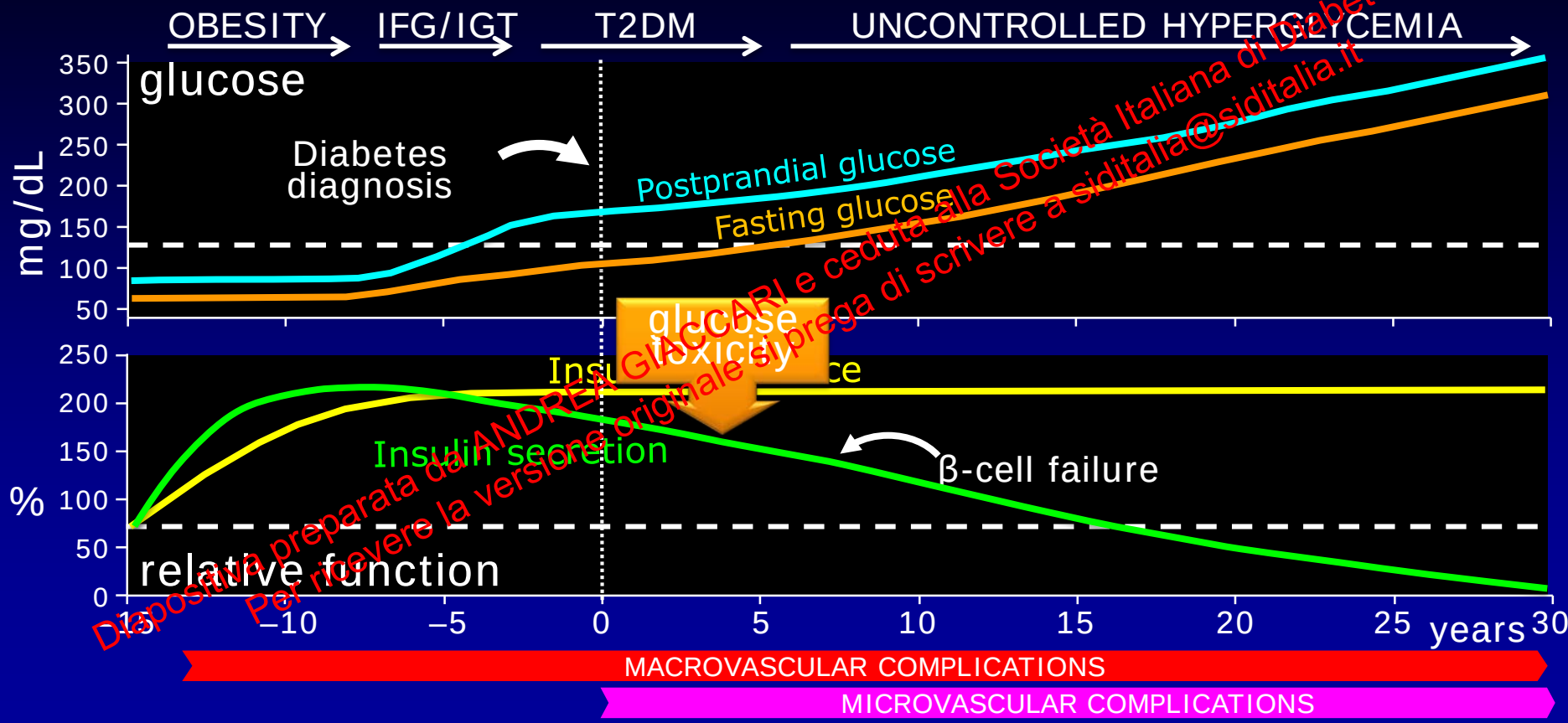
disclosure

Il dr. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Sanofi

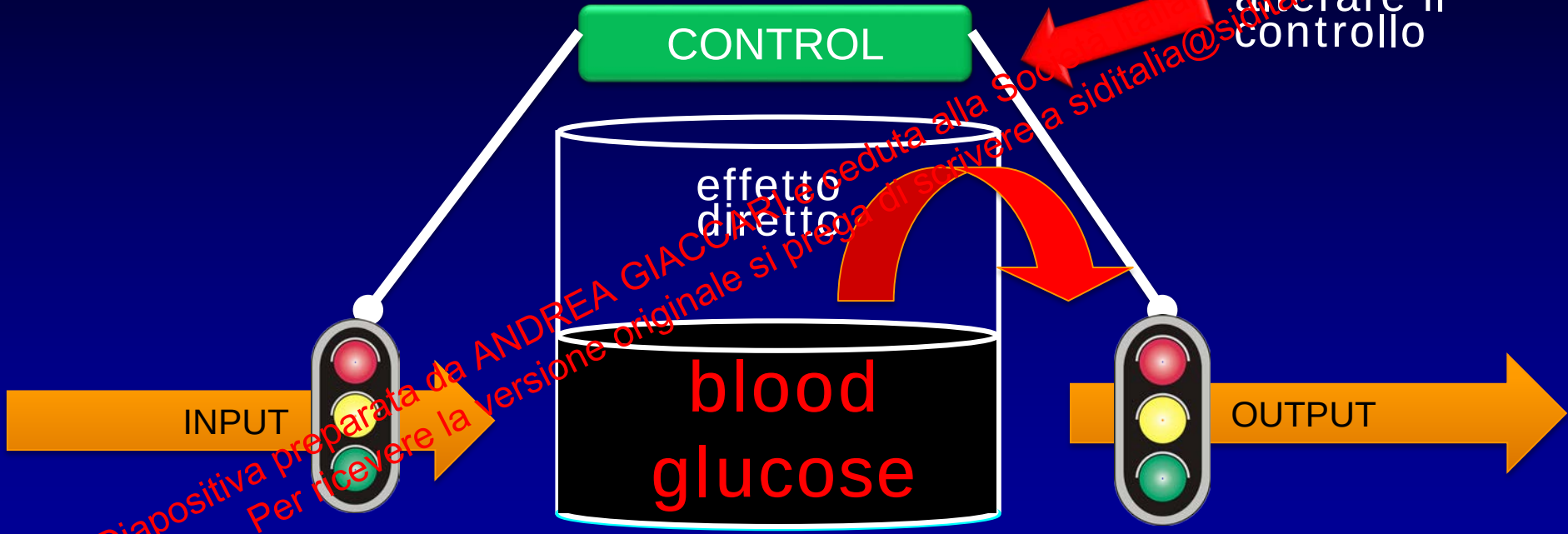
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

natural history of type 2 diabetes



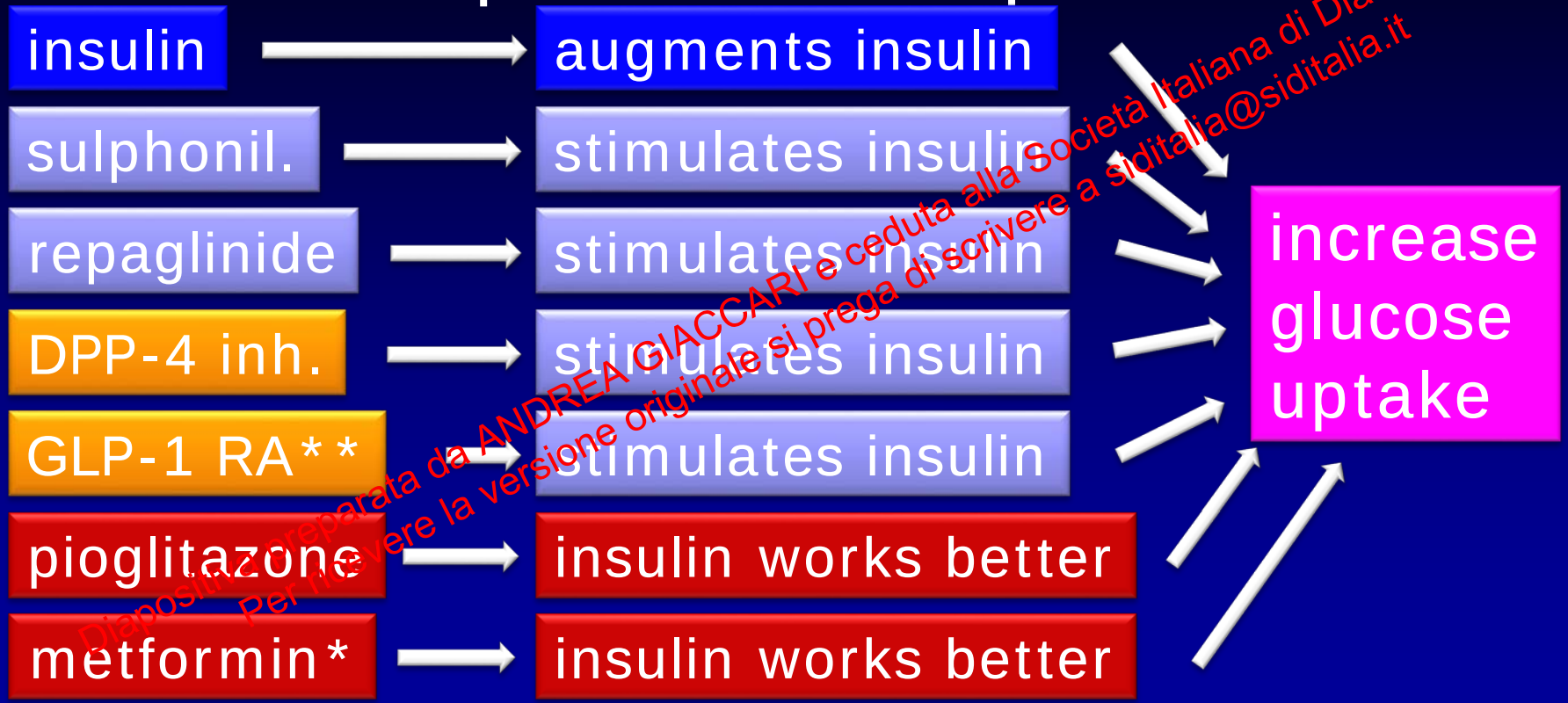
Bailey T. The AmJMedicine 126:S10, 2013

glucose fluxes in humans



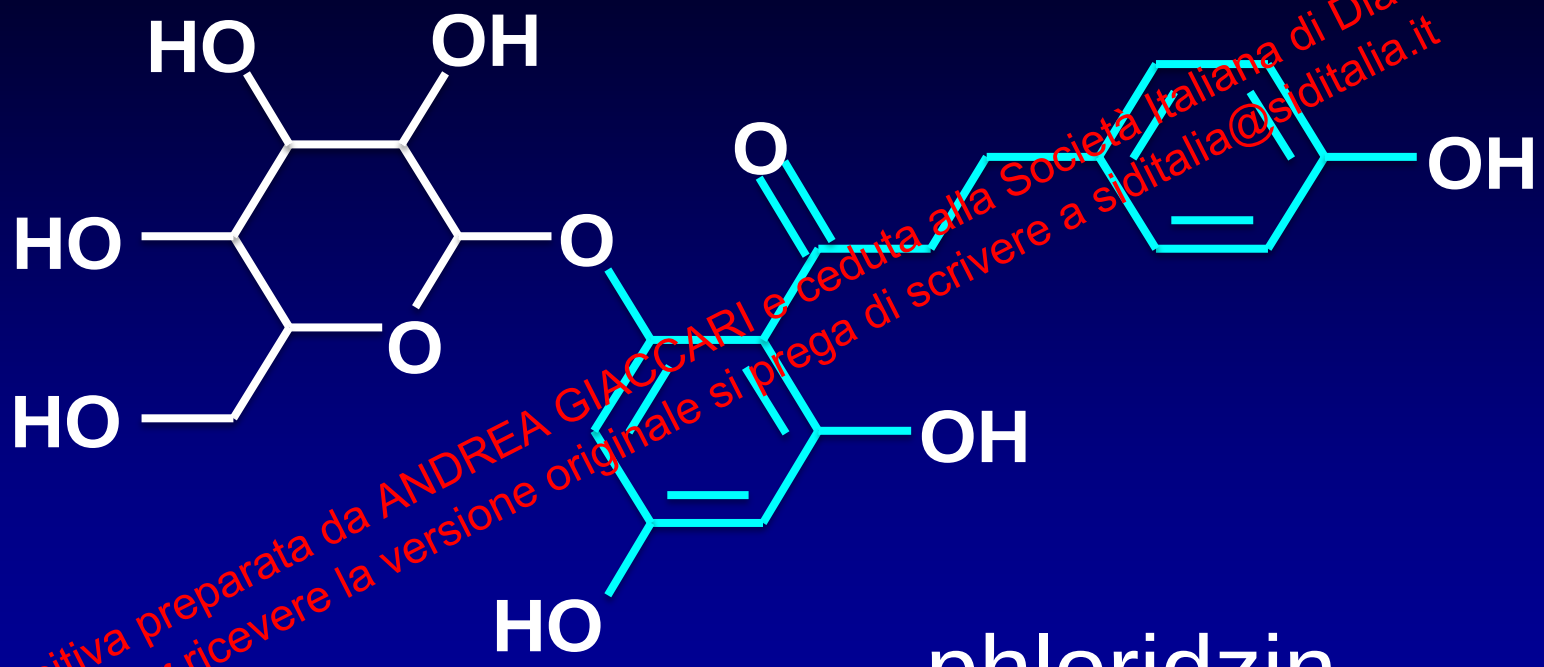
how to examine glucose toxicity

possible therapies



* anorectic effect

phloridzin, a glucose «analogue»



phloridzin

phloridzin is a natural compound, present in the apple tree cortex (and others)

phloridzin, a glucose «analogue»

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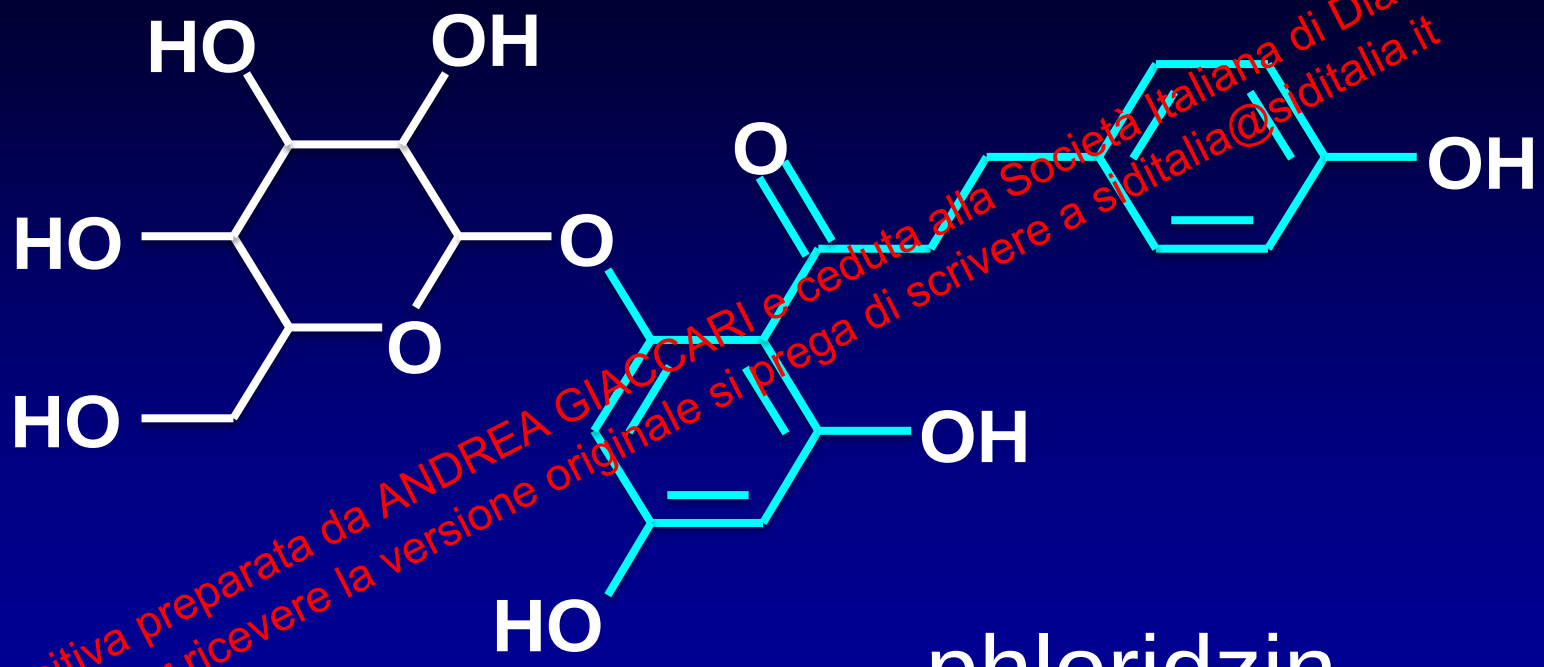
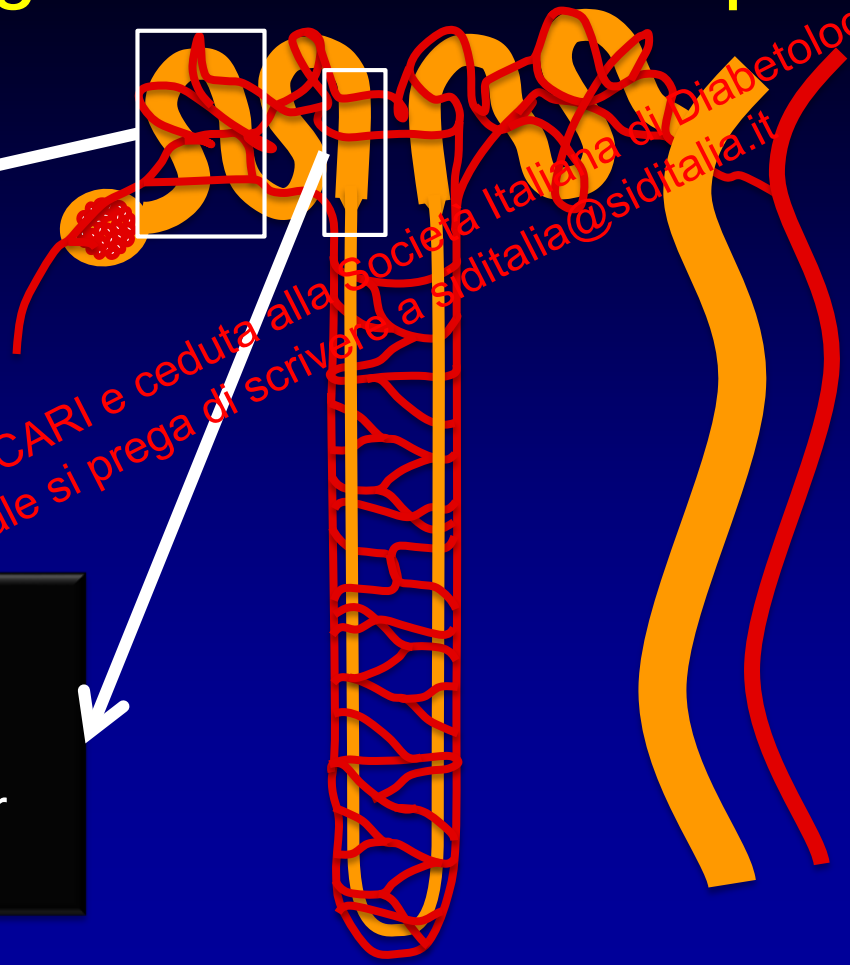


phloridzin

phloridzin is a natural compound, present in the apple tree cortex (and others)

