

“Al
CUORE
del **DIABETE**”

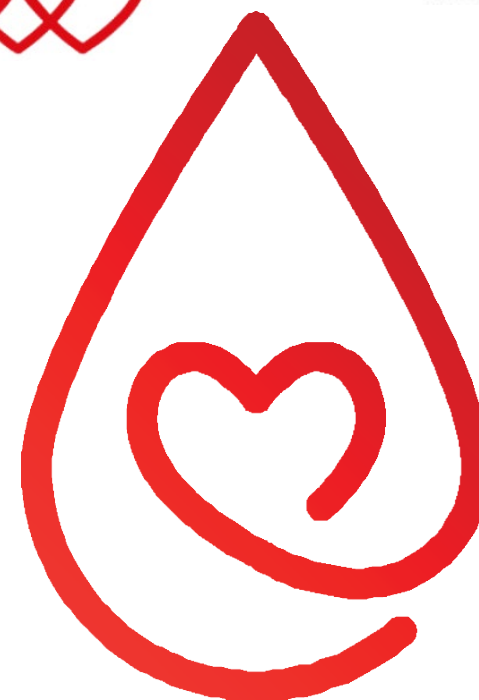
SGLT-2i e cuore

Andrea Giaccari



SID

Società Italiana
di Diabetologia



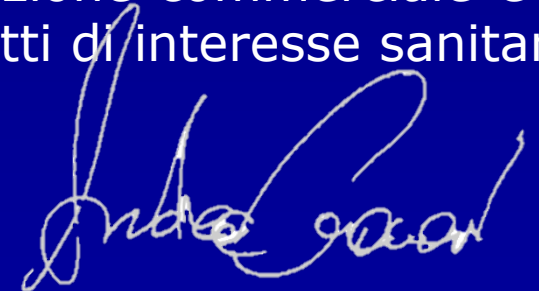
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DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

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

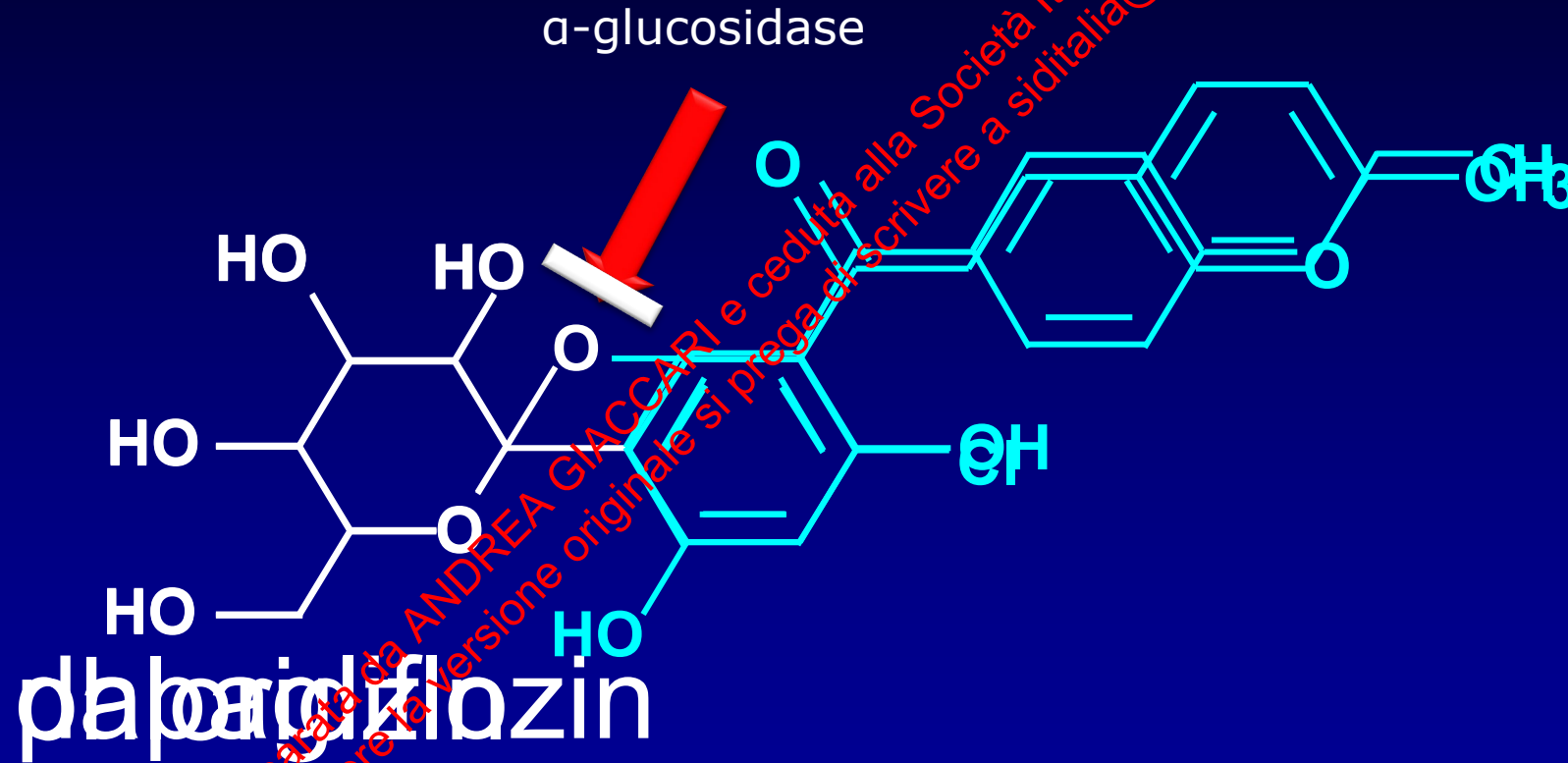
- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- Novo-Nordisk
- Sanofi

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.).



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SGLT-2i are phloridzin analogues



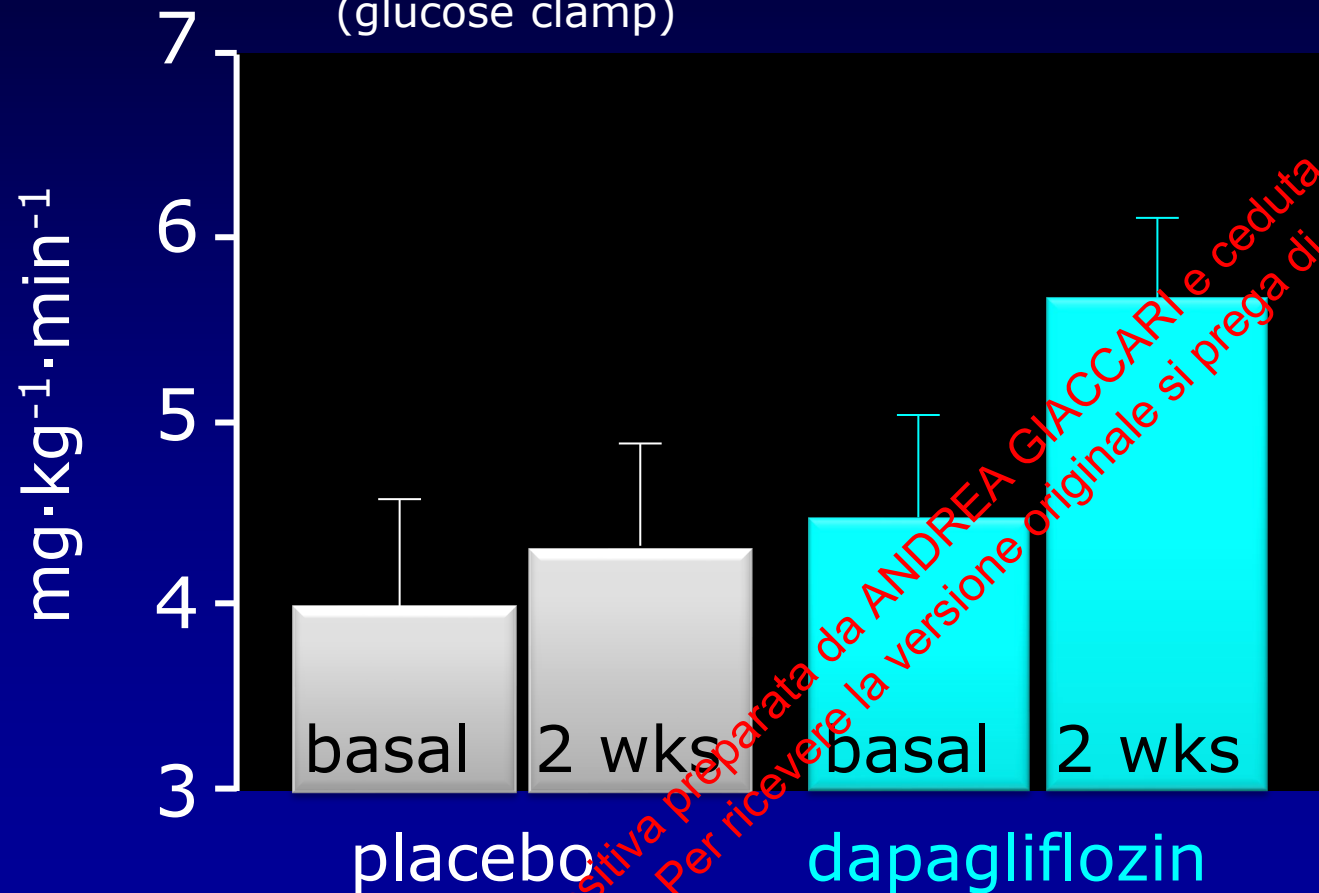
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SGLT-2i act on glucose toxicity

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

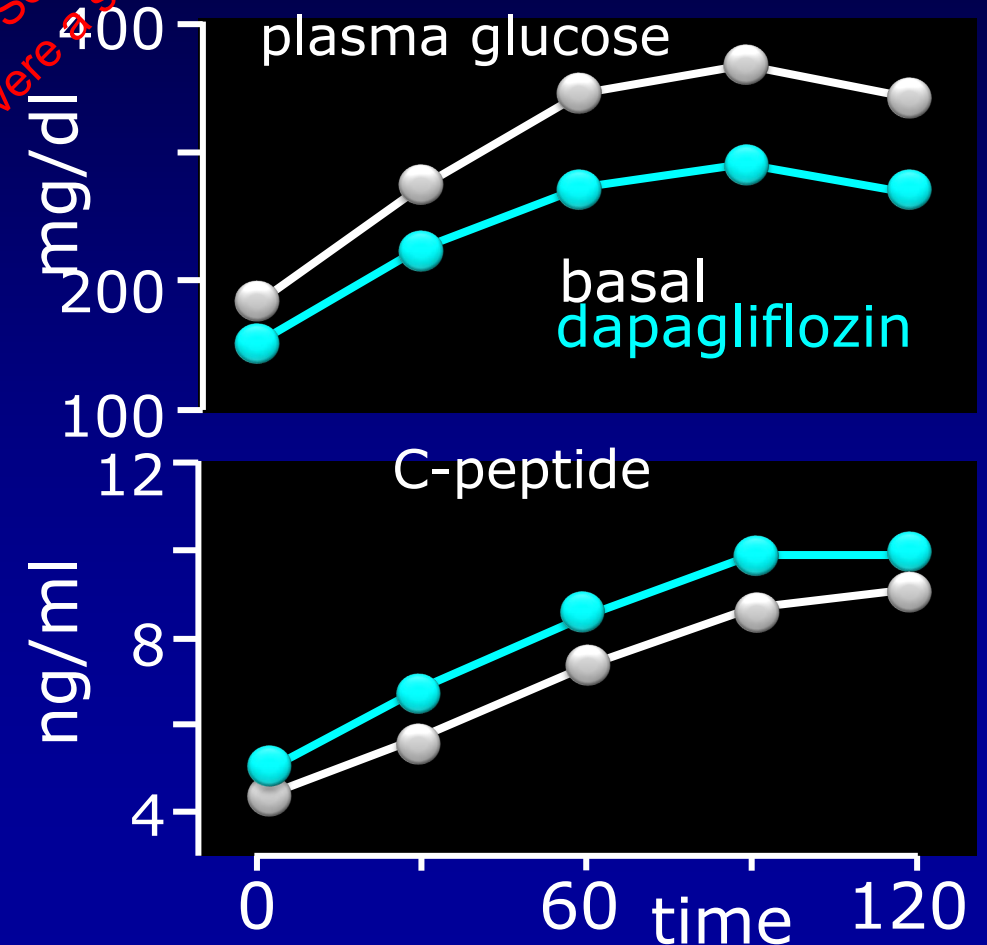
insulin sensitivity

(glucose clamp)



insulin secretion

(OGTT)



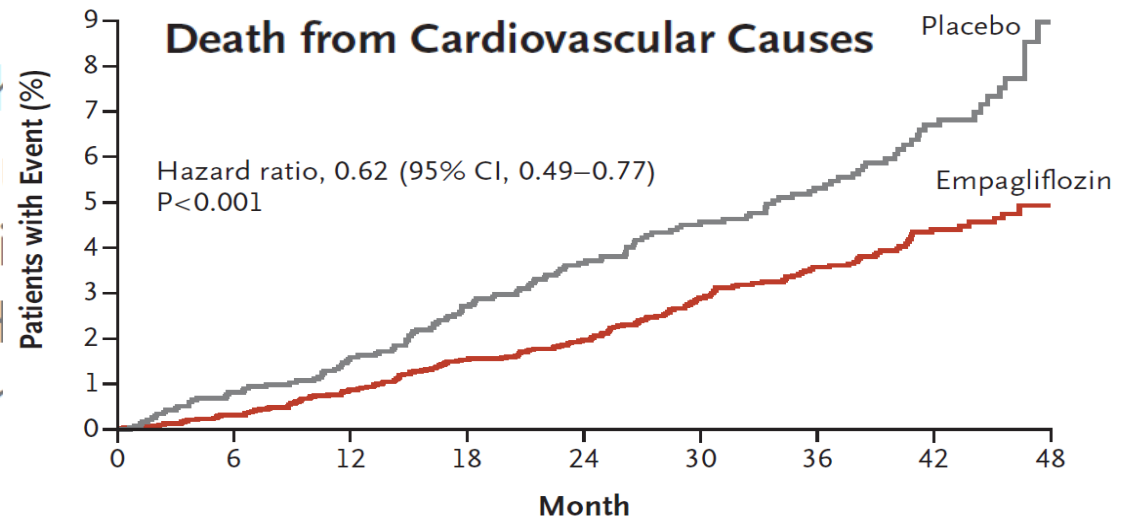
Merovci A et al.: JCI 124: 509; 2014

Merovci A et al.: JCEM 100:1927; 2015

ORIGINAL ARTICLE

This article was published on September 17, 2015, at NEJM.org.