SGLT handling of glucose in the nephron



seg. 1 of proximal tubule

SGLT-2

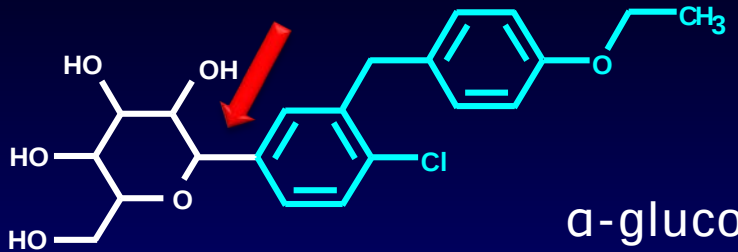
reabsorbs 95 % of glucose

seg. 3 of proximal tubule

SGLT-1

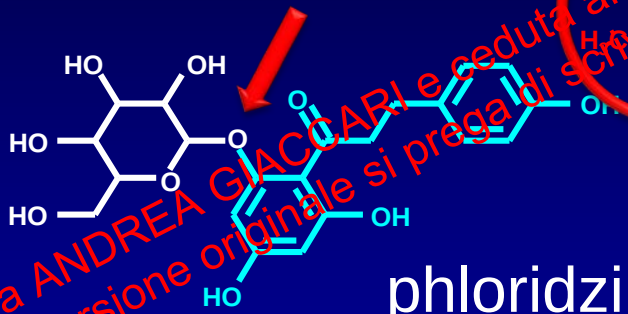
reabsorbs 5 % of glucose or
40% of remaining glucose

gliflozins are phloridzin analogues

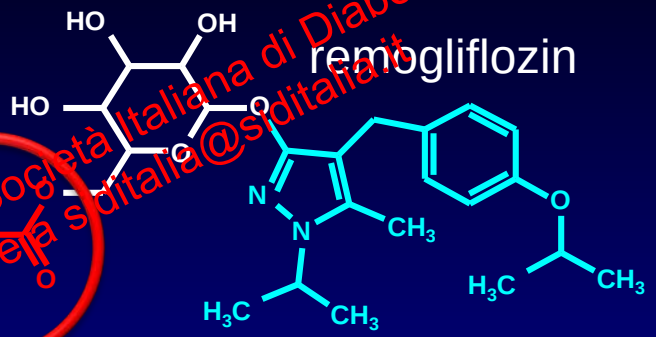


dapagliflozin

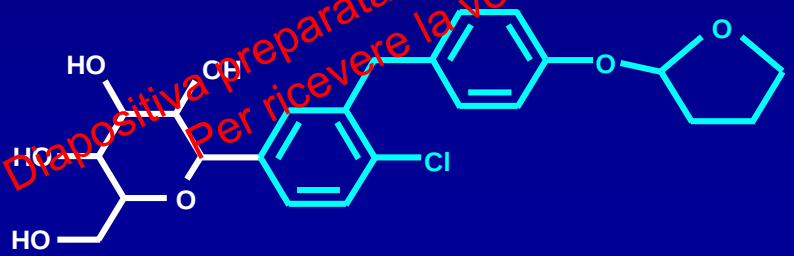
α-glucosidase



phloridzin



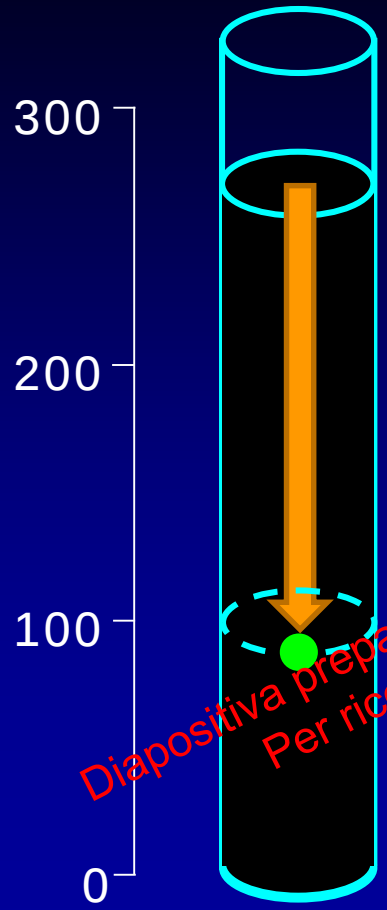
remogliflozin



empagliflozin

canagliflozin

flux in glycosuria



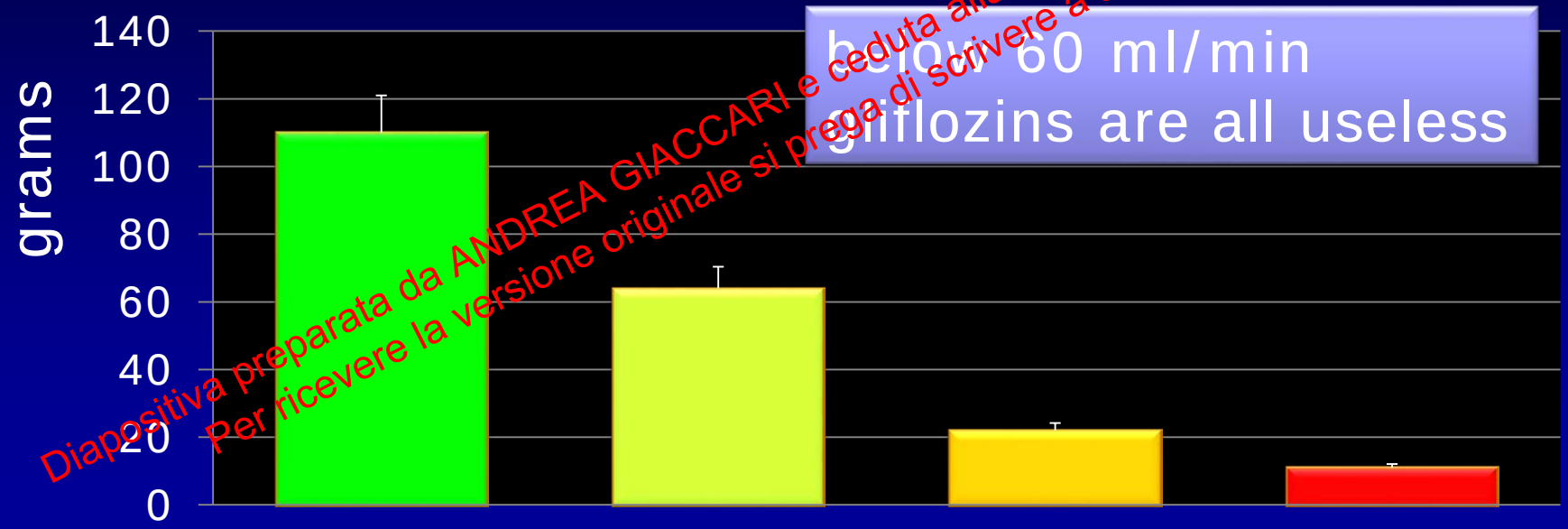
the amount of glucose lost in the urine depends exclusively from:

1. glycaemia
2. renal function (eGFR)

when blood glucose reaches normal values glycosuria is virtually absent

gliflozins in CKD

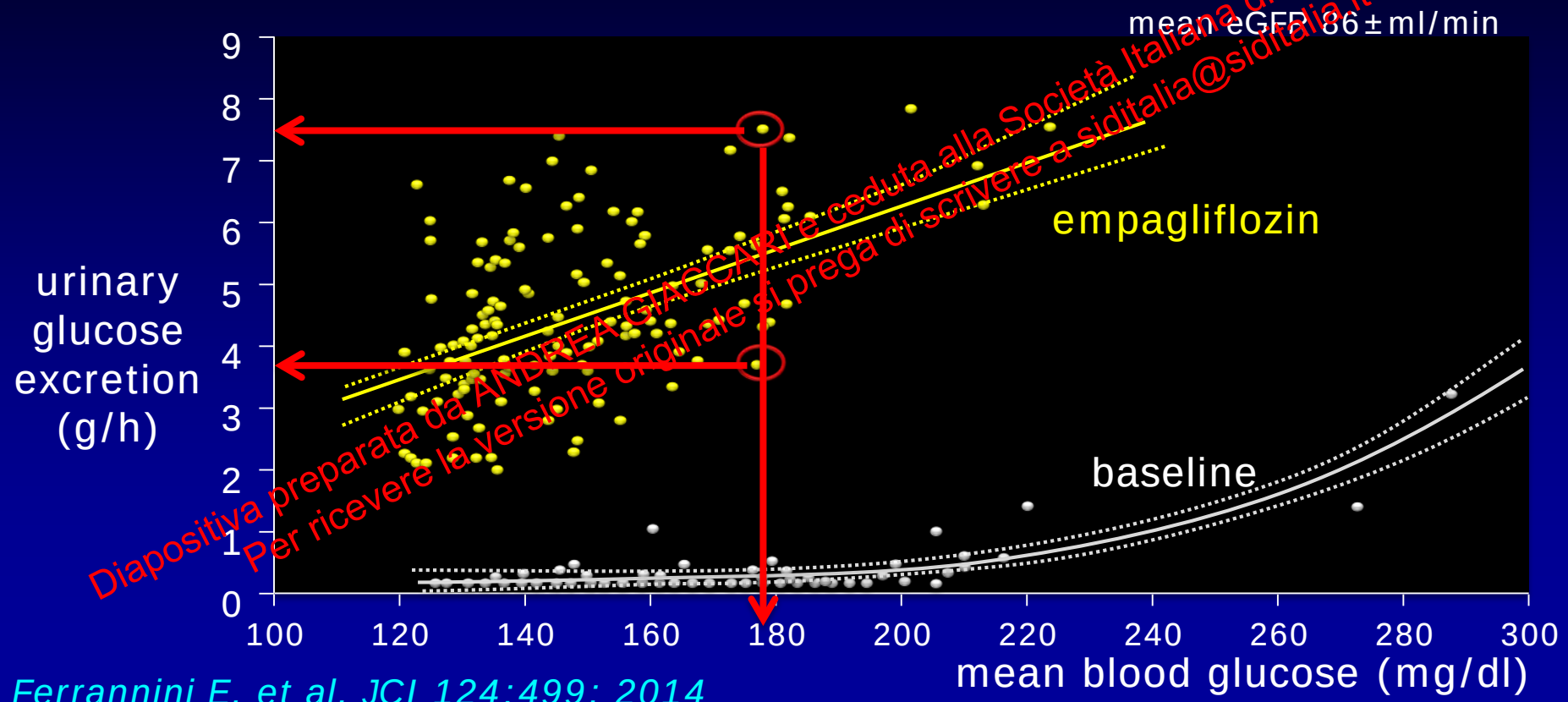
24 h glycosuria according to eGFR



FDA Advisory Committee 19th July 2011:
http://www.fda.gov

do blood glucose and glycosuria correlate?

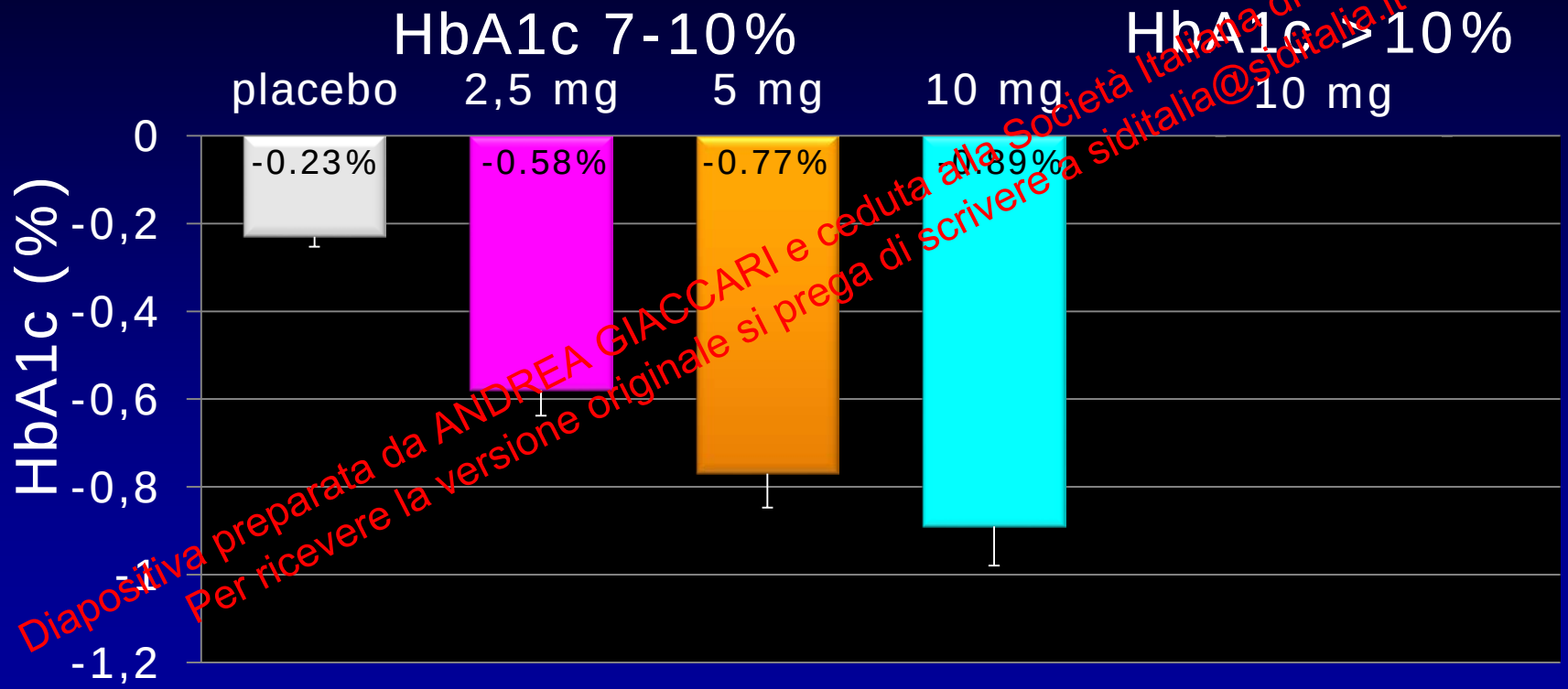
urinary glucose excretion with empagliflozin



Ferrannini E. et al. JCI 124:499; 2014

gliflozin (monotherapy)

dapagliflozin - drug naïve patients



Ferrannini E Diabetes Care 33:2217, 2010

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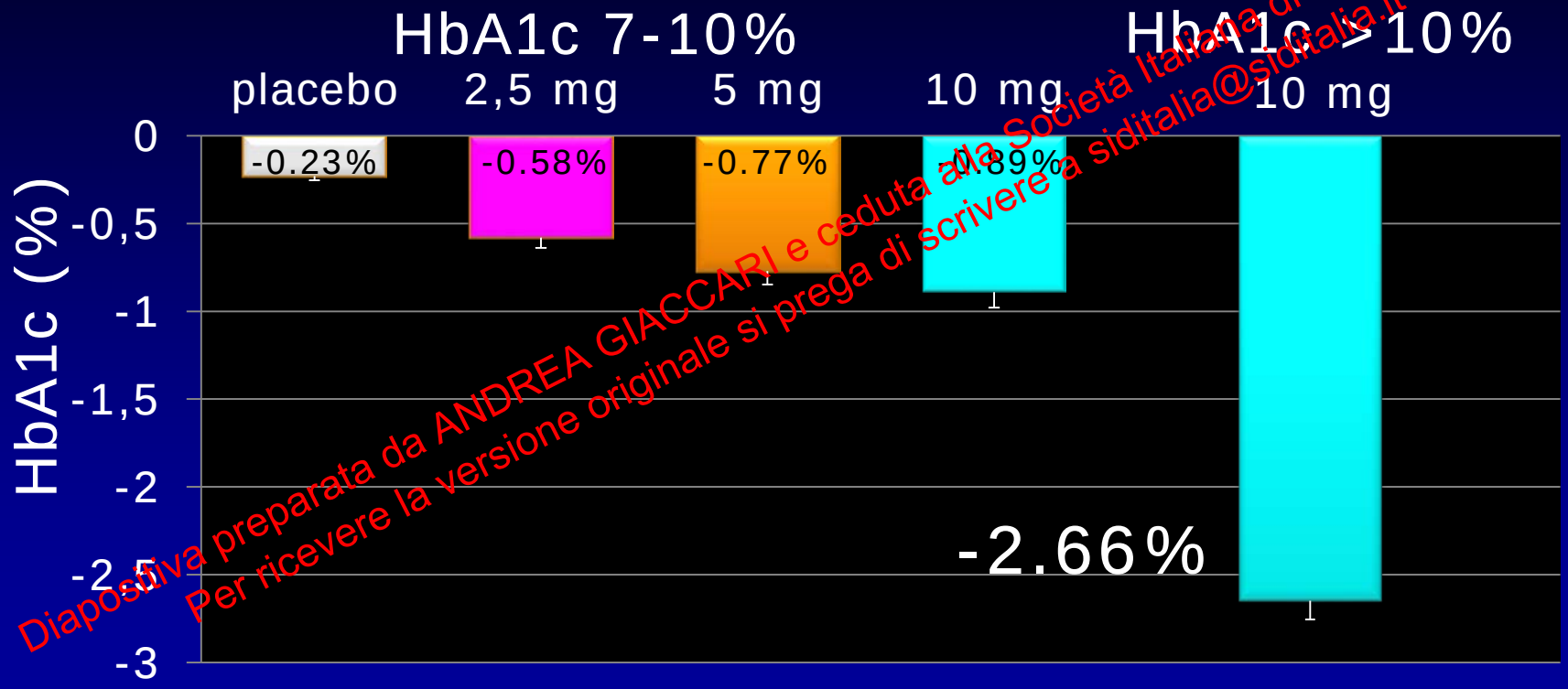