Bernard Zinman, M.D., Christoph
David Fitchett, M.D., Erich Bl
Michaela Matthaeus, Dipl. Bi
Odd Erik Johansen, M.D., Ph.D., H
and Silvio E. Inzucchi, M.D., for th





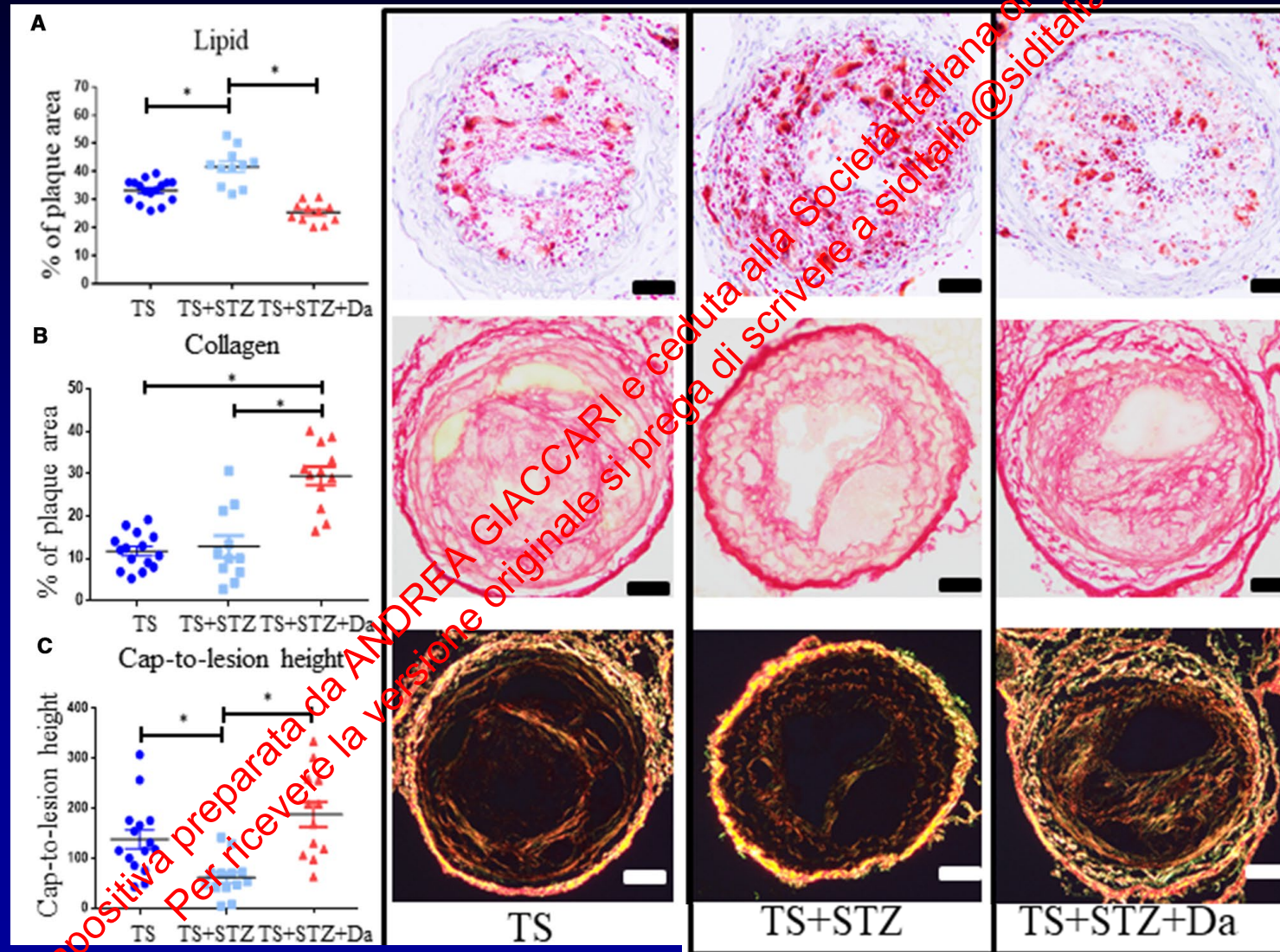
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possible mechanisms for CV protection

- reduced atherosclerosis
- vasoconstriction glomerular afferent arteriole
- other transporters
- hemoglobin
- hematocrit increase / fluid loss
- increased β OH oxidation
- increased glucose oxidation
- improved FFA oxidation
- many others!

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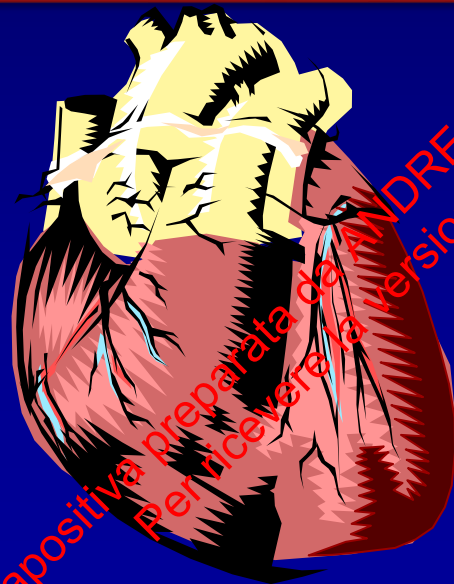
SGLT-2i stabilize Diabetes-Induced Atherosclerotic Plaque Instability



Shift in Fuel Energetics

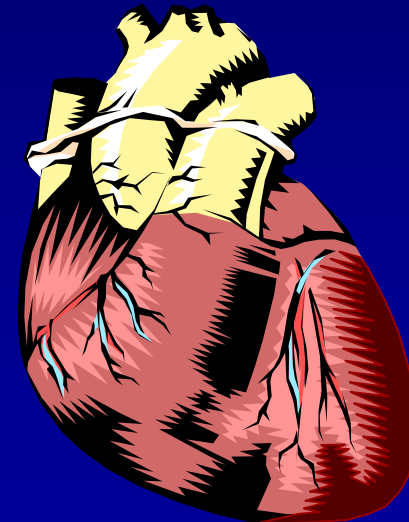
diabetic heart

- ↑ fat oxidation
- ↓ glucose uptake/oxidation
- ↓ P/O ratio
- ↓ cardiac work efficiency

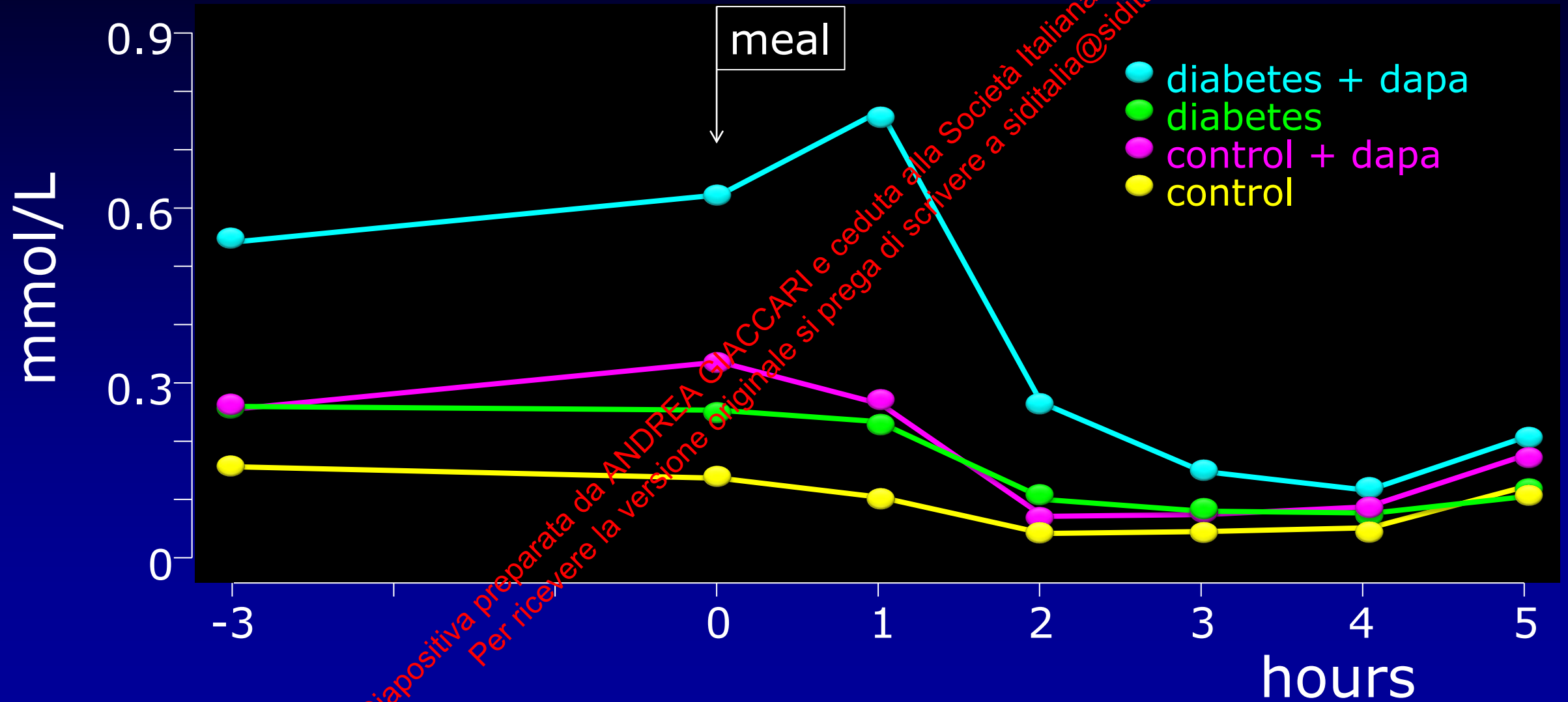


SGLT-2i effect

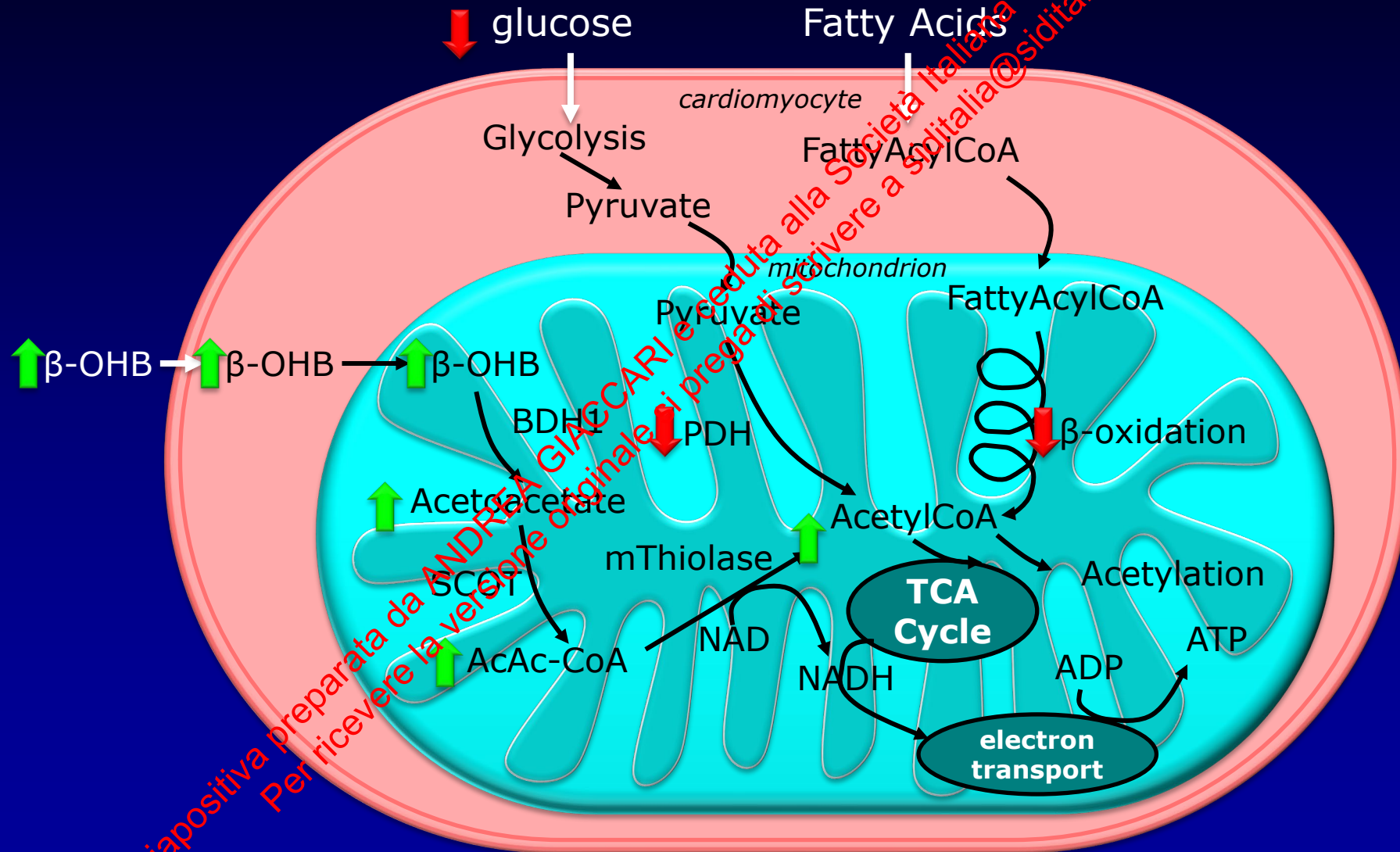
- ↓ fat oxidation
- ↑ glucose uptake/oxidation
- ↑ P/O ratio
- ↑ cardiac work efficiency



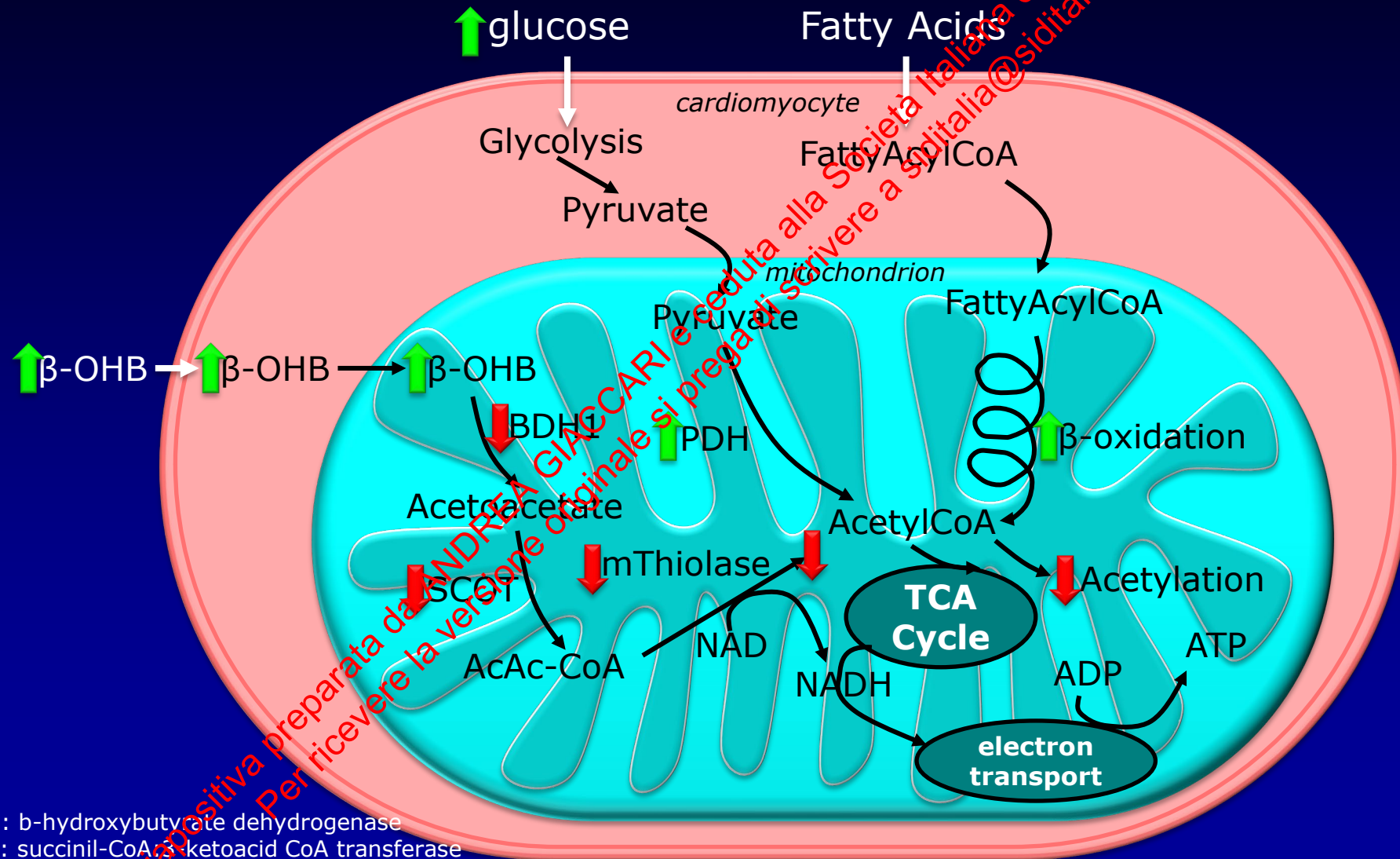
SGLT-2i increase β -OH-butyrate



Thrifty Substrate Hypothesis



Fuel Hypothesis: Not so Soon



BDH1: b-hydroxybutyrate dehydrogenase
SCOT: succinyl-CoA:3-ketoacid CoA transferase

Lopaschuk GD and Verma S. Cell Metab. 24:200, 2016

the β OHB hypotheses compared

Author	glucose oxidation	FFA oxidation	β OHB oxidation
Mudaliar ¹			
Ferrannini ²			
Lopaschuk ³			

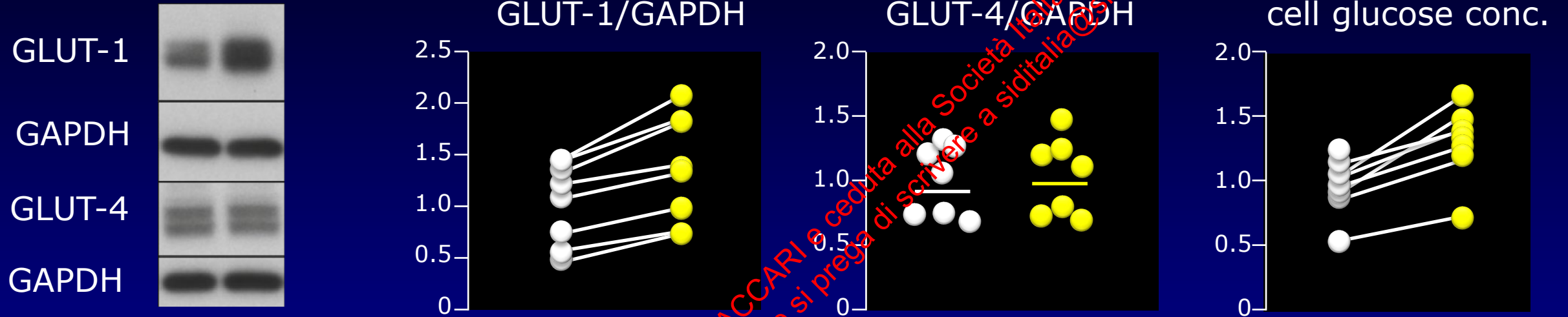
1. *Diabetes Care* 39:1108, 2016. doi: 10.2337/dc16-0330.

2. *Diabetes Care* 39:1115, 2016. doi: 10.2337/dc16-0542.

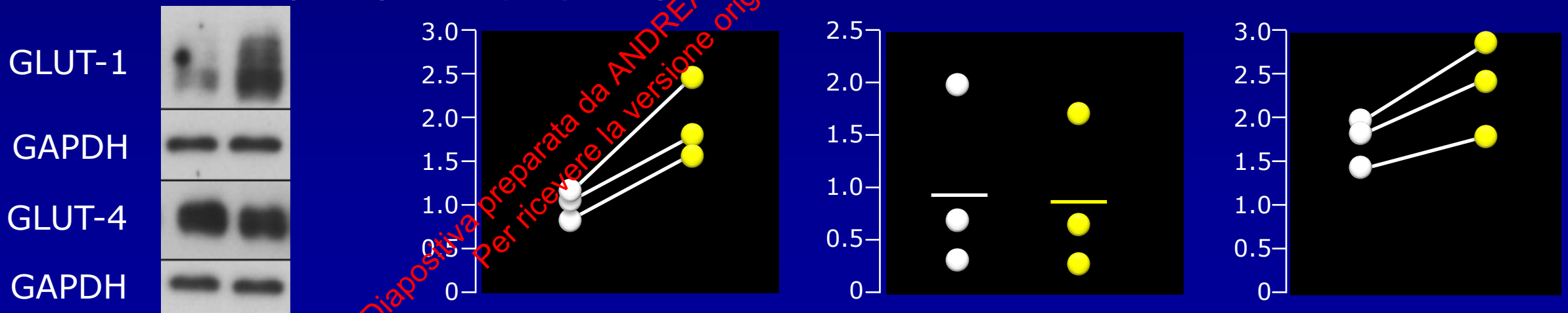
3. *Cell Metab* 24:200, 2016. doi: 10.1016/j.cmet.2016.07.018

SGLT-2i increase GLUT-1 (in vitro)

mice model of HF



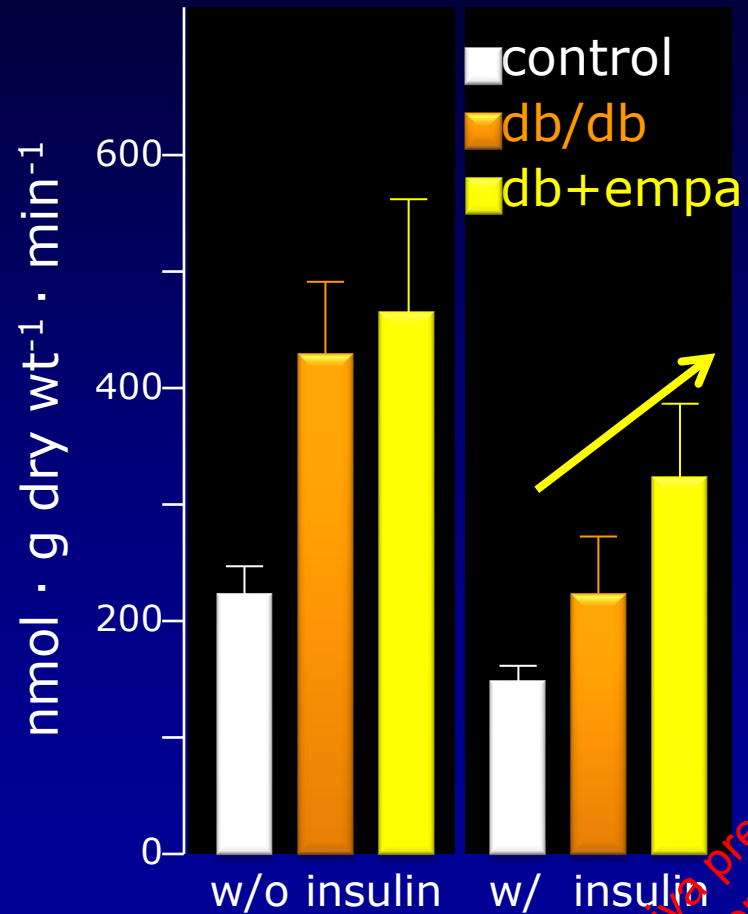
human cells from HF



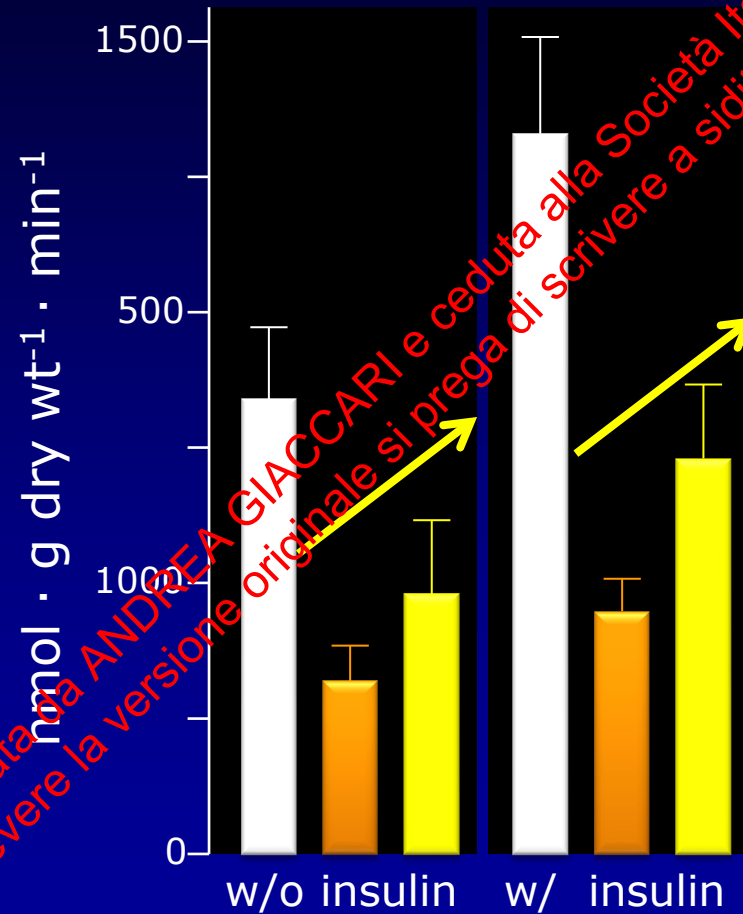
SGLT-2i increase glucose oxidation

(in isolated hearts)