Ferrannini E Diabetes Care 33:2217, 2010

domanda 1

L’uso delle gliflozine modifica profondamente il metabolismo della persona con diabete;
in particolare si osserva:

A. un miglioramento della condizione di insulino-resistenza e quindi un aumento della captazione di glucosio

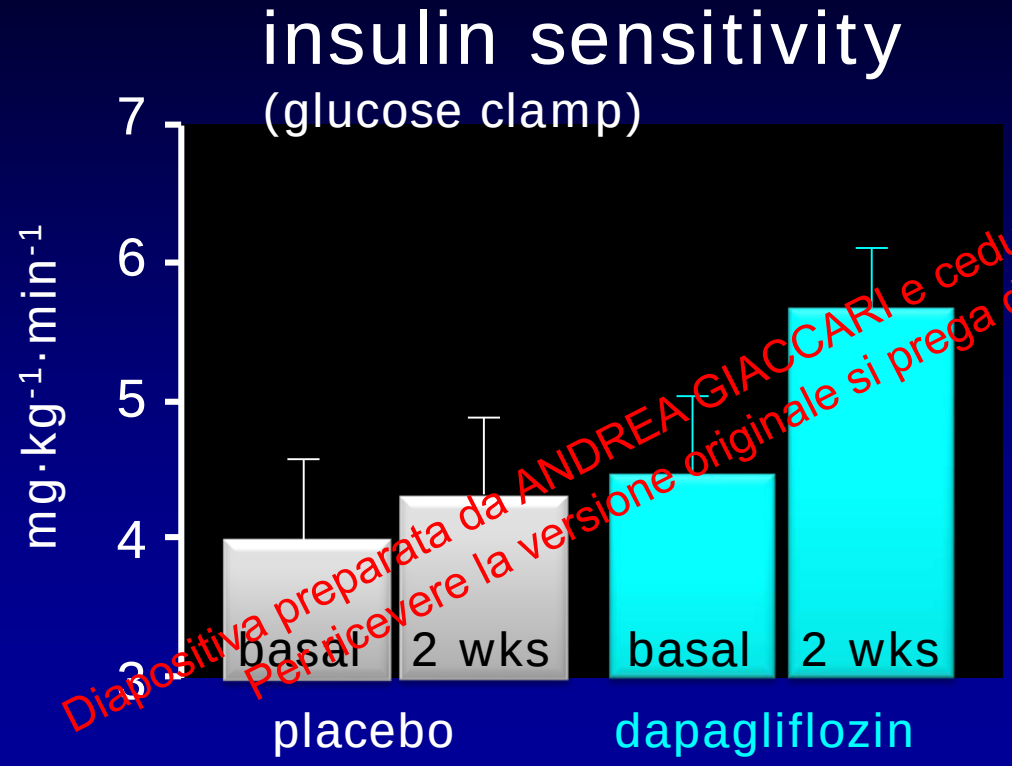
B. una riduzione della glucotossicità e quindi un aumento della captazione di glucosio

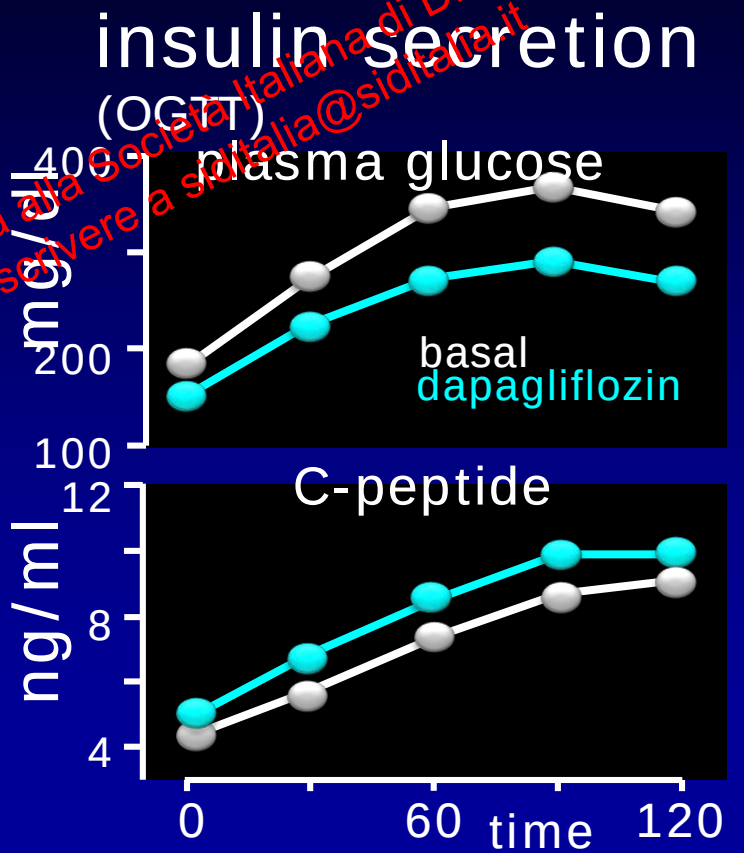
C. una riduzione della lipotossicità e quindi un aumento della captazione di glucosio

D. un aumento della ossidazione degli FFA

gliflozins act on glucose toxicity

both on insulin-resistance and secretion (dapagliflozin vs. placebo)

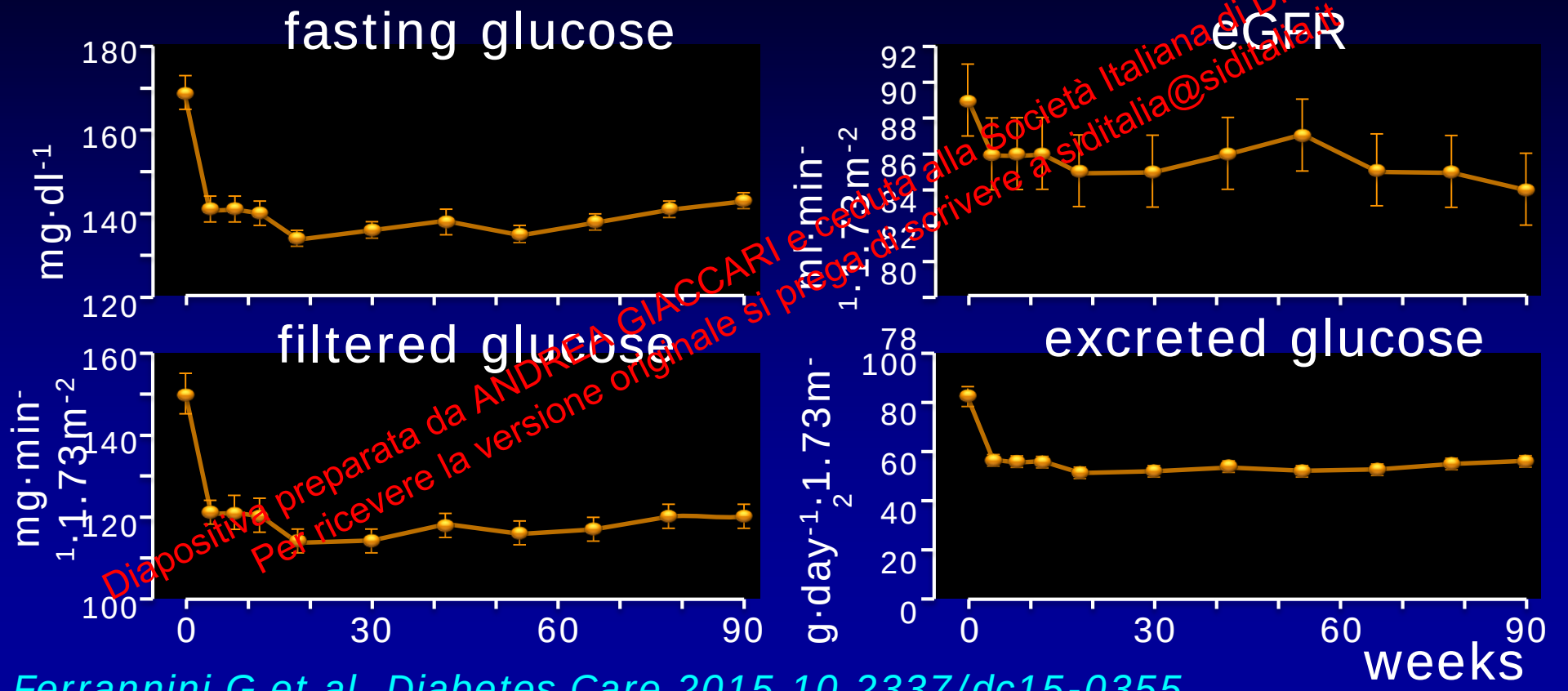




Merovci A et al.: JCI 124: 509; 2014
Merovci A et al.: JCEM 100:1927; 2015

estimated glucose loss with SGLT2i

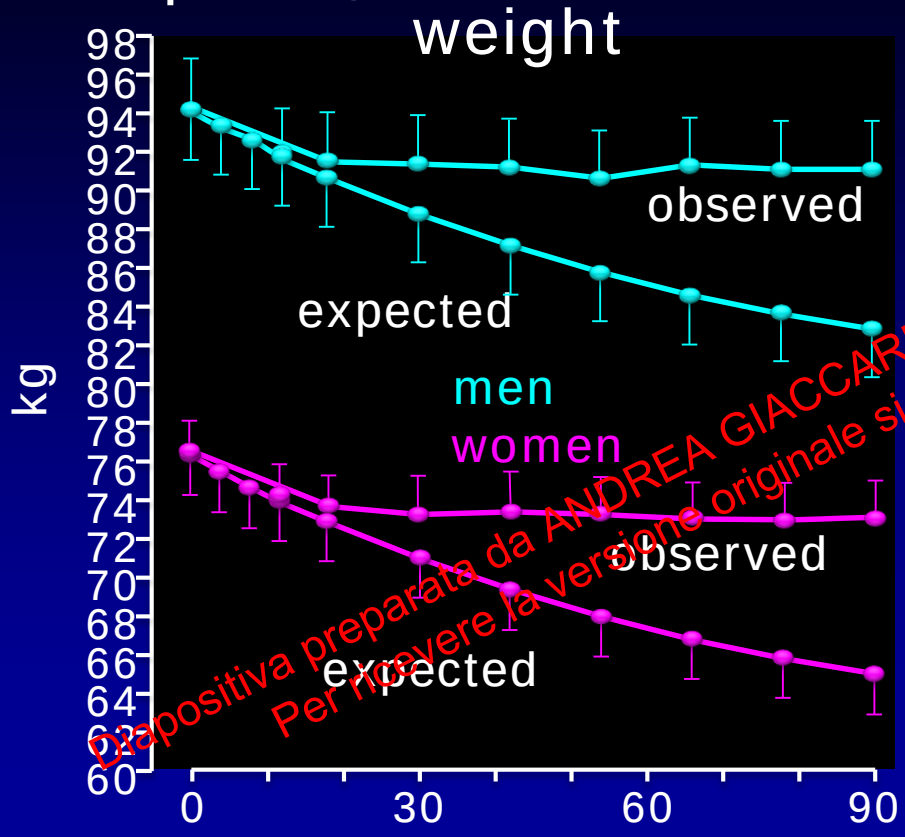
empa 25, ext. of 2 12-w trials; HbA1c: 7.8 BMI: 29.8

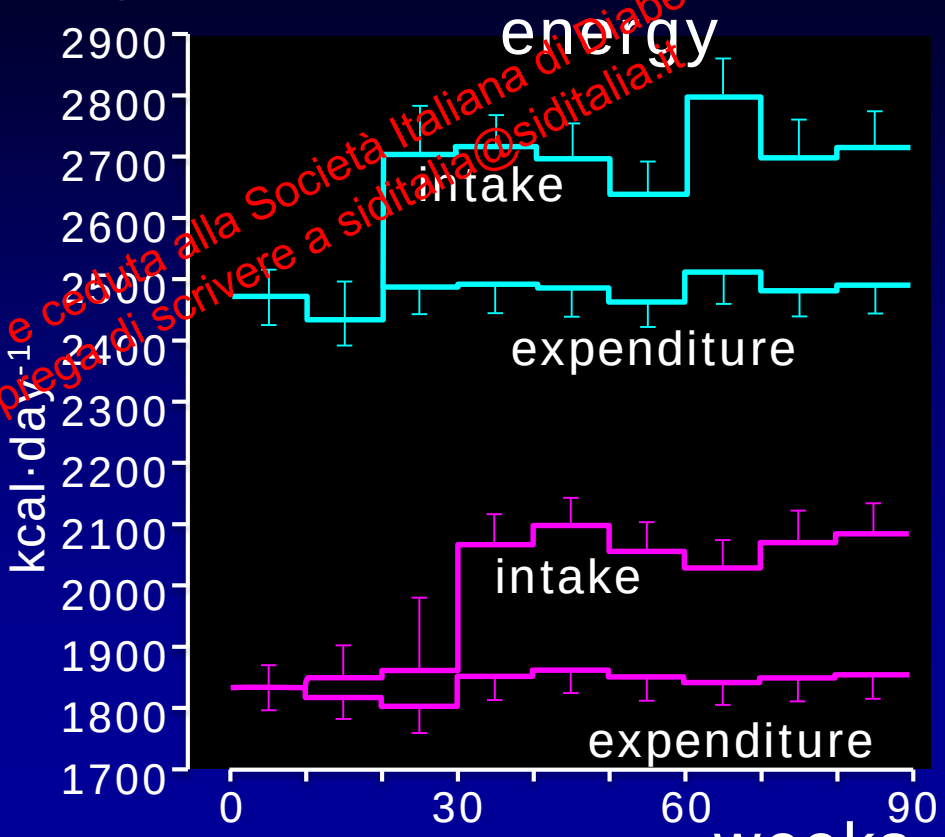


Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355

energy balance with SGLT2i

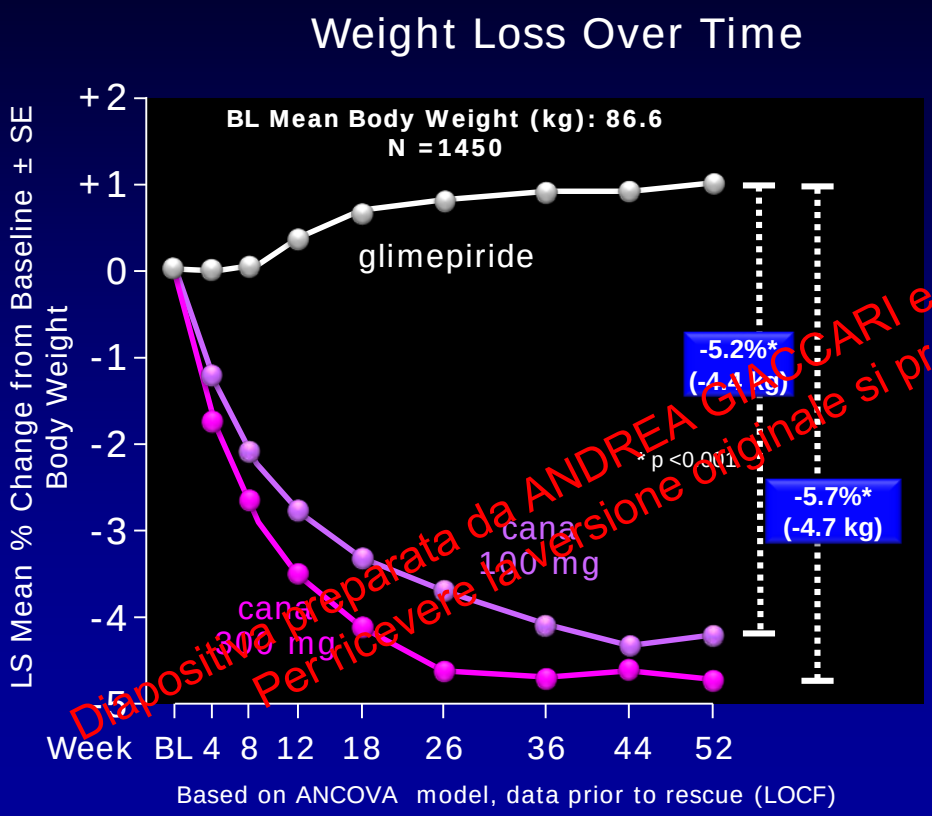
empa 25, ext. of 2 12-w trials; HbA1c: 7.8 BMI: 29.8

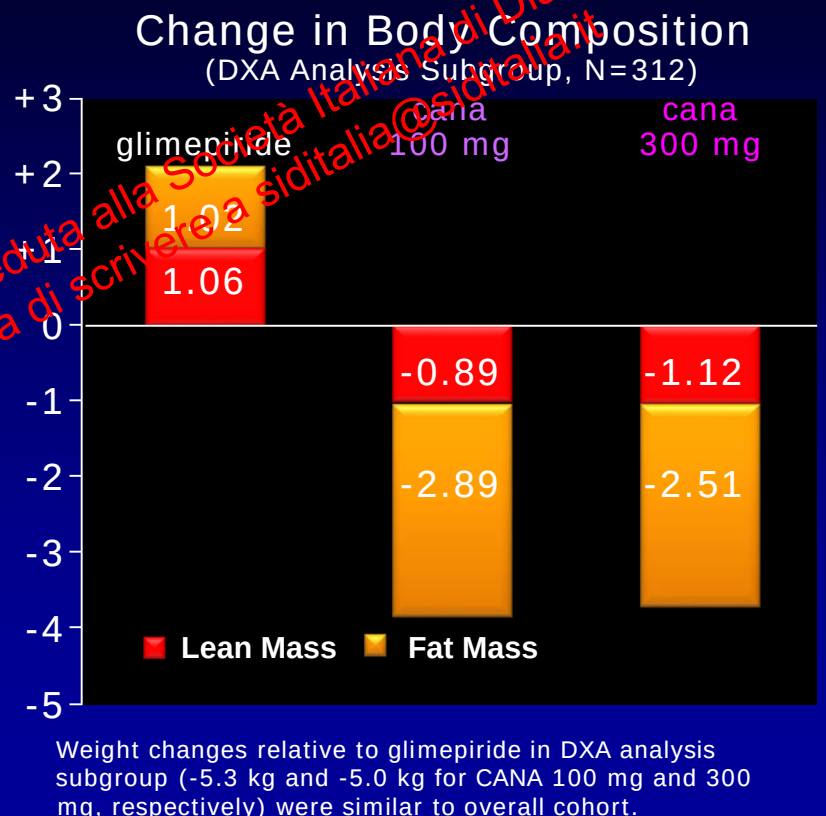




Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355

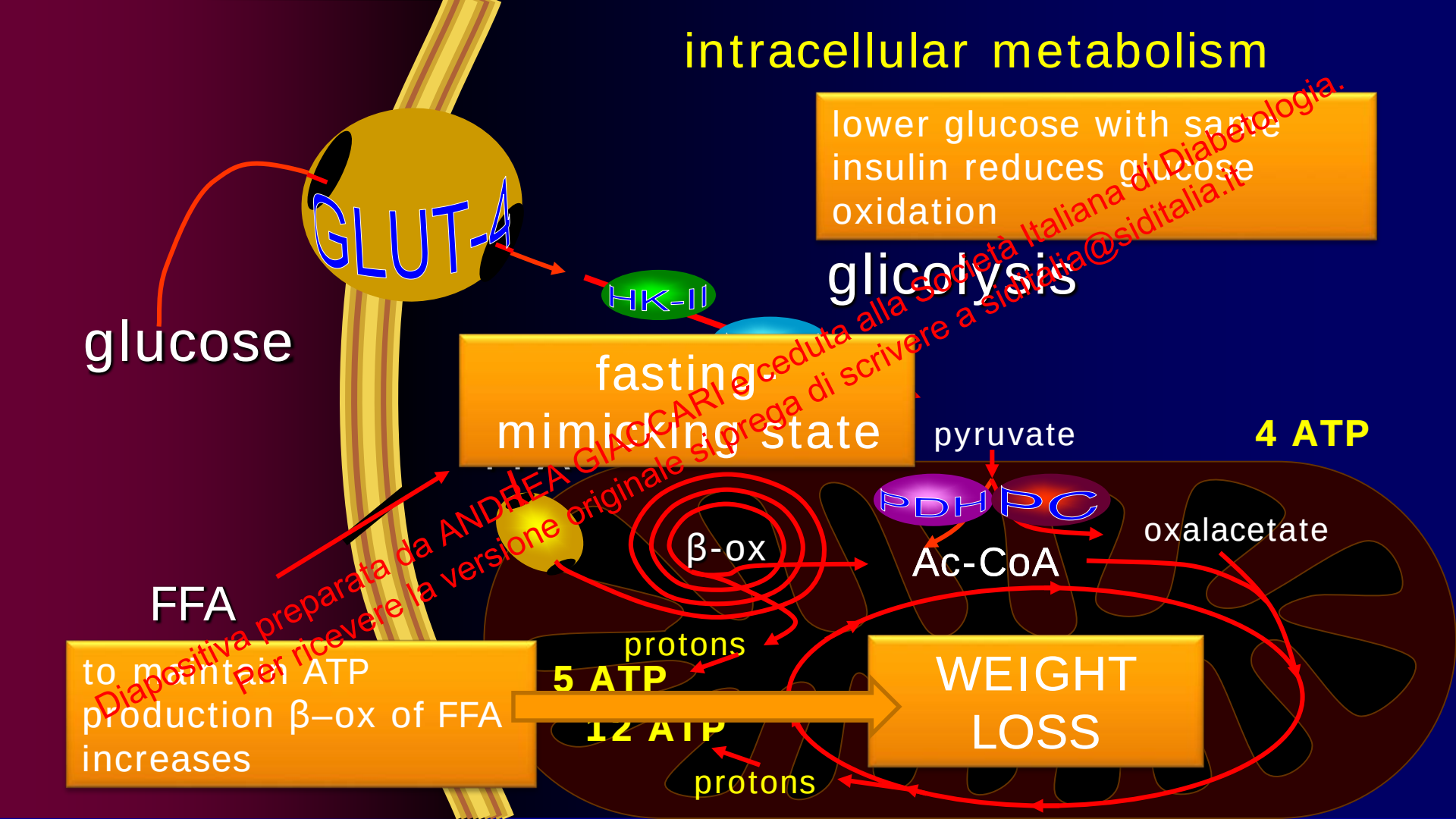
gliflozins mostly reduce fat mass





Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

Cefalu WT et al. Lancet 382:941, 2013

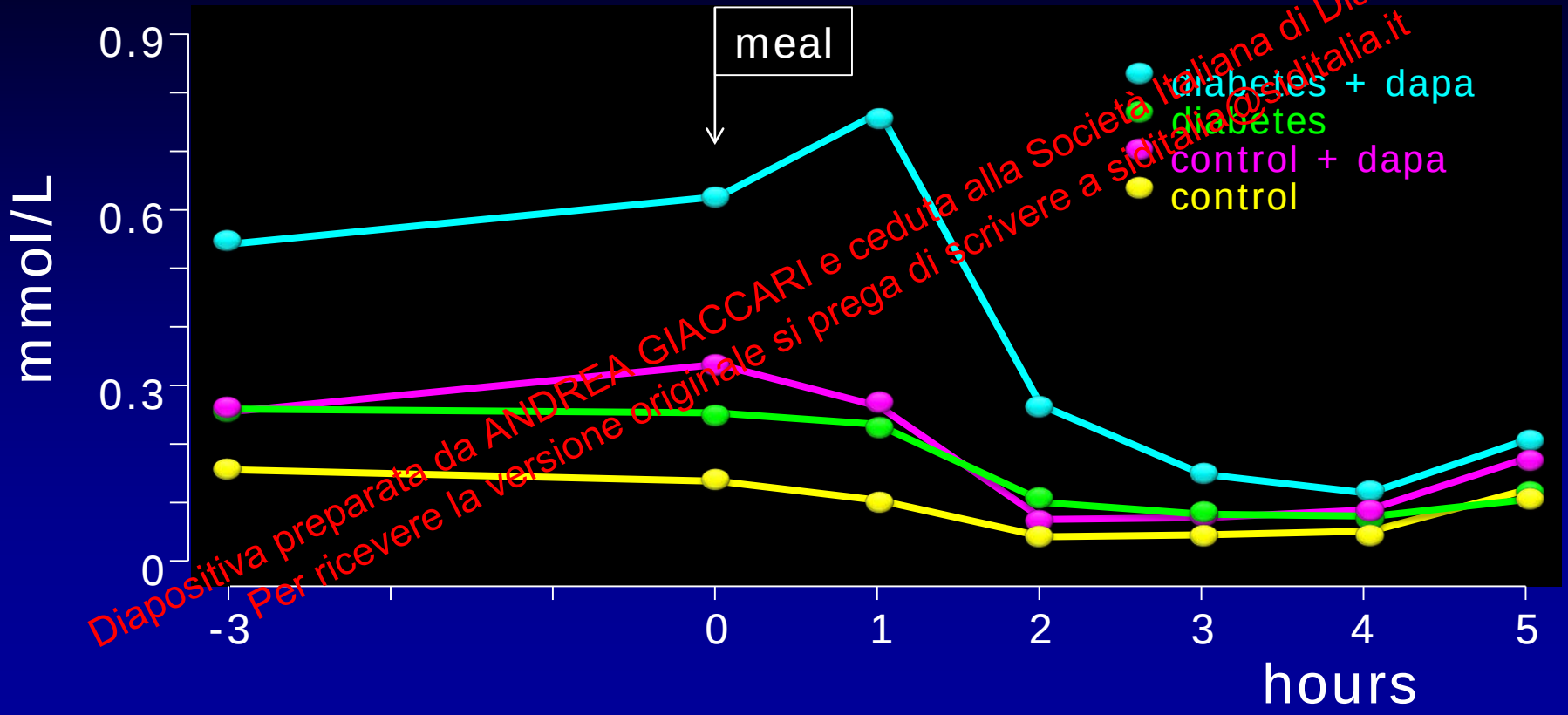

intracellular metabolism
lower glucose with same insulin reduces glucose oxidation
glucose
GLUT-4
HK-II
glicolysis
fasting mimicking state
pyruvate
4 ATP
PDH
PC
β-ox
Ac-CoA
oxalacetate
FFA
protons
5 ATP
12 ATP
protons
to maintain ATP production β–ox of FFA increases
WEIGHT LOSS
Diapositiva preparata da ANDREA GIACCARI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

hyperglycemia

secretagogues and sensitizers

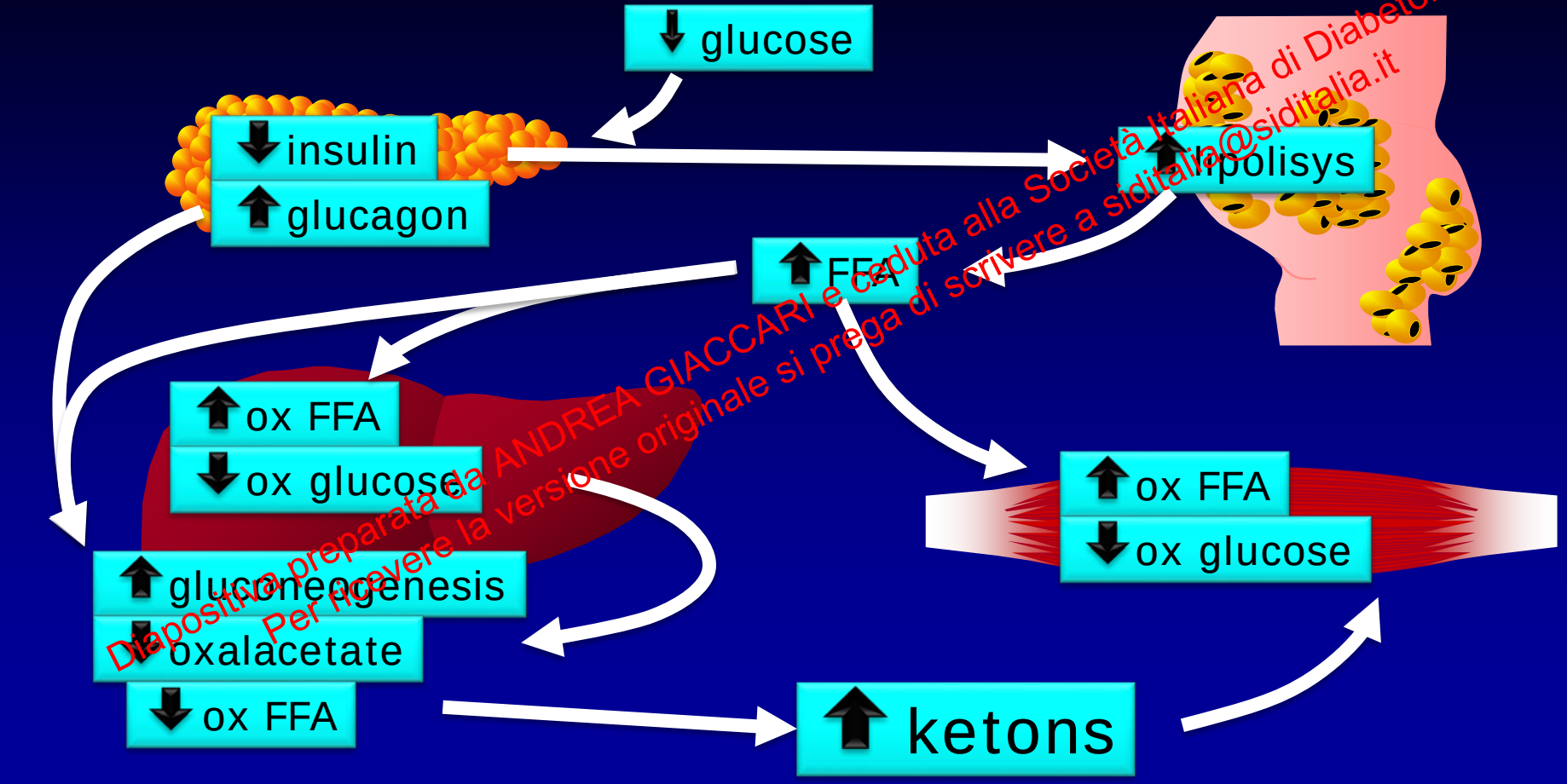
gliflozins

SGLT-2i increase ß-OH-butyrate

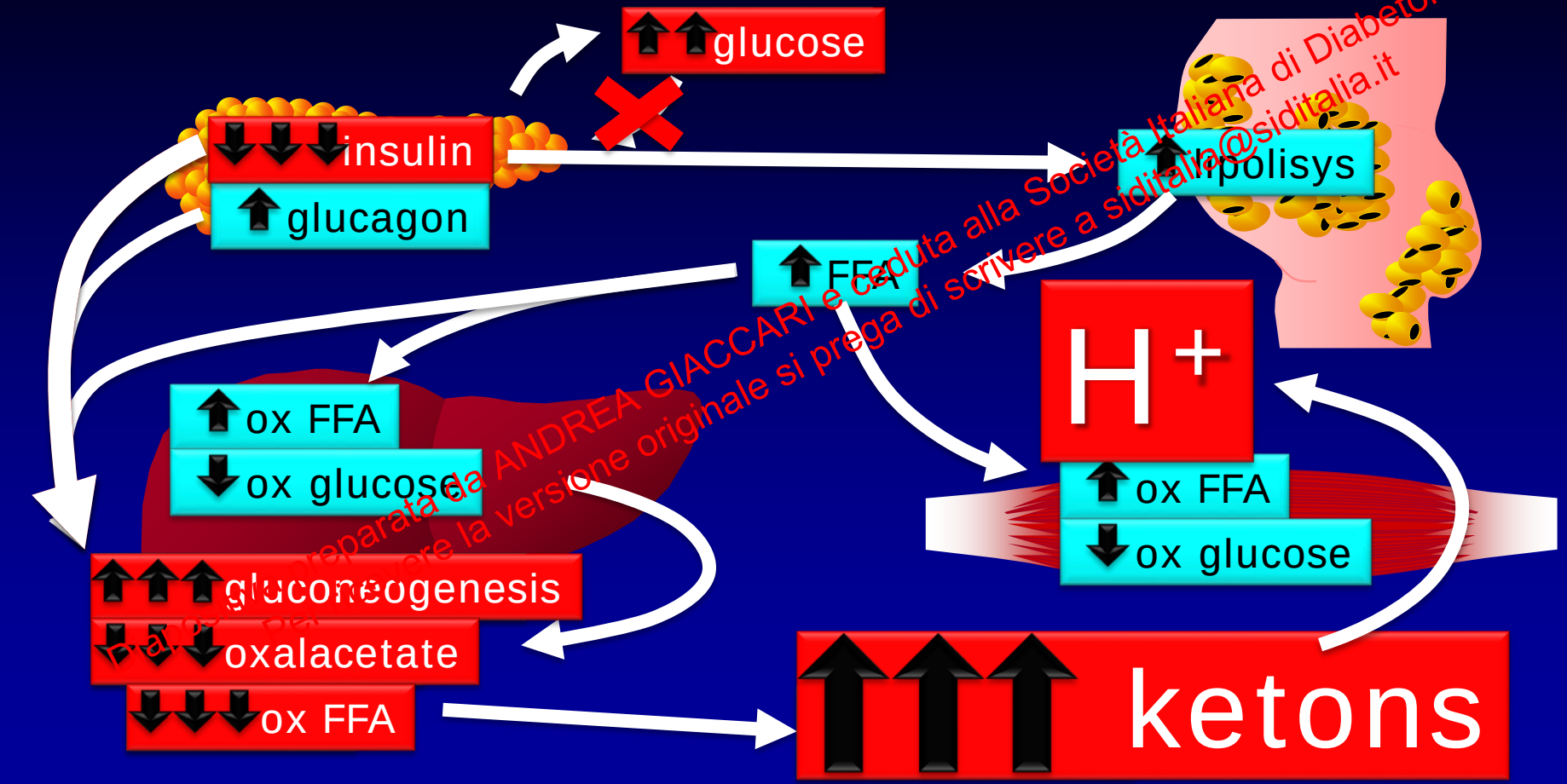


Ferrannini E et al.: Diabetes 65:1190, 2016 doi: 10.2337/db15-1356

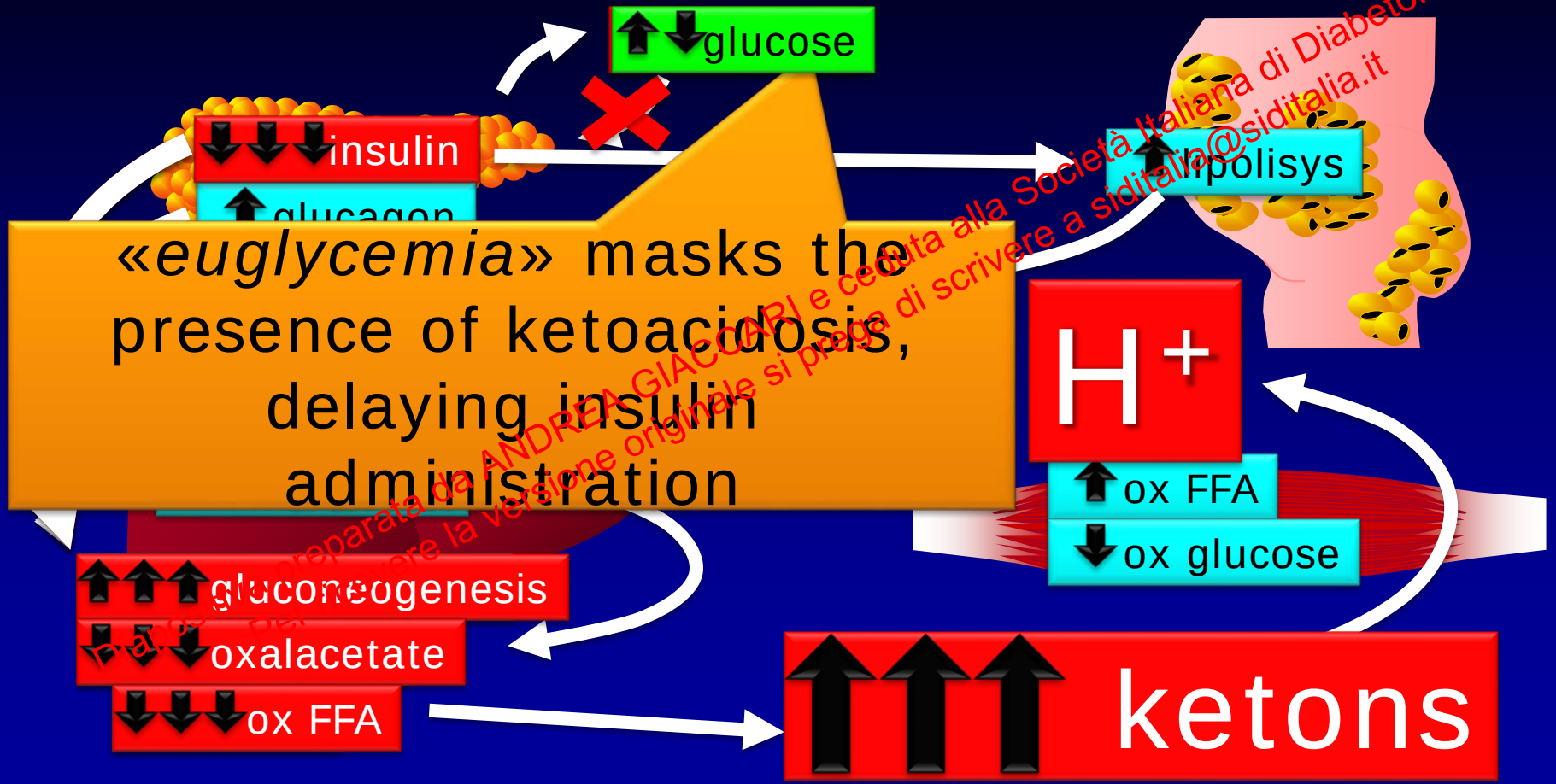
effects of prologed fasting



pathogenesis of diabetic ketoacidosis



eugycemic diabetic ketoacidosis



domanda 2

L’uso delle gliflozine riduce significativamente la glicemia della persona con diabete;
in particolare si osserva:

A. una riduzione soprattutto della glicemia a digiuno

B. una riduzione soprattutto della glicemia postprandiale

C. una riduzione sia della glicemia a digiuno che post-prandiale

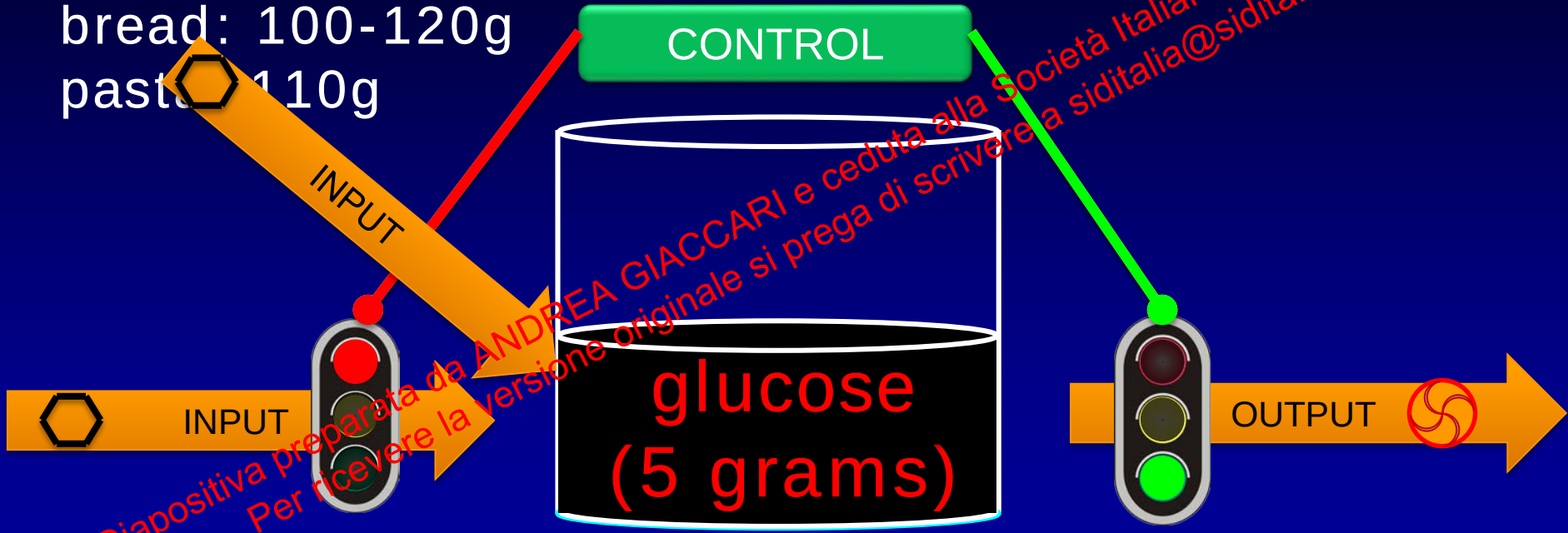
D. una riduzione delle glicemie più elevate, sia a digiuno che post-prandiali

«unmet needs» nel diabete tipo 1

- l'insulina è iniettata in periferia (non in porta):
  - aumento del glucosio captato da tessuti periferici
  - diminuita lipolisi
  - aumento di peso
- l'azione dell'insulina non ha "limiti":
  - rischio per ipoglicemie
- non adeguata per iperglicemia post-prandiale:
  - necessità di insuline fast acting (?)

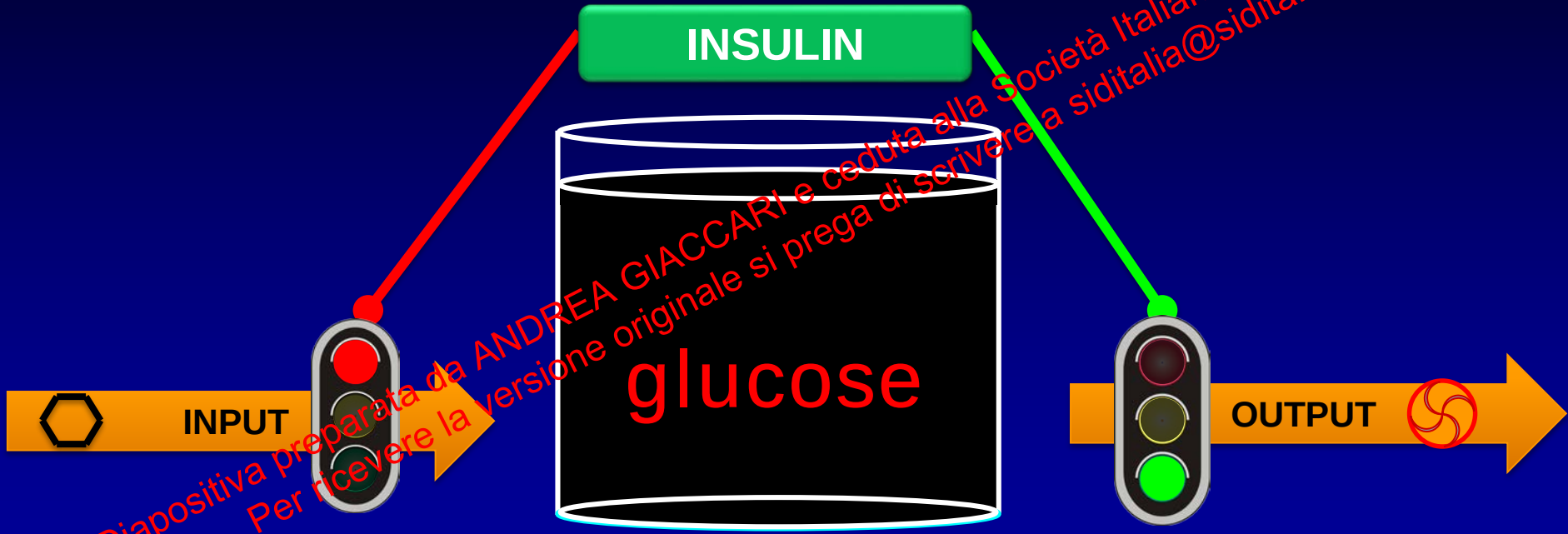
glucose fluxes in humans

OGTT: 75g
bread: 100-120g
pasta: 110g

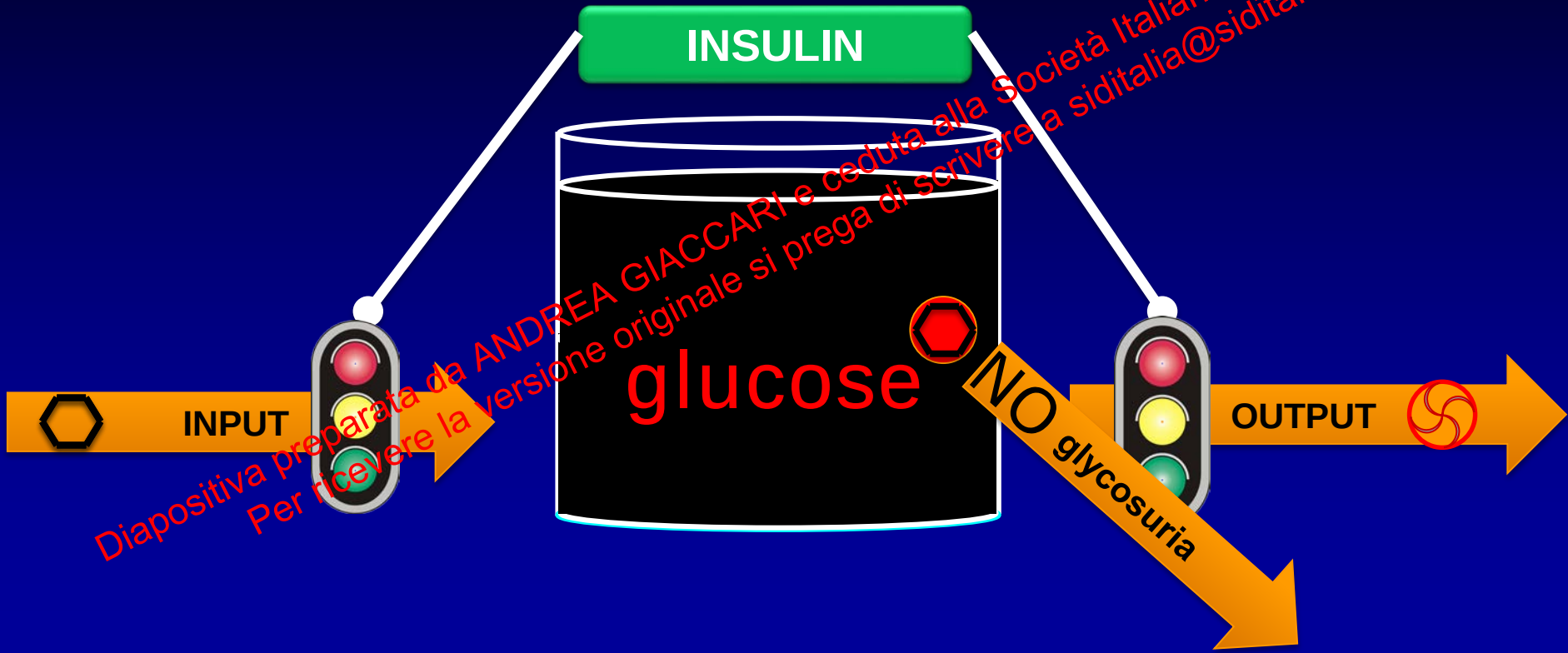


glucose fluxes in insulin-treated diabetes

risk of hypoglycemia



glucose fluxes in insulin-treated diabetes



SGLT inhibitors affinity for SGLT 1 or 2

Molecule	SGLT2 (IC50 nM)	SGLT1 (IC50 nM)	SGLT2 selectivity over SGLT1
Empagliflozin	3.1	8,300	~2,500-fold
Ertugliflozin	0.87	1,960	~2,000-fold
Dapagliflozin	1.2	1,400	~1,200-fold
Canagliflozin	2.7	710	~250-fold
Sotagliflozin	1.8	36	~20-fold
Phlorizin	2,800	4,200	~1.5-fold

Abbreviations: IC50, half-maximal inhibitory concentration; SGLT, sodium-glucose cotransporter.

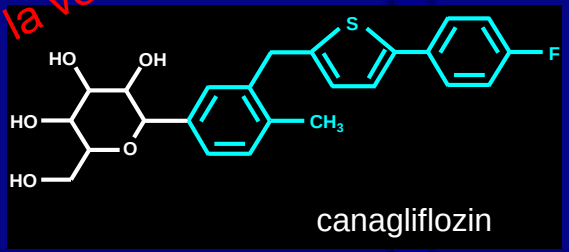
reviewed by Cinti F et al.: Drug Des Devel Ther. 11:2905, 2017. Original data from Mascitti V et al: J Med Chem 54:2952, 2011; Grempler R et al.: DOM 14:83, 2012; Zambrowicz B et al.: Clin Pharmacol Ther 92:158, 2012; Lapuerta P et al.: Diabetes Vasc Dis Res 12:101, 2015; Castaneda F et al.: Int J Med Sci 4:131, 2007.

gliflozins are phloridzin analogues

SGLT-2 selective

dapagliflozin

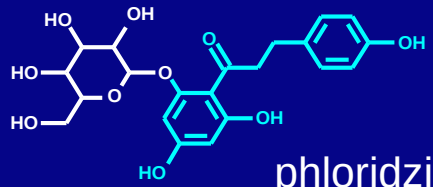
empagliflozin



canagliflozin

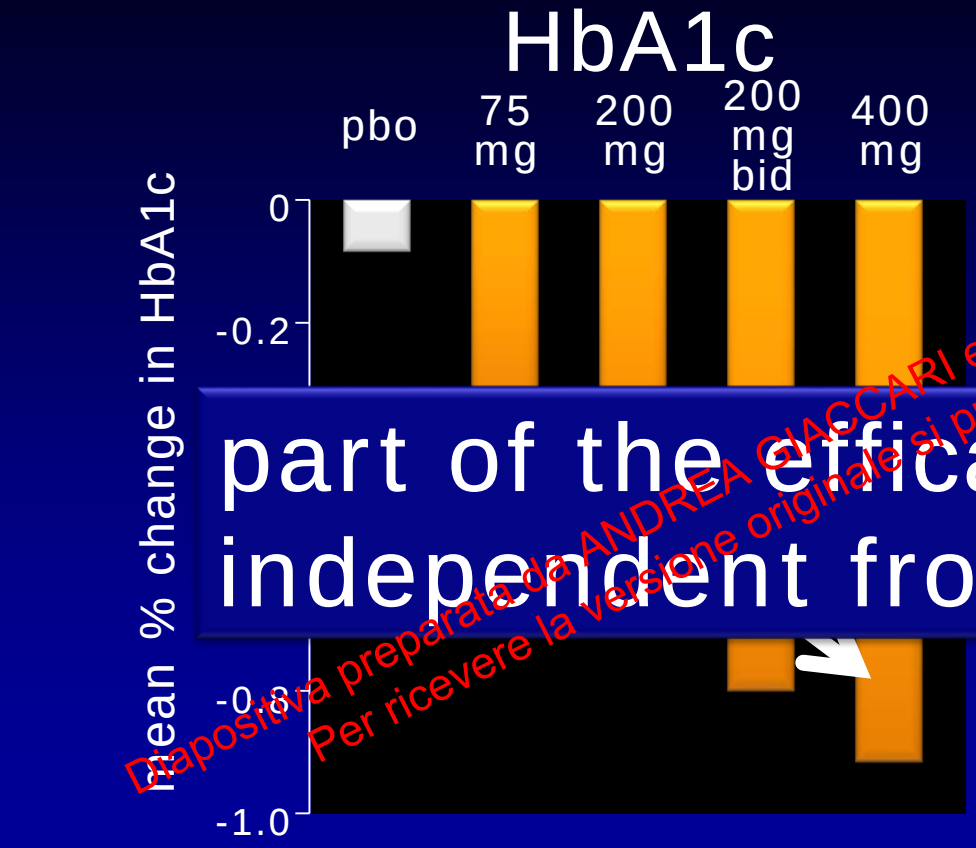
dual SGLT inhibitor

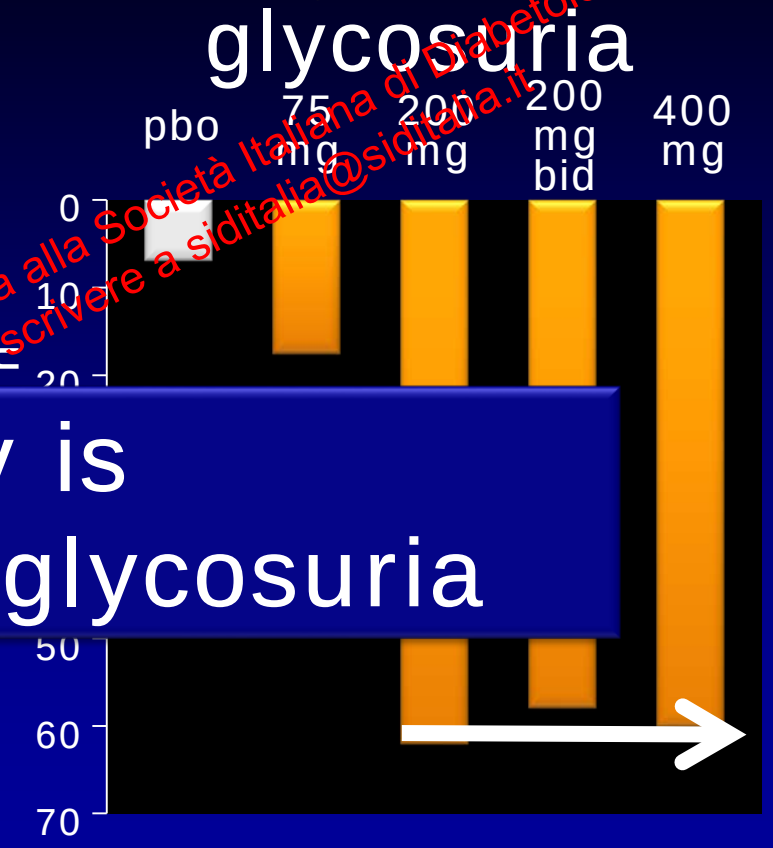
sotagliflozin



phloridzin

SGLT-1,2i in T2DM (sotagliflozin)