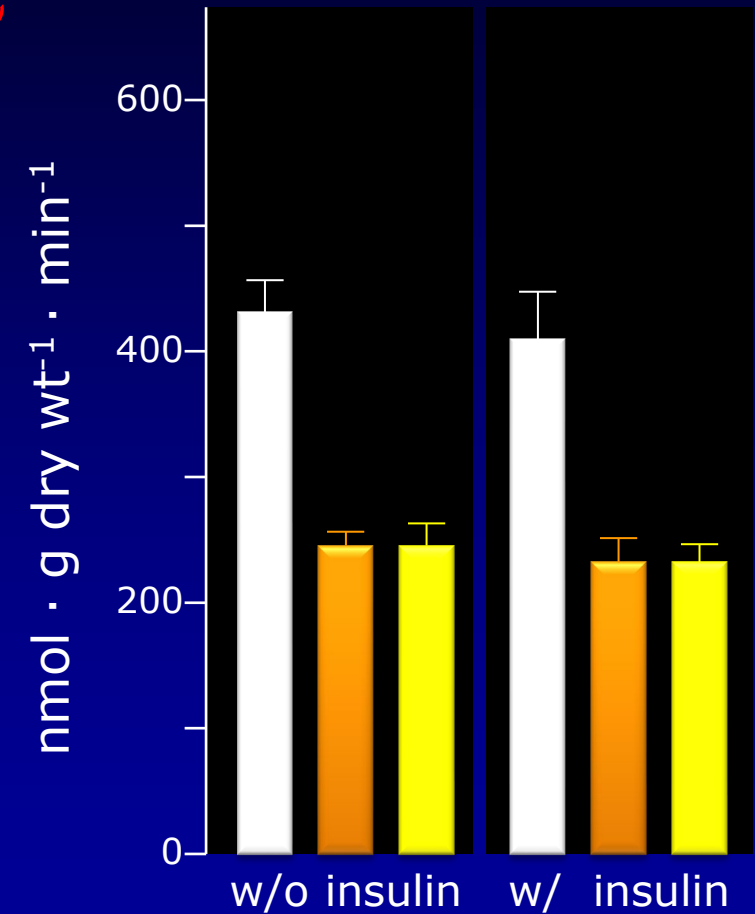
palmitate oxidation



glucose oxidation

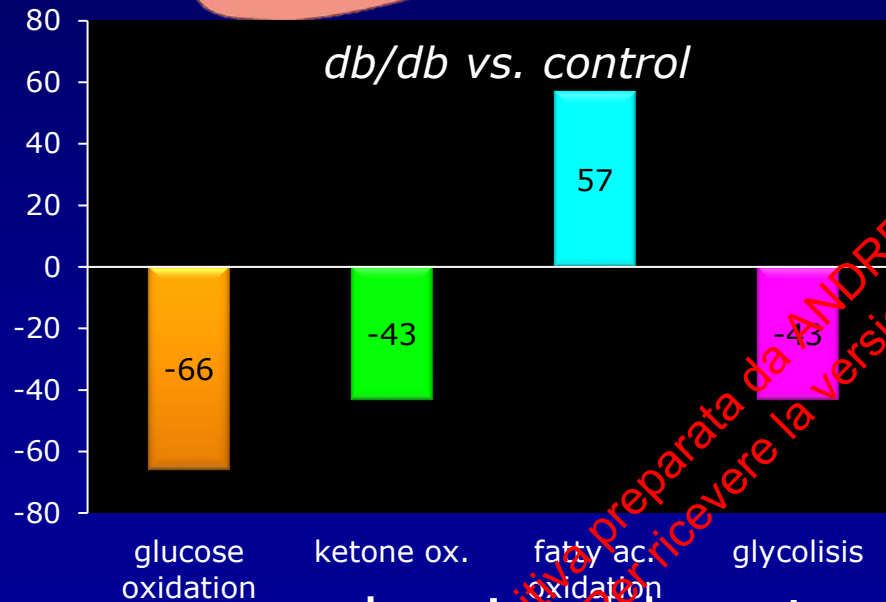
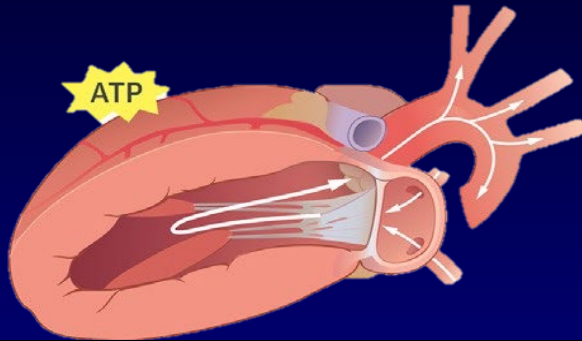


β -OHB oxidation



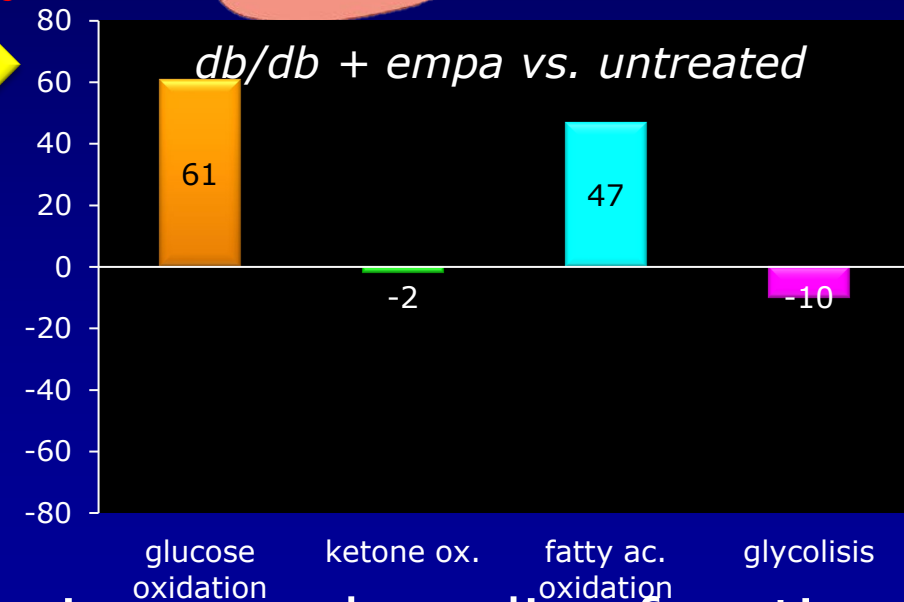
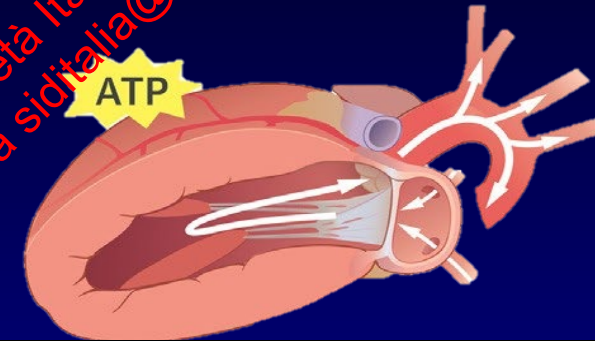
SGLT-2i improve metabolic efficacy (in isolated hearts)

reduced ATP production



energy deprived heart

improved ATP production

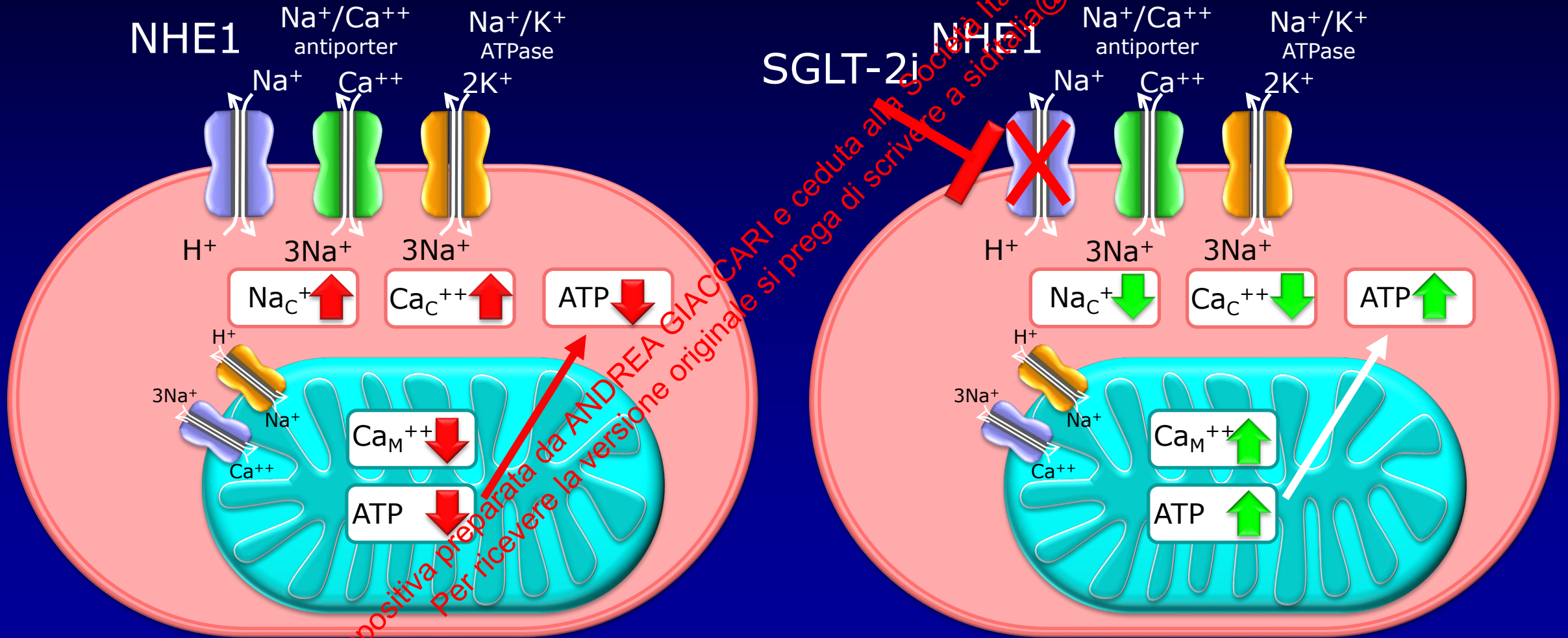


improved cardiac function

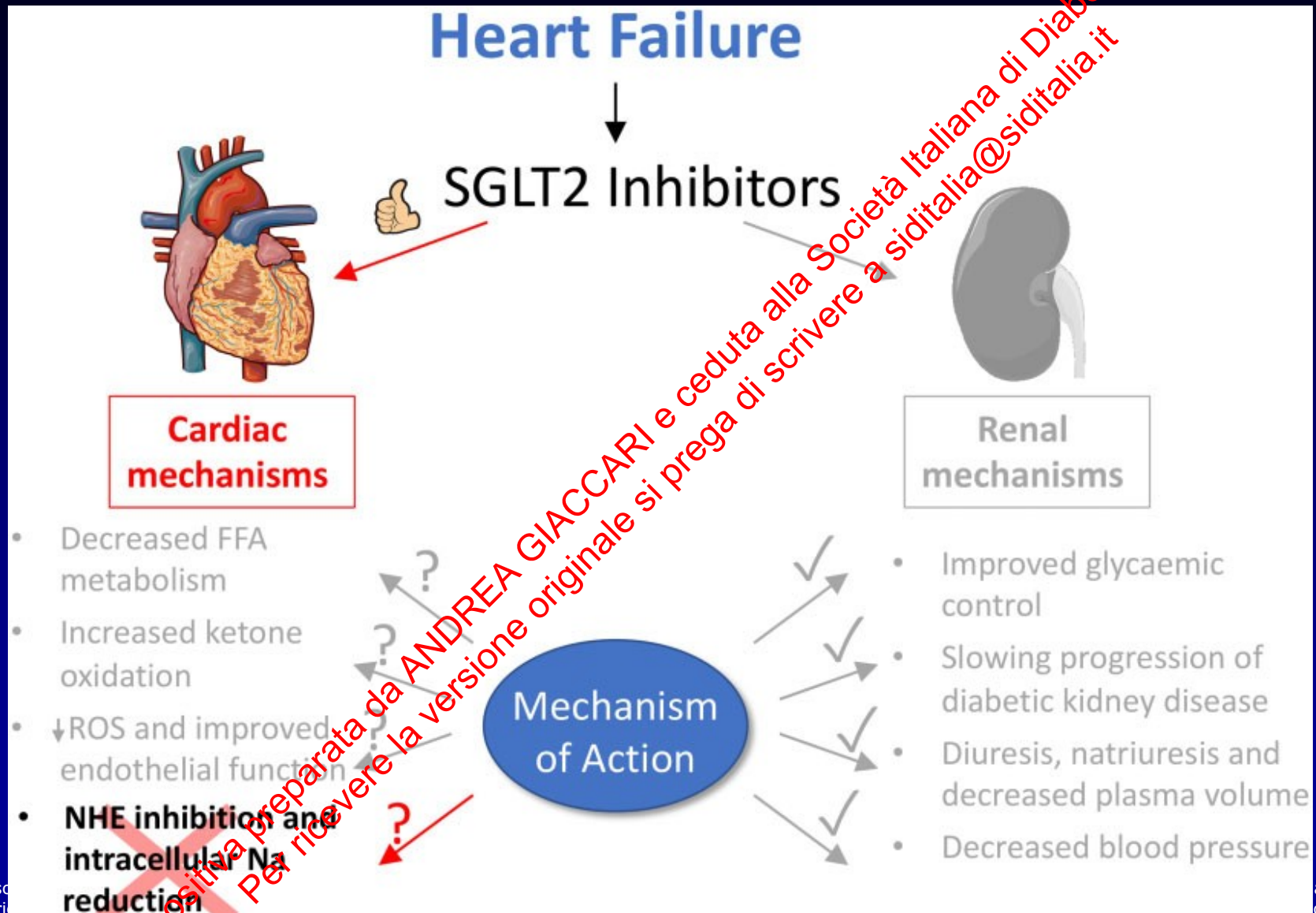
SGLT-2i may directly inhibit cardiomyocyte NHE1

diabetes and/or heart failure

SGLT-2i on NHE1

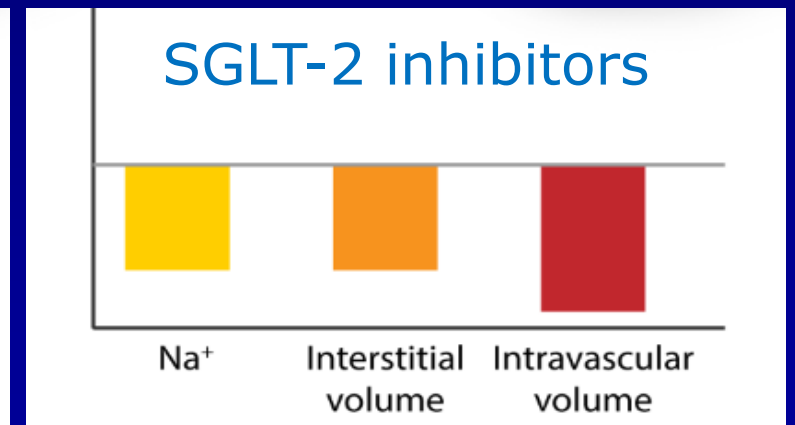
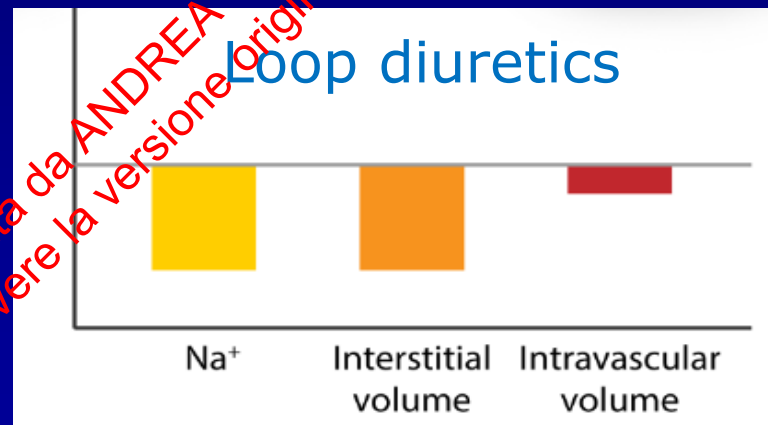


SGLT-2i do not inhibit cardiac NHE1 or lower $[Na^+]_i$

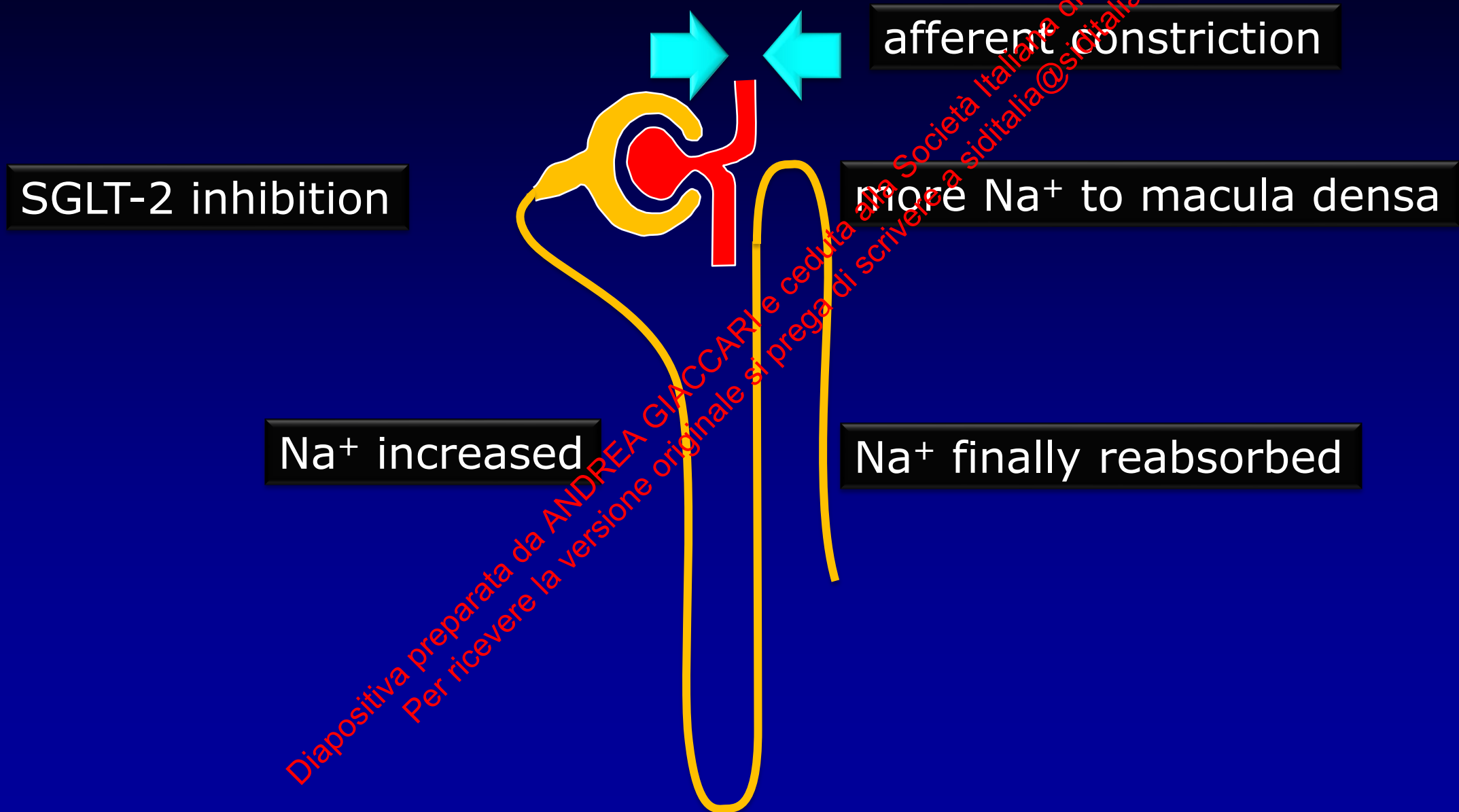


EMPA does not inhibit NHE1 flux in iso... or blue lines show best fit through ori... cariporide (Carip.). (G) Steady-state p... at the concentrations indicated. Red... onships for EMPA, DAPA, CANA, and... 49 cells from three rats per condition. For DAPA and CANA, n = 31-43 cells from two rats per condition. *P < 0.05 by one-way ANOVA.

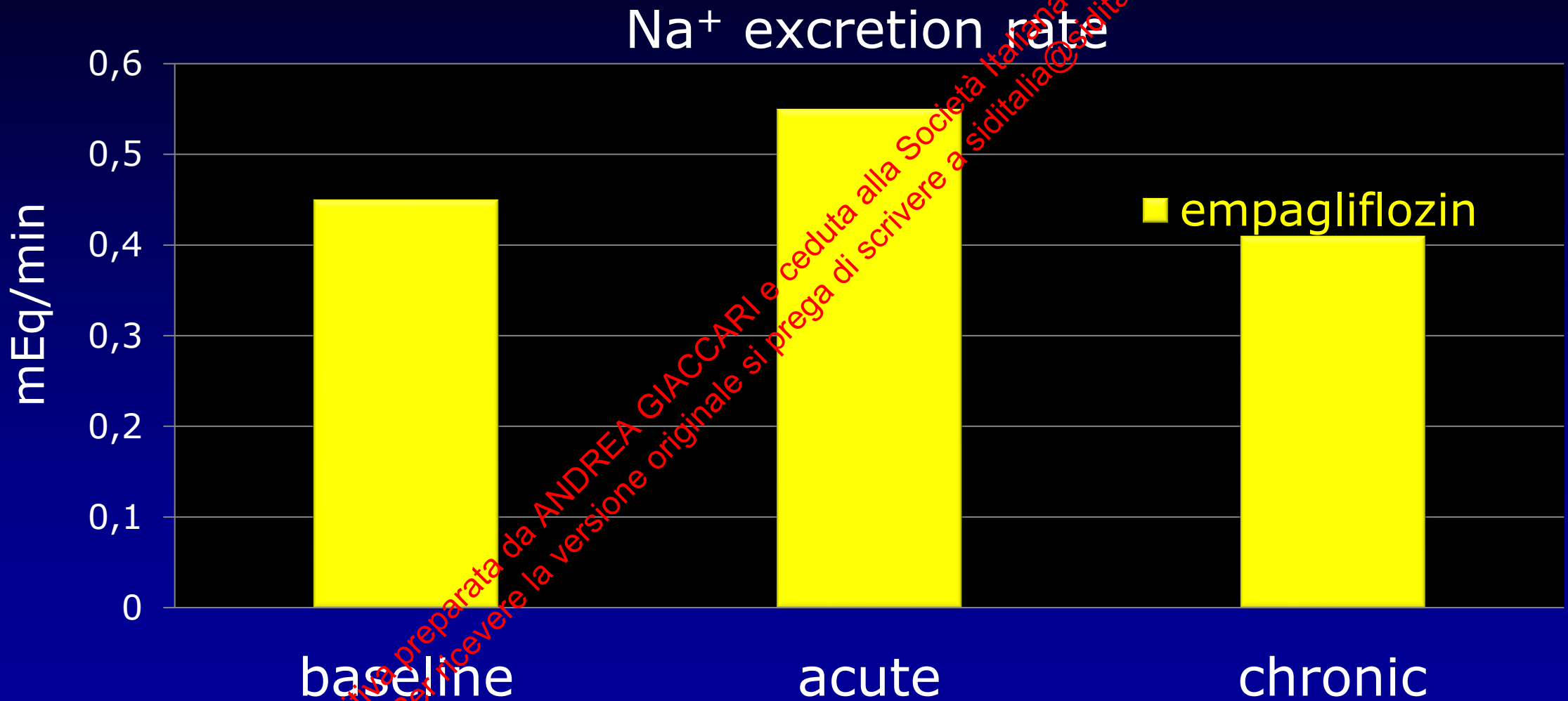
SGLT-2i differentially regulate the interstitial vs intravascular compartments