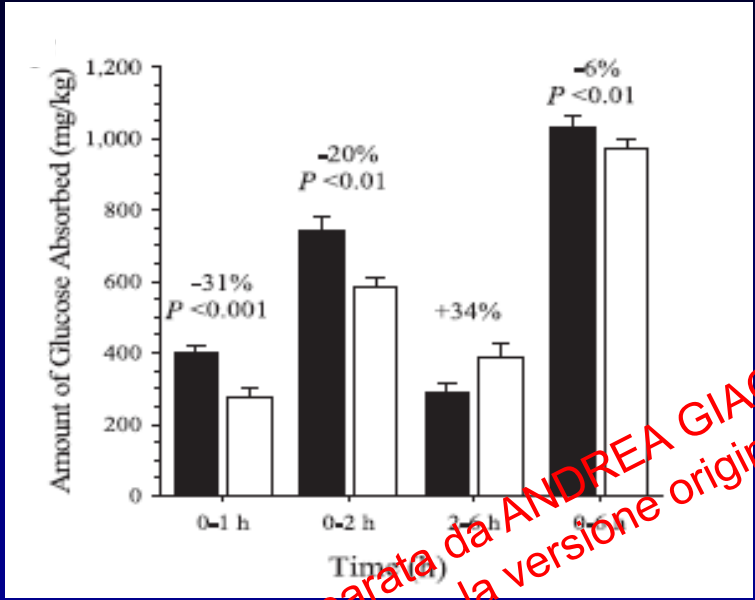


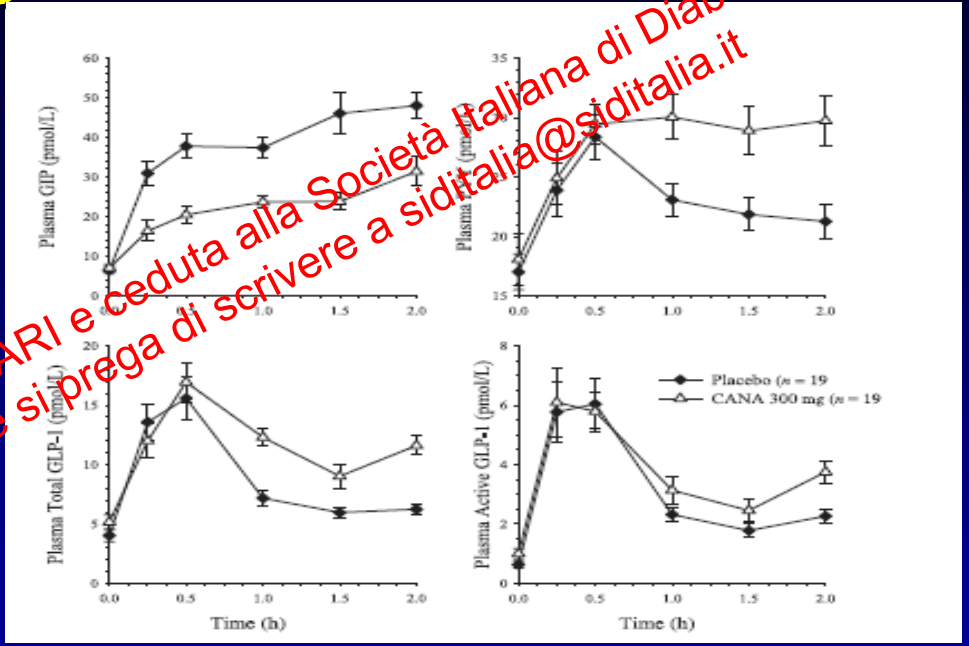


part of the efficacy is independent from glycosuria

Rosenstock J et al.: Diabetes Care 38:431, 2015

Canagliflozin ed assorbimento intestinale del glucosio



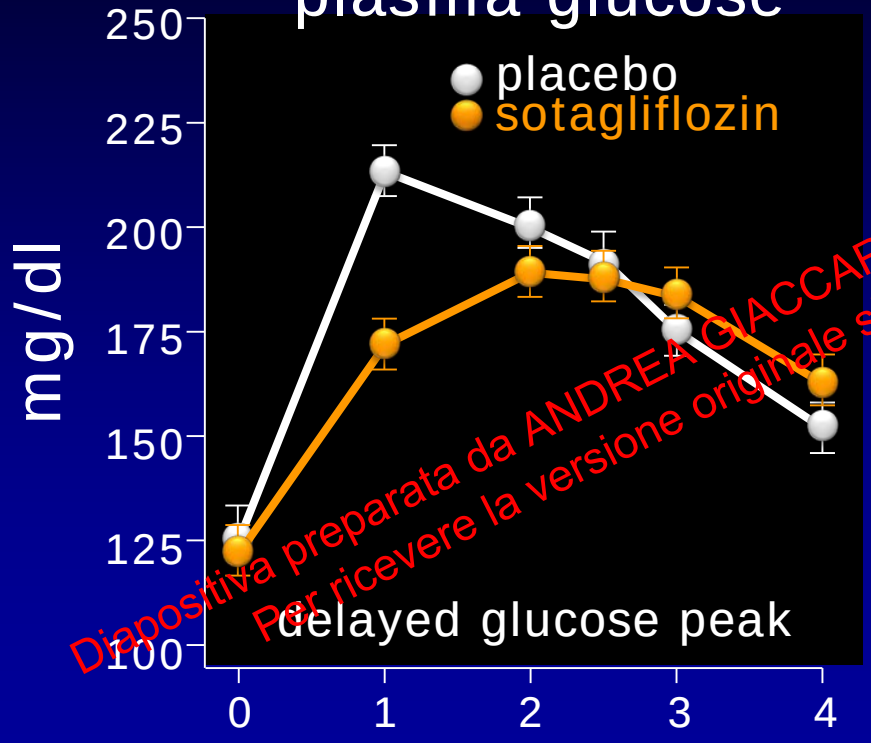


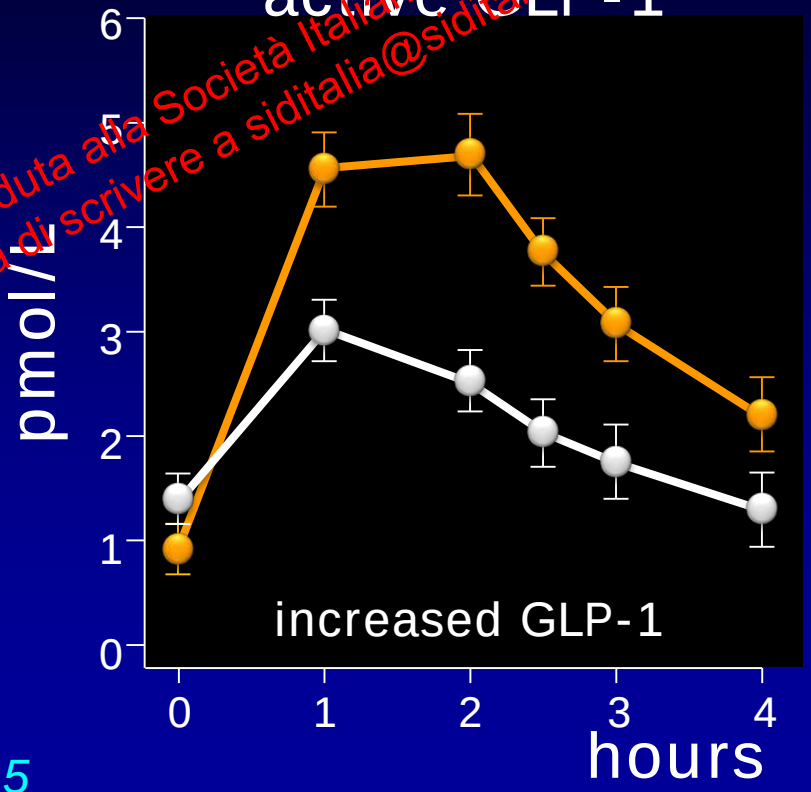
ΔAUC insulina
dopo canagliflozin: 0-1 h: -43%;
0-2 h: -43%;
0-6 h: -33%

Polidori D, Diabetes Care 2013

SGLT-1,2i (sotagl.) in T2DM+CKD

eGFR< 60 ml/min; efficacy based only on gut





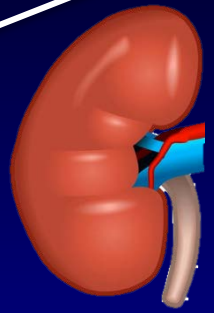
Zambrowicz B et al.: Clin Ther 37:71, 2015

MoA of dual SGLT inhibition

sota/canagliflozin

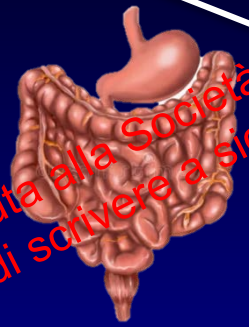
SGLT-2 inhibition

renal SGLT-1 inhibition appears negligible



glycosuria

lower blood glucose (mostly fasting)



SGLT-1 inhibition

slow glucose absorption

lower post-prandial glucose

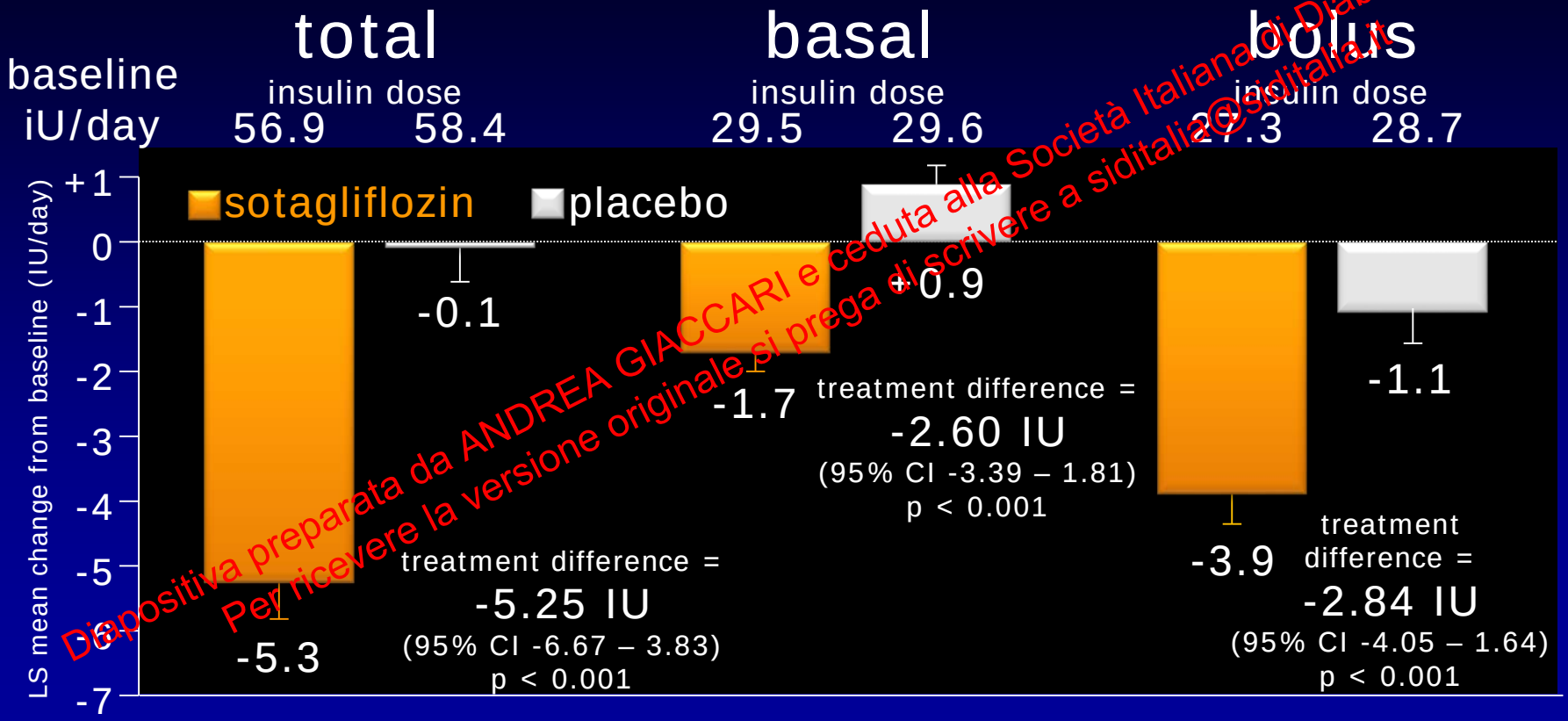
euglycemia

increased GLP-1

other potential protective effects on CV

dual SGLTi in type 1 diabetes: inTandem 3

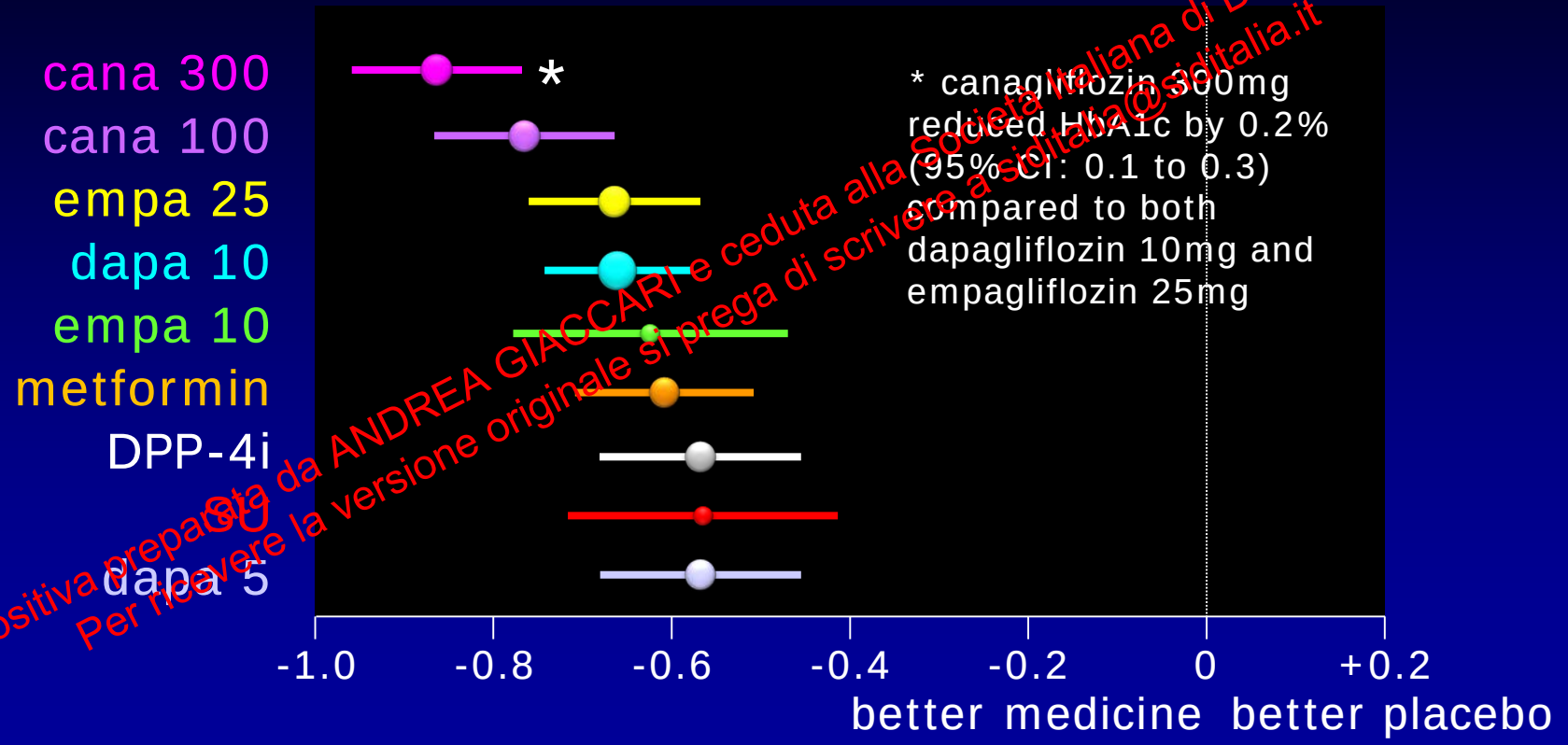
mean change in basal and bolus insulin doses