SGLT-2 inhibition and Na^+ handling



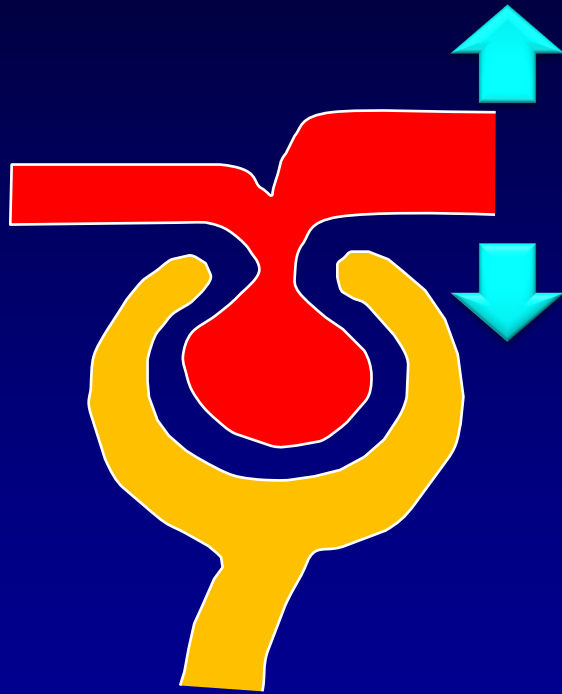
effect of SGLT-2i on renal sodium handling in patients with T2D



the renal hypothesis

afferent

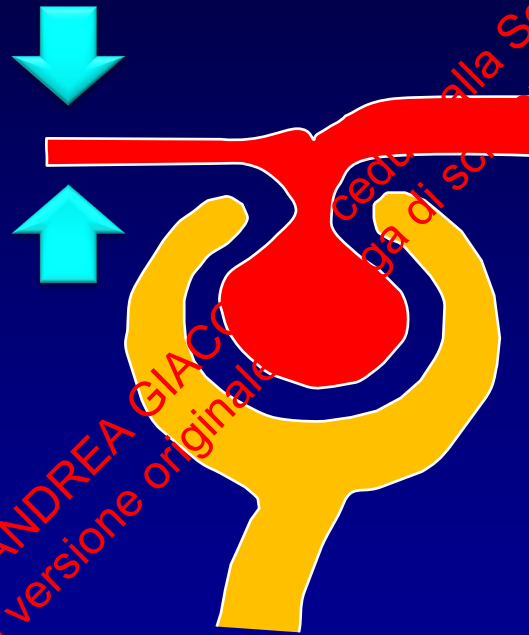
efferent



RAAS blockade

afferent

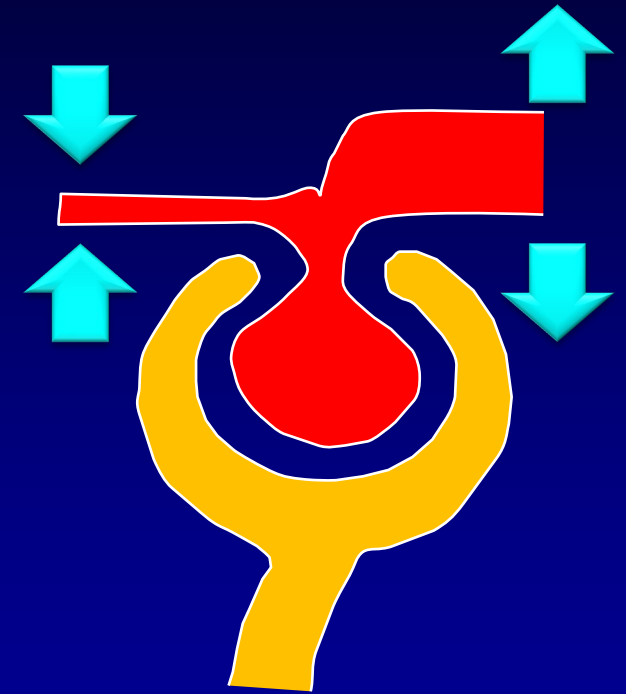
efferent



SGLT-2 inhibition

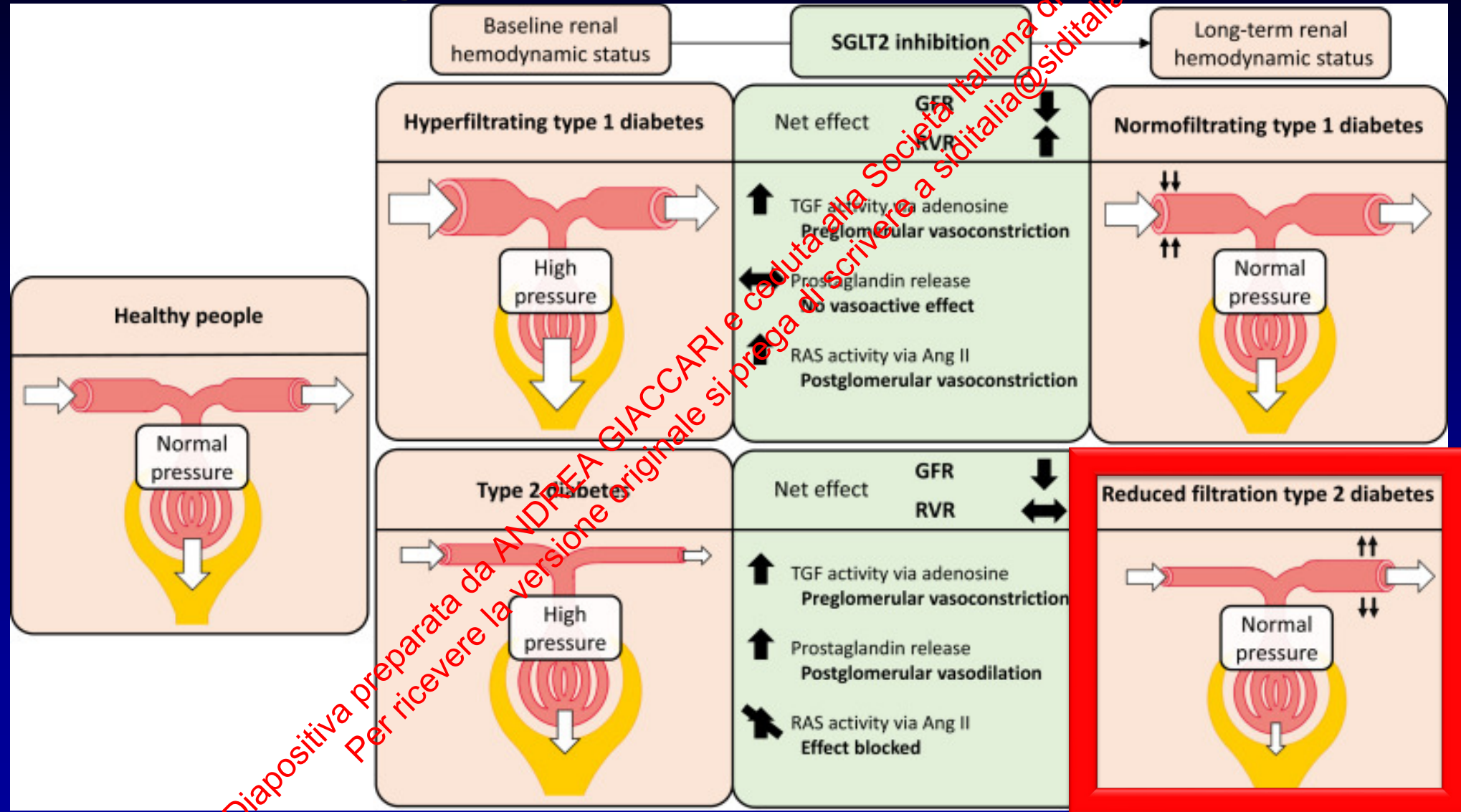
afferent

efferent



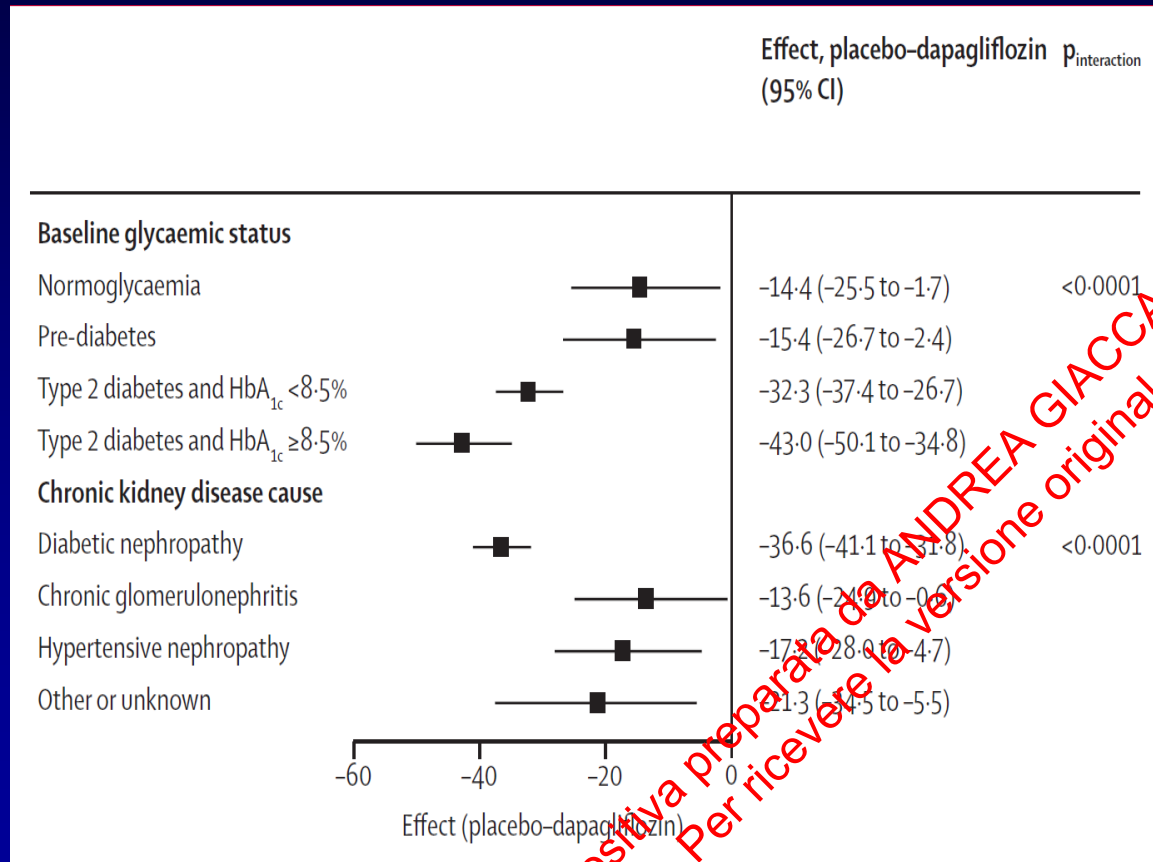
RAAS blockade +
SGLT-2 inhibition

in type 2 diabetes, SGLT-2i dilate efferent glomerular arteriole



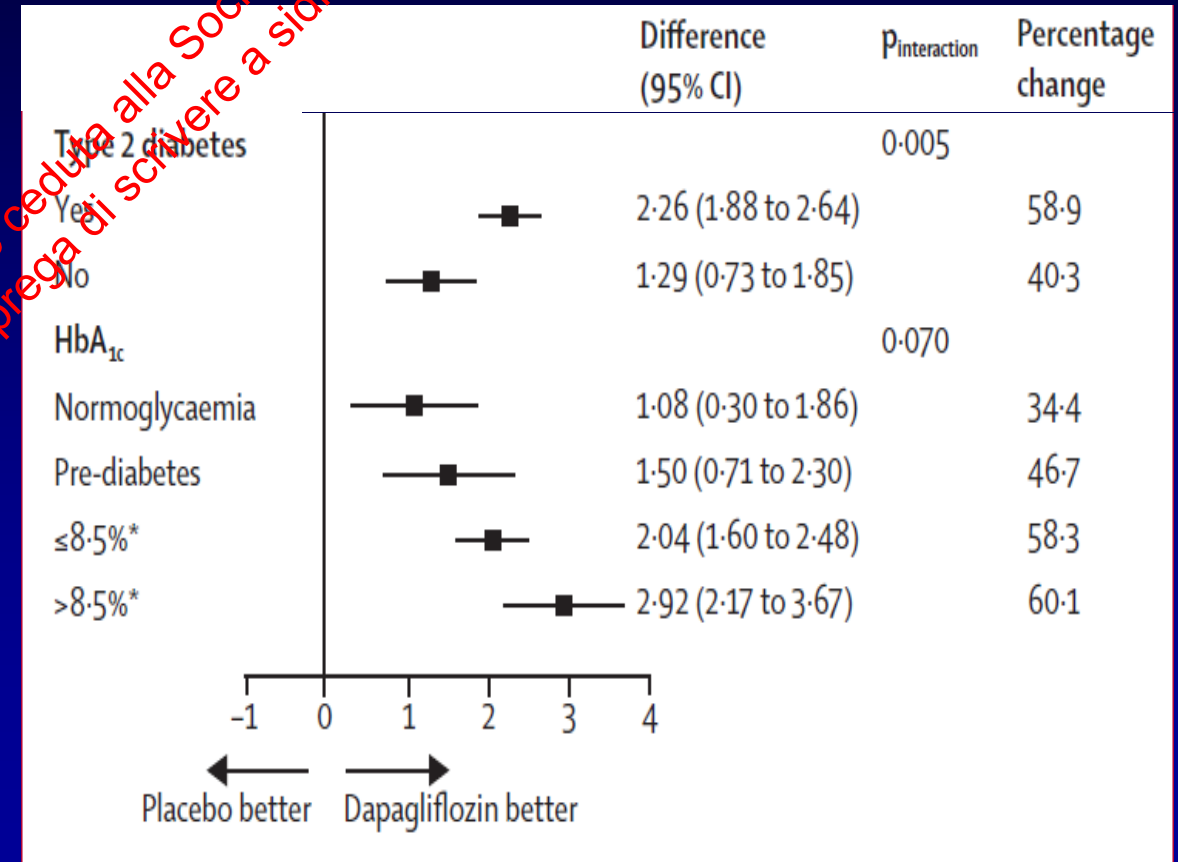
Dapa-CKD: with vs. w/o diabetes analysis

effect on albuminuria



Jongs N et al.: Lancet DE 2021 Nov;9(11):755-766
doi: 10.1016/S2213-8587(21)00243-6.

effect on eGFR decline



Heerspink HJL et al.: Lancet DE 2021 Nov;9(11):743-754
doi: 10.1016/S2213-8587(21)00242-4

domanda

con quale affermazione sei più d'accordo

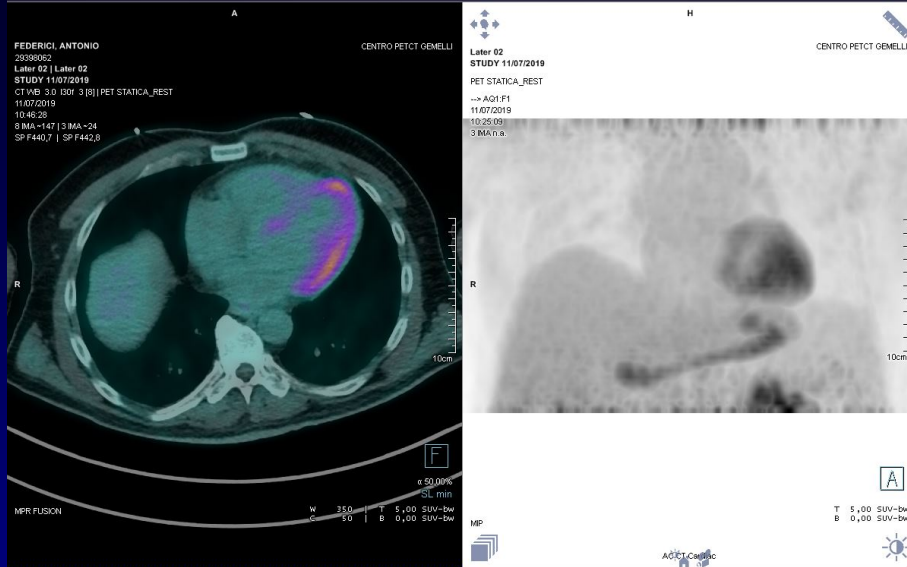
gli effetti cardio-nefro protettivi sono principalmente mediati da:

- A. modulazione del metabolismo
- B. effetti puramente emodinamici
- C. modulazione della pressione intraglomerulare
- D. tutti e nessuno: non sono ancora ben definiti

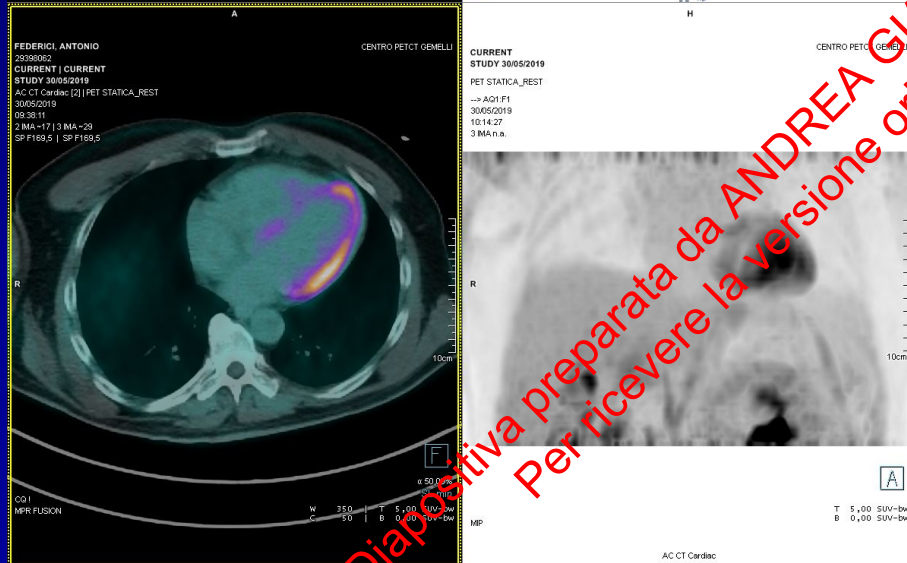
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viewing (and measuring) myocardial metabolism and blood flow (before and after an SGLT-2i)