Garg SK et al.: NEJM 377:2337, 2017

oral medicines vs. placebo: HbA1c

a meta-analysis



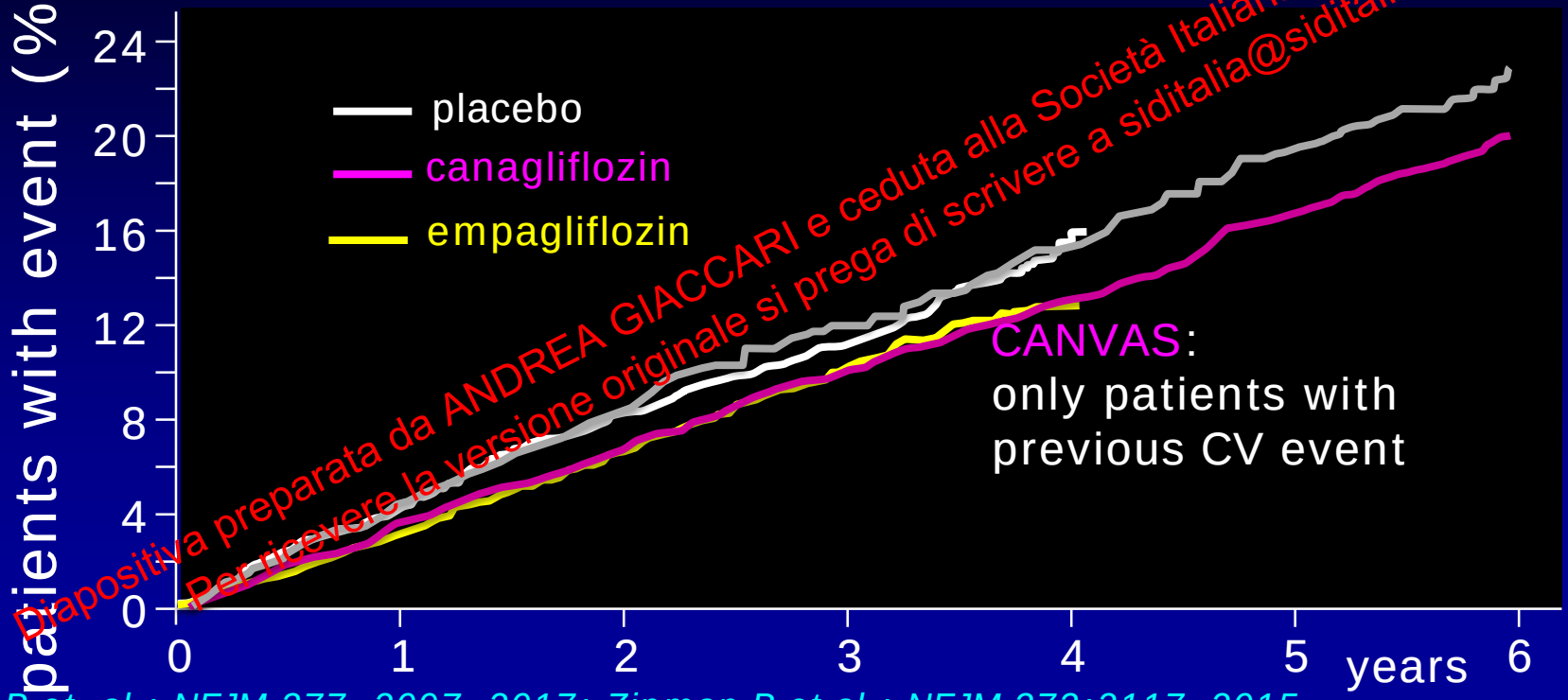
Zaccardi F et al.: DOM 18:783 doi: 10.1111/dom.12670

in conclusione

- le gliflozine modificano profondamente (e favorevolmente) il metabolismo nel diabete
- aumentando (di poco) il rischio di eDKA
- canа 300 (e sota) riducono anche la glicemia post-prandiale

CANVAS & EMPAREG: MACE (primary outcome)

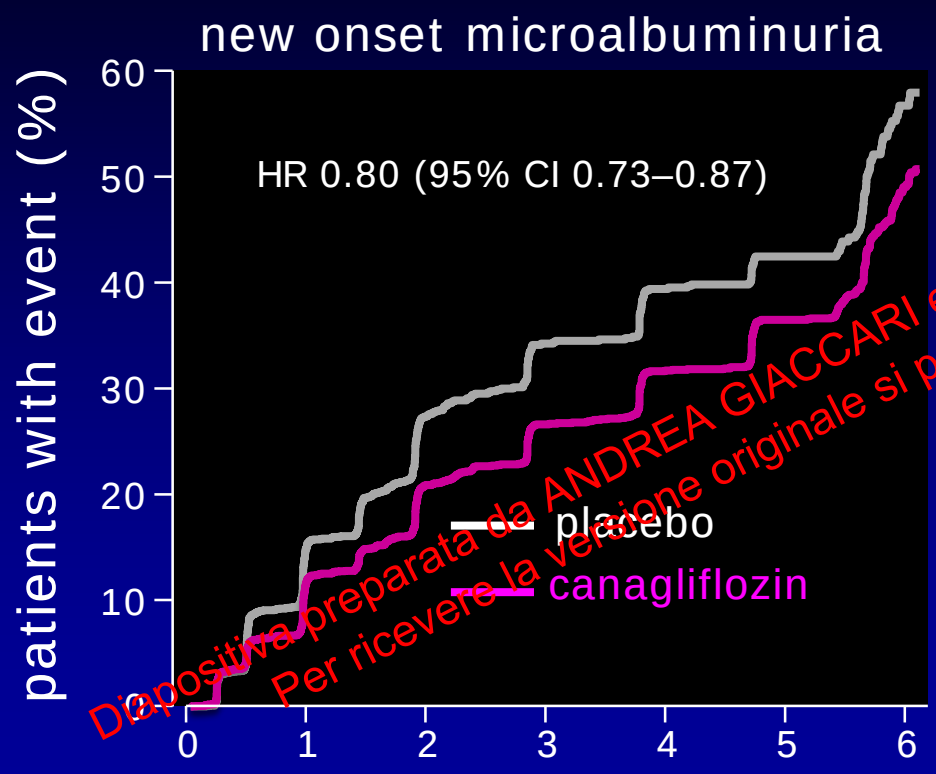
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

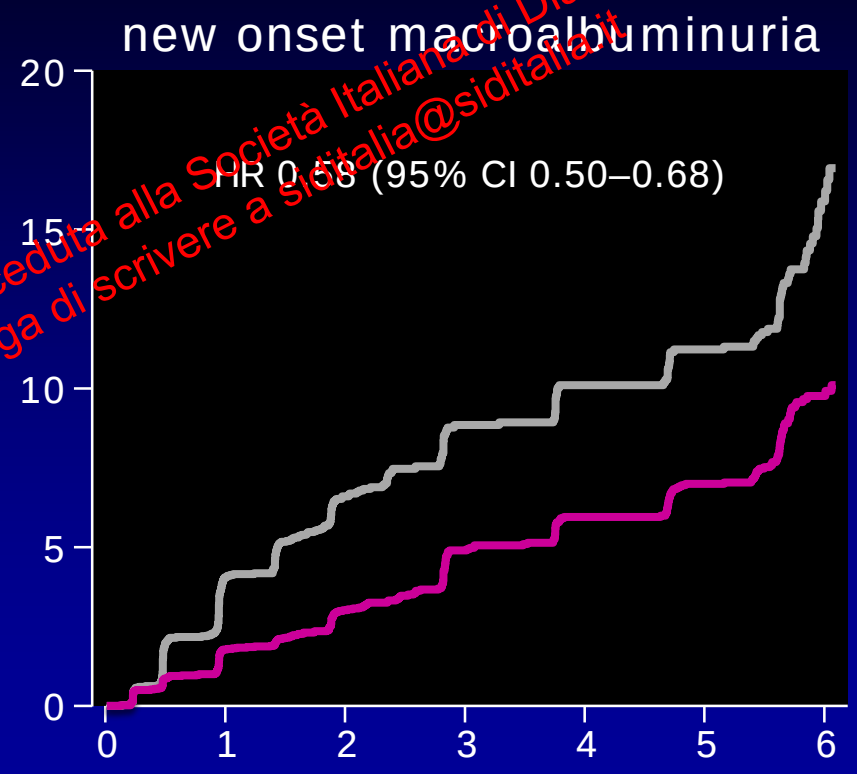


Neal B et al.: NEJM 377, 2097, 2017; Zinman B et al.: NEJM 373:2117, 2015
Wanner K et al.: NEJM 375:323, 2016; Mahaffey KW et al.: Circulation 137:323, 2018

CANVAS: renal outcomes

new onset of micro and macro albuminuria

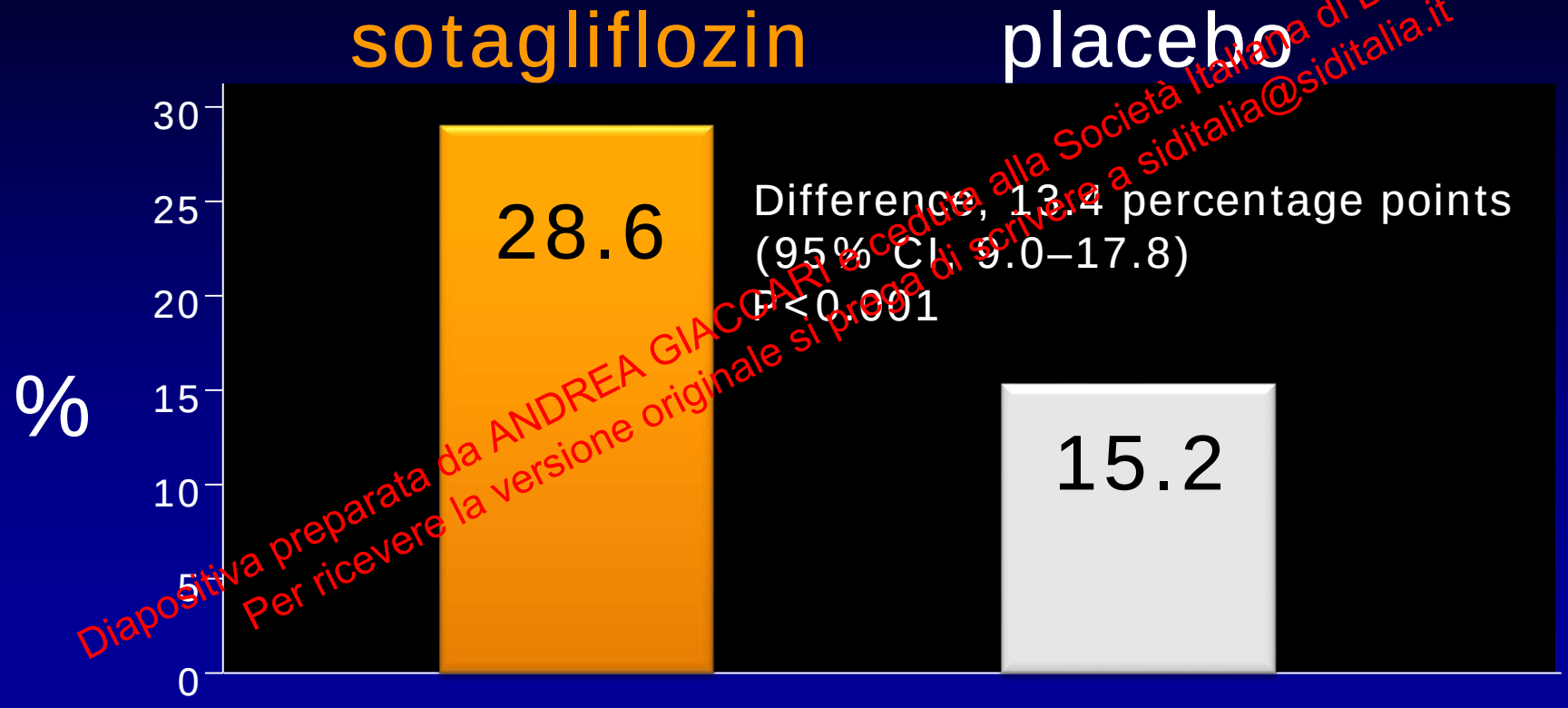




Perkovic V, et al. Lancet DE 6:691, 2018

dual SGLTi in type 1 diabetes: inTandem 3

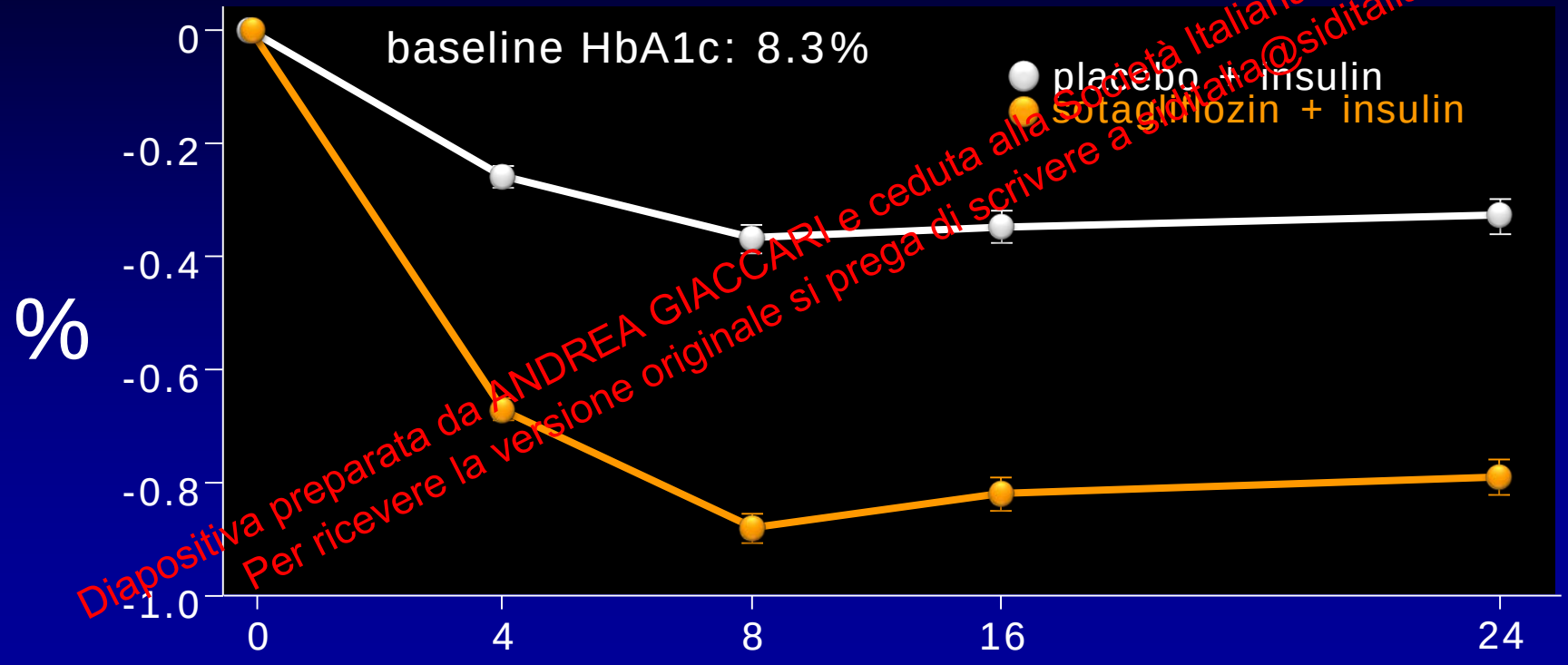
primary endpoint: HbA1c<7% + no sev. hypo + no DKA



Garg SK et al.: NEJM 377:2337, 2017

dual SGLTi in type 1 diabetes: inTandem 3

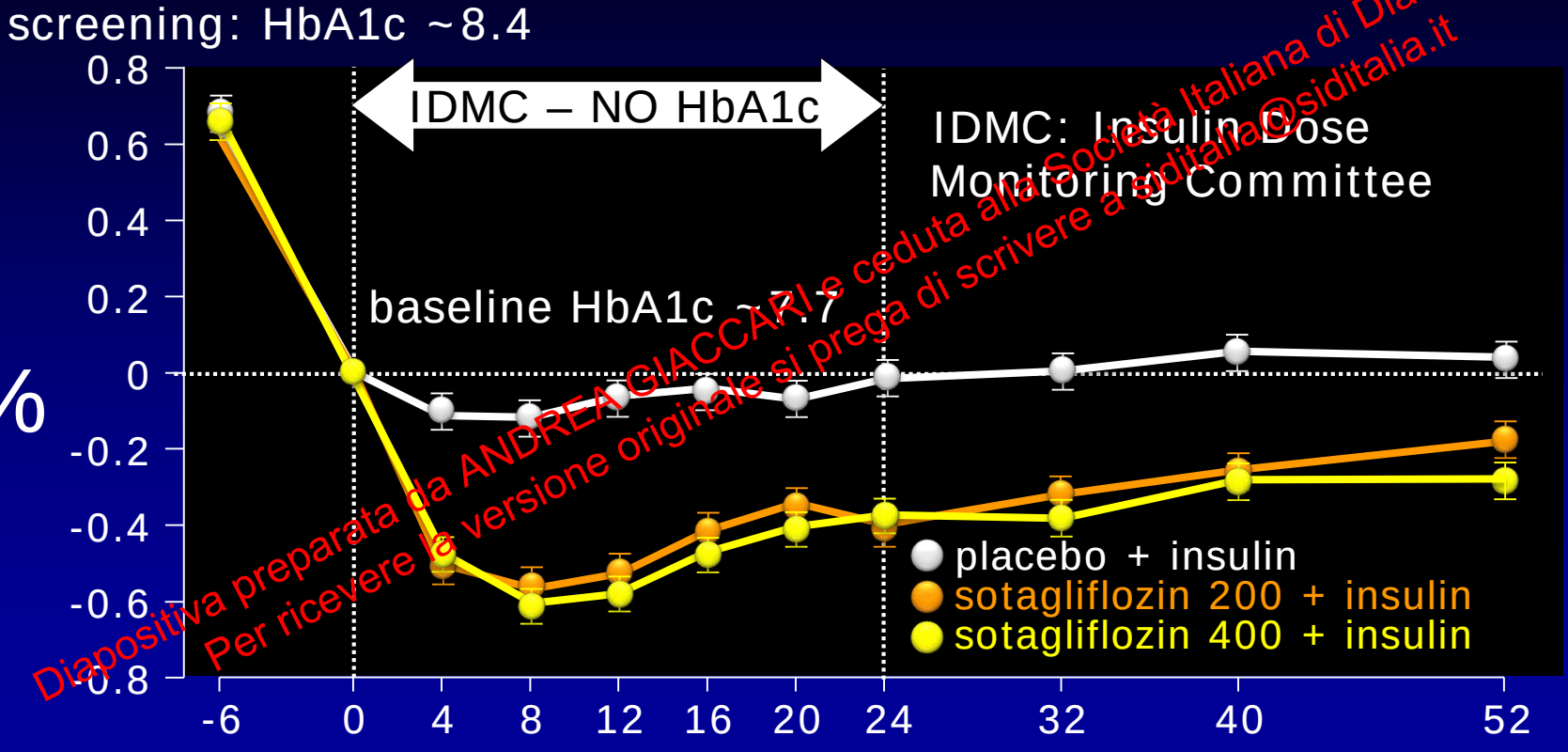
change in HbA1c over 24 weeks



Garg SK et al.: NEJM 377:2337, 2017

dual SGLTi in type 1 diabetes: inTandem 2

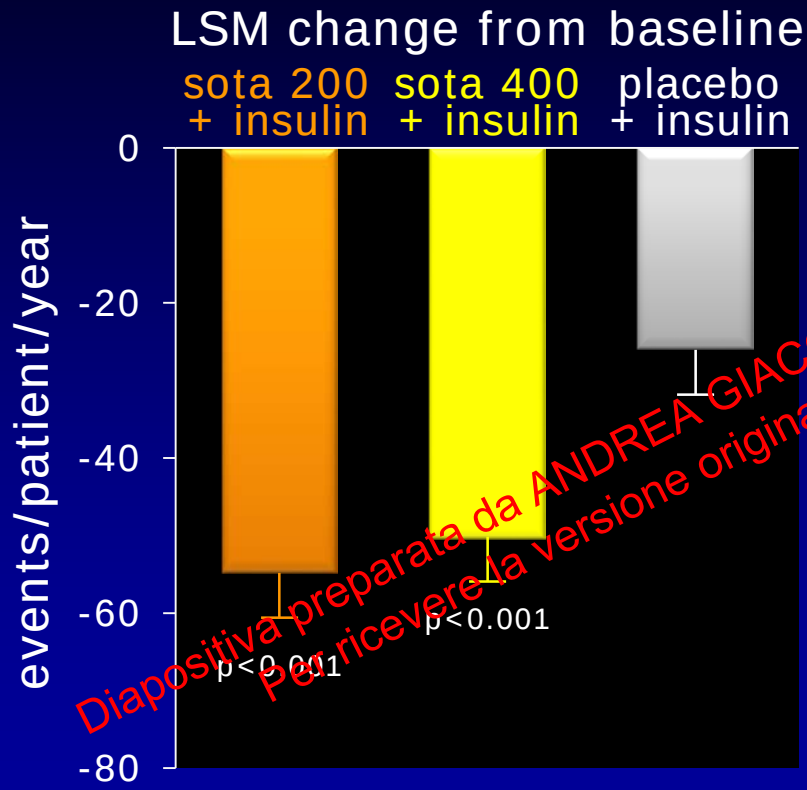
change in HbA1c after insulin optimization

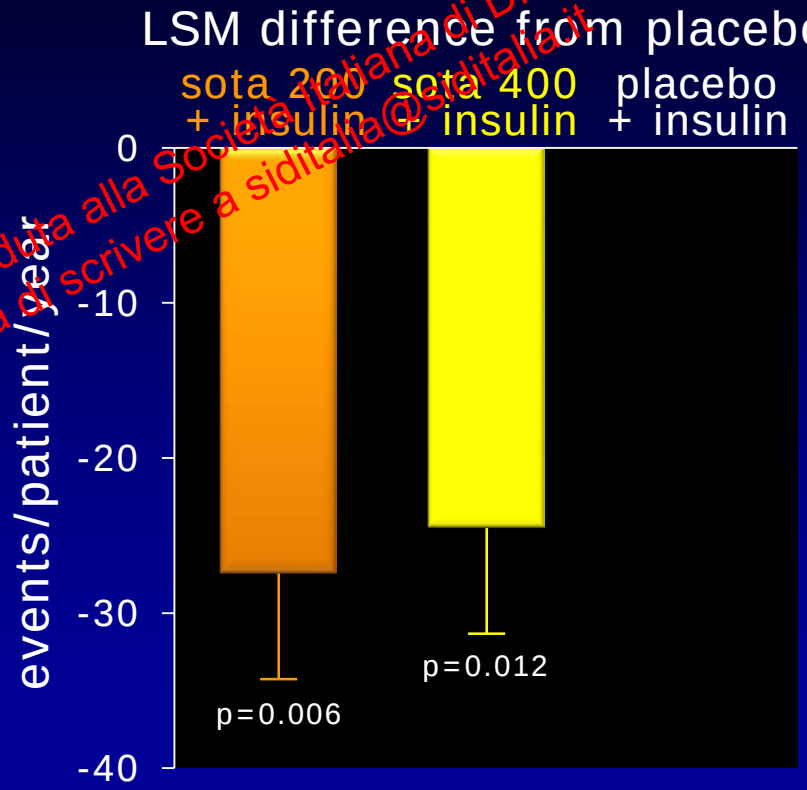


Danne T et al.: Diabetes Care 41:1981, 2018

dual SGLTi in type 1 diabetes: inTandem 2

documented blood glucose ≤70 mg/dL, 52 wks





Danne T et al.: Diabetes Care 41:1981, 2018

gliflozine nel DM1

- le gliflozine NON sostituiscono l'insulina
- è necessaria educazione per prevenire *e*DKA

tuttavia

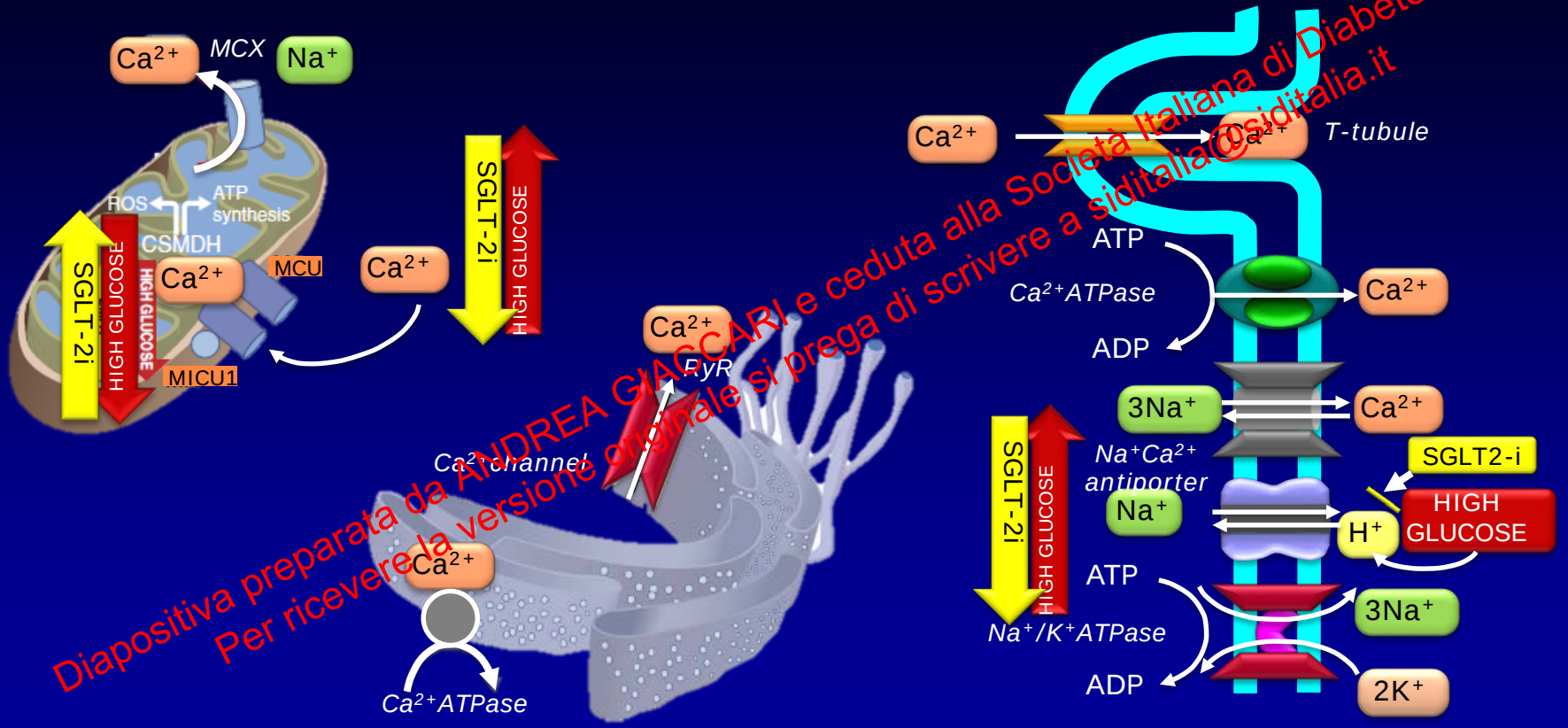
- le gliflozine riducono HbA1c e gran parte degli effetti dell'insulinizzazione periferica
- senza aumentare il rischio per ipoglicemie

«unmet needs» nel diabete tipo 1

- l'insulina è iniettata in periferia (non in porta):
  - aumento del glucosio captato da tessuti periferici
  - diminuita lipolisi
  - aumento di peso
- l'azione dell'insulina non ha "limiti":
  - rischio per ipoglicemie
- non adeguata per iperglicemia post-prandiale:
  - necessità di insuline fast acting (?)

- vantaggi degli SGLT-2i insieme con terapia insulinica:
  - riduzione del glucosio captato da tessuti periferici
  - aumento lipolisi
  - riduzione di peso
- l'azione dell'insulina non ha "limiti":
  - ridotto rischio per ipoglicemie
- non adeguata per iperglicemia post-prandiale (solo sota):
  - insuline fast acting inutili (?)

the electrolyte hypothesis



Vettor R, Inzucchi S and Fioretto P: Diabetologia 60:395, 2017

SGLT-2 inhibition and Na^+ handling

afferent constriction

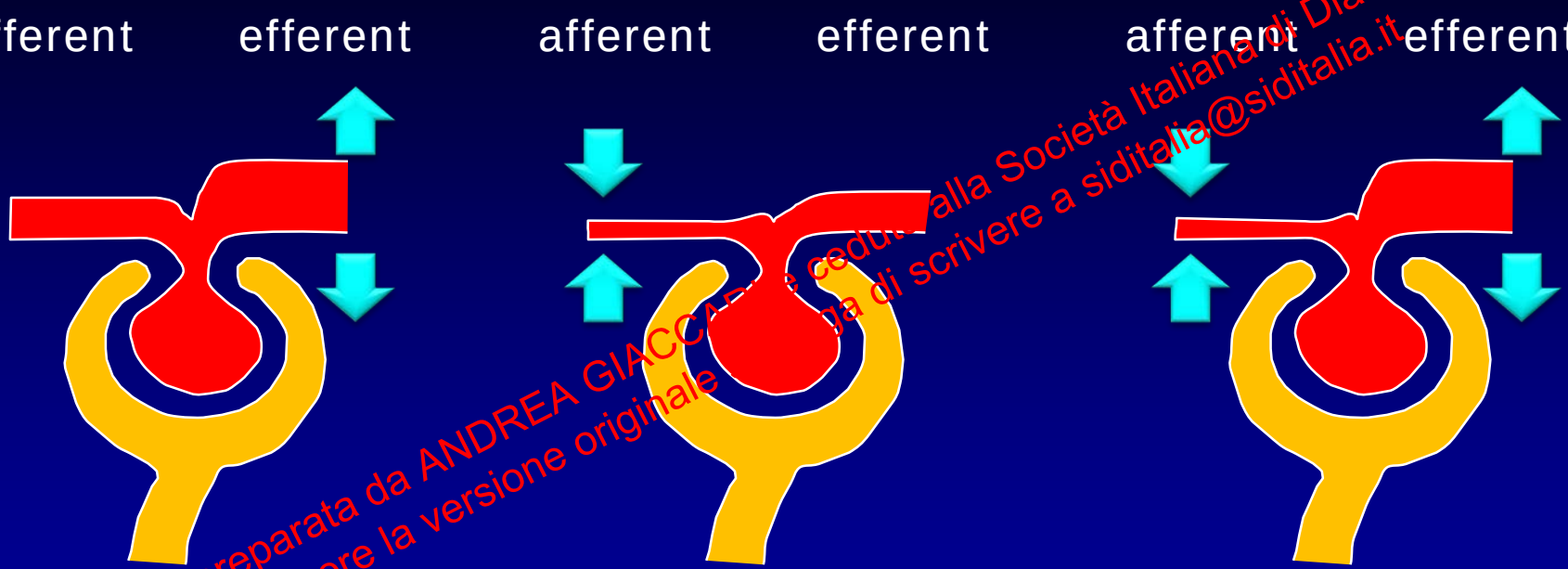
SGLT-2 inhibition

more Na^+ to macula densa

Na^+ increased

Na^+ finally reabsorbed

the renal hypothesis



RAAS blockade

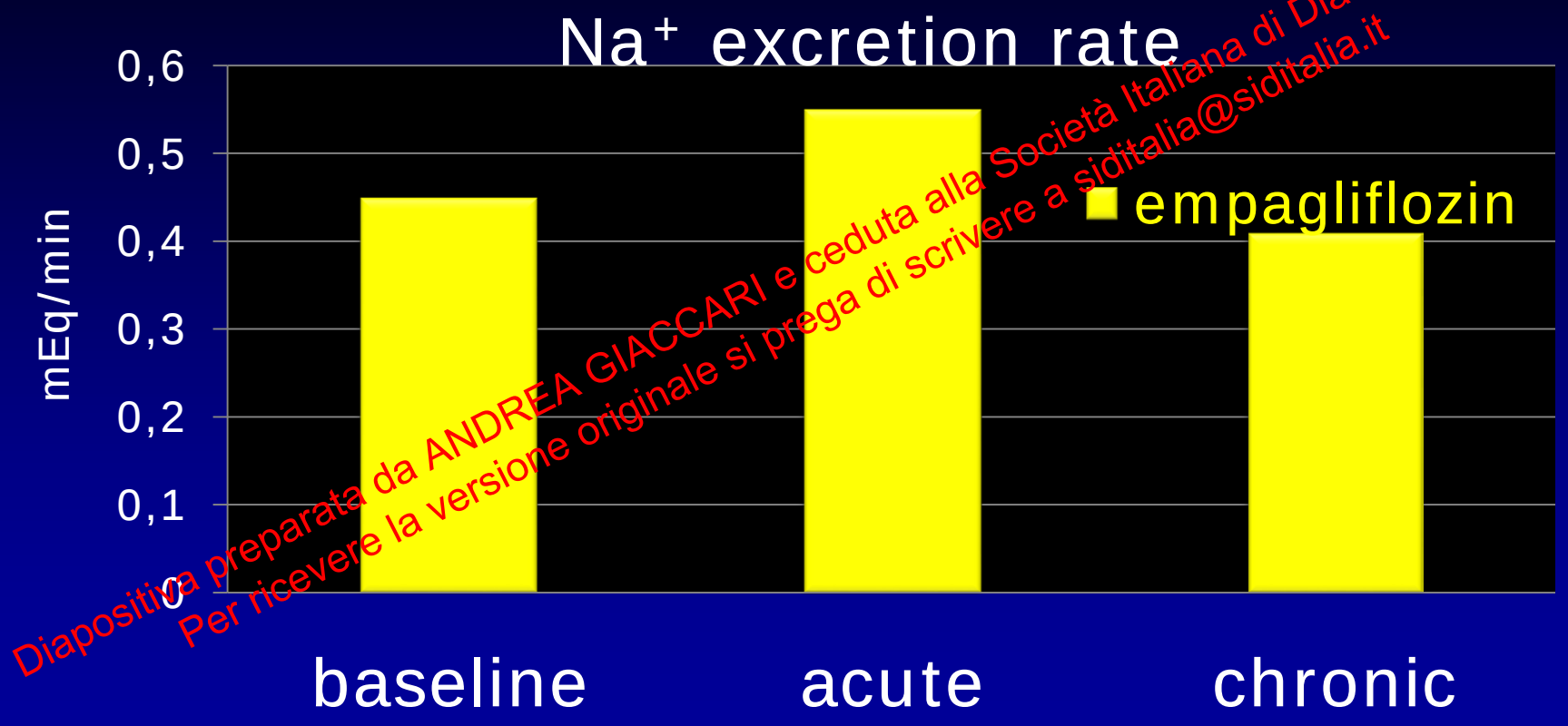
SGLT-2 inhibition

RAAS blockade +
SGLT-2 inhibition

Cherney DZ Circulation 129:587, 2014

effect of gliflozins on renal sodium handling

in patients with T2D



Ferrannini E. et al.: 40:771, 2017 doi: 10.2337/dc16-2724

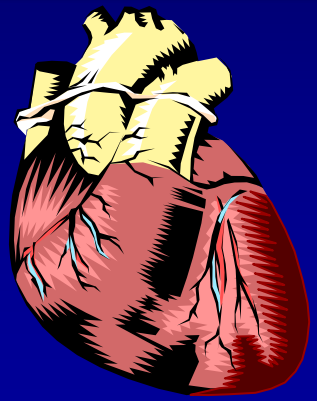
Shift in Fuel Energetics

diabetic heart

- ⬆ fat oxidation
- ⬇ glucose uptake/oxidation
- ⬇ P/O ratio
- ⬇ cardiac work efficiency

SGLT-2i effect

- ⬇ fat oxidation
- ⬆ glucose uptake/oxidation
- ⬆ P/O ratio
- ⬆ cardiac work efficiency



Mudaliar S et al.: Diabetes Care 39:1115, 2016

the βOHB hypotheses compared

Author	glucose oxidation	FFA oxidation	βOHB oxidation
Mudaliar	↑	↓	↑
Ferrannini	↓	↓	↑↑
Lopaschuk	↑↑	↑	=

DapaHeart

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Trial record 1 of 4 for: giaccari

Previous Study | Return to List | Next Study

Effects of SGLT2 Inhibition on Myocardial Insulin Sensitivity (DapaHeart)

ClinicalTrials.gov Identifier: NCT03313752

Recruitment Status : Recruiting
First Posted : October 18, 2017
Last Update Posted : January 24, 2018

See **Contacts and Locations**

Sponsor:
Andrea **Giaccari**

Information provided by (Responsible Party):
Andrea **Giaccari**, Catholic University of the Sacred Heart

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Brief Summary:

A Phase III, single-centre, randomized, 2-arm, parallel-group, double blind, placebo-controlled study, consisting of a screening phase (Days -14 to -1), a 4-week double-blind, placebo-controlled treatment phas

Subjects: Type 2 diabetic patients with coronary artery disease (CAD) not requiring revascularization, with sub-optimal glycemic control (HbA1c 7.5-8.5%) on their current anti-hyperglycemic regimen

Subjects will be randomized in a 1:1 ratio to dapagliflozin or placebo.

Subjects will undergo screening assessment in the 14-day period preceding administration of the first dose of study drug on Day 1.

organ specific insulin-resistance