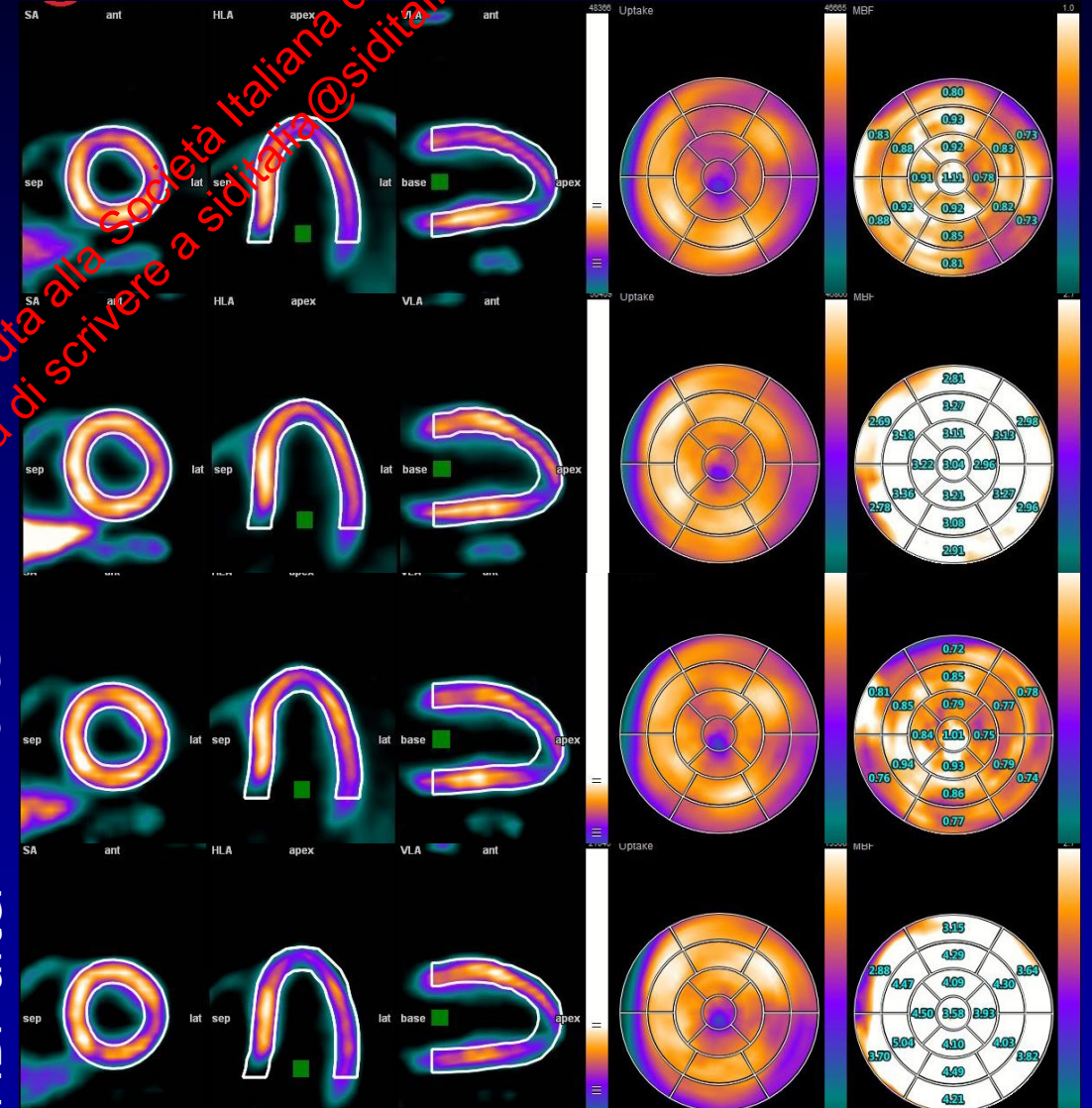
MGU before dapa



MGU after dapa

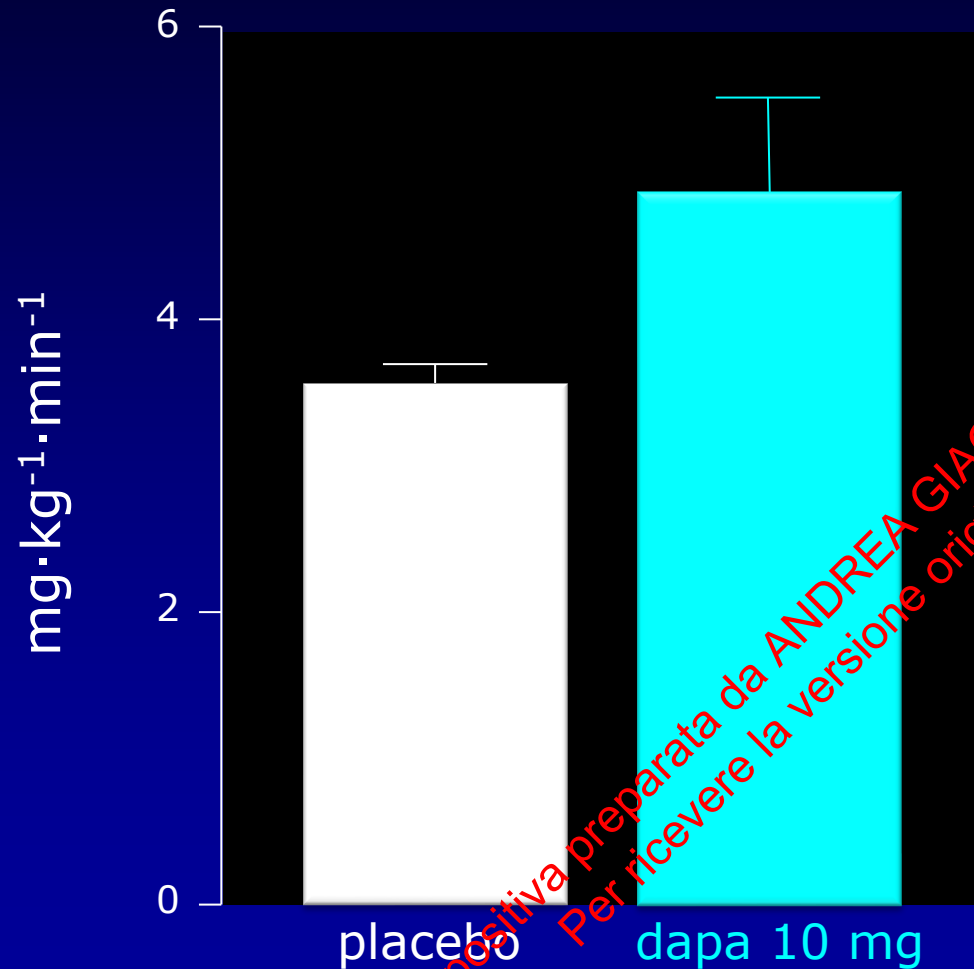


resting MBF before
stress MBF before
resting MBF after
stress MBF after

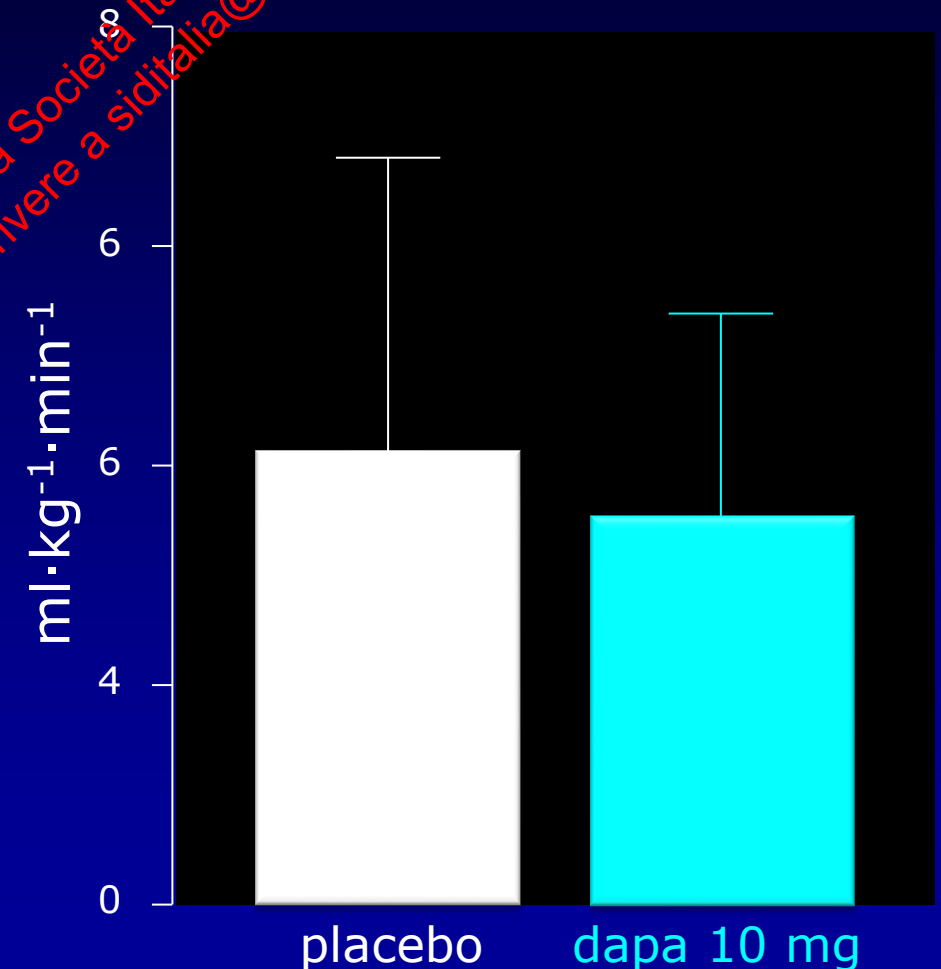


SGLT-2i DO NOT improve myocardial glucose uptake

Whole Body Glucose Uptake

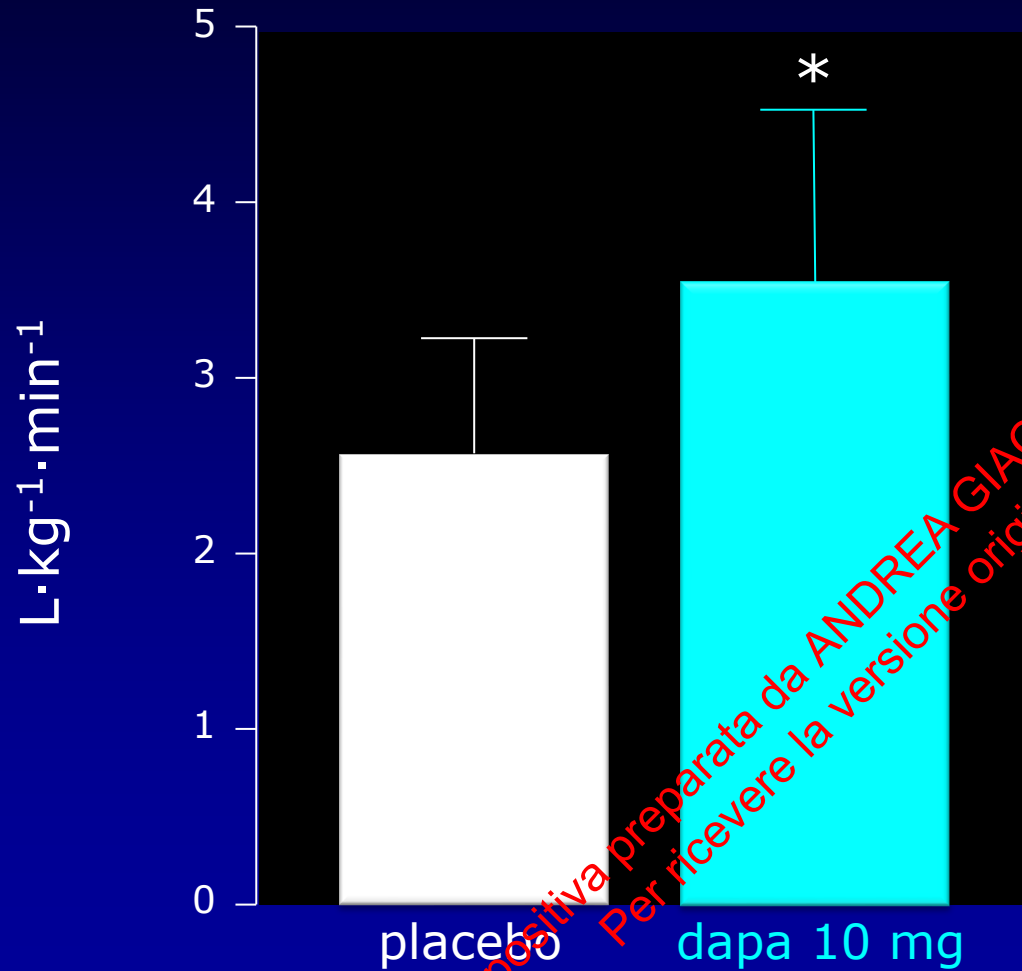


Myocardial Glucose Uptake

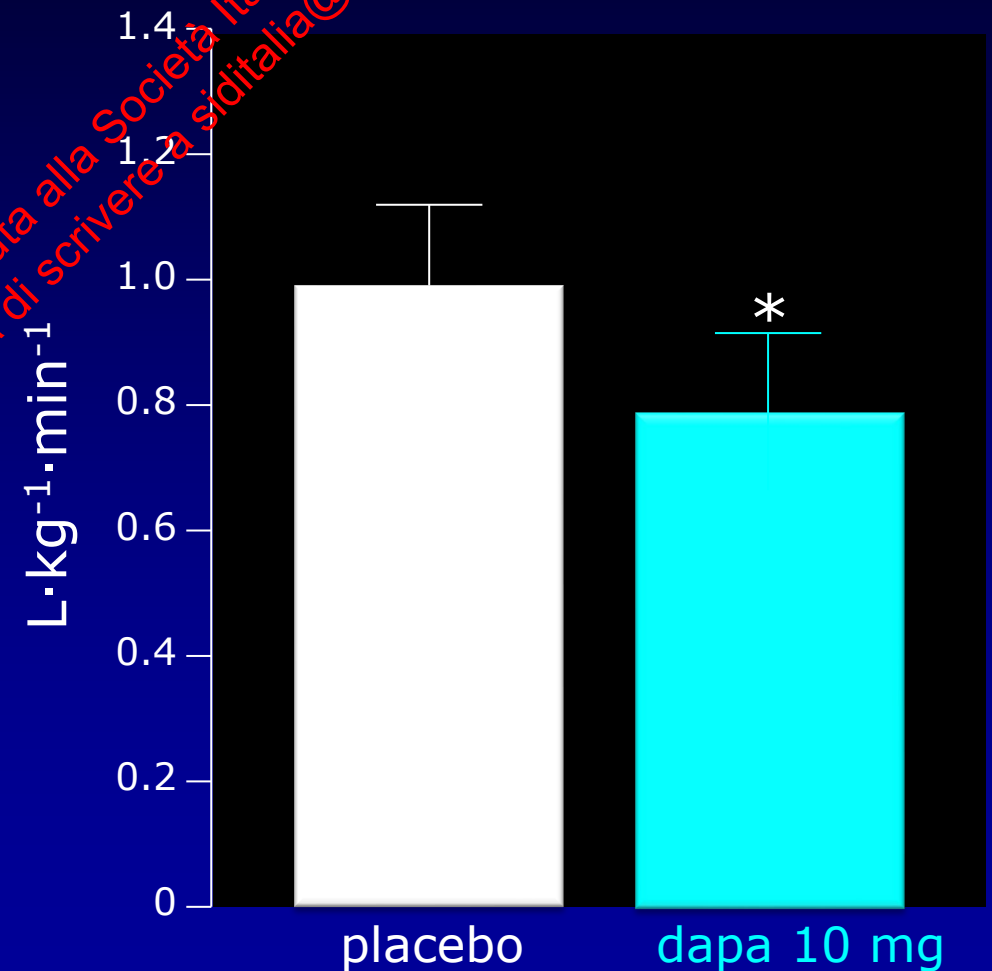


SGLT-2i improve myocardial blood flow

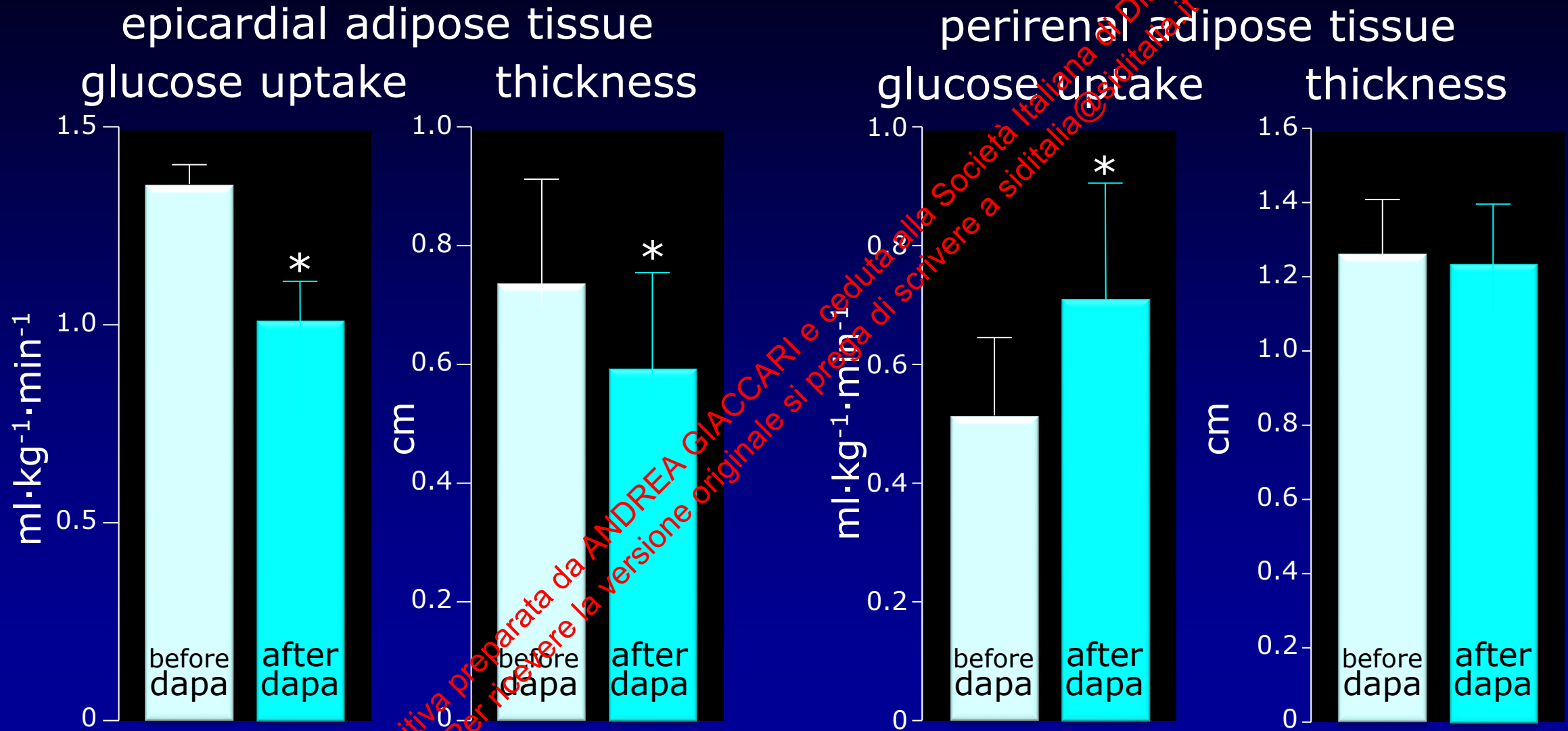
Coronary Flow Reserve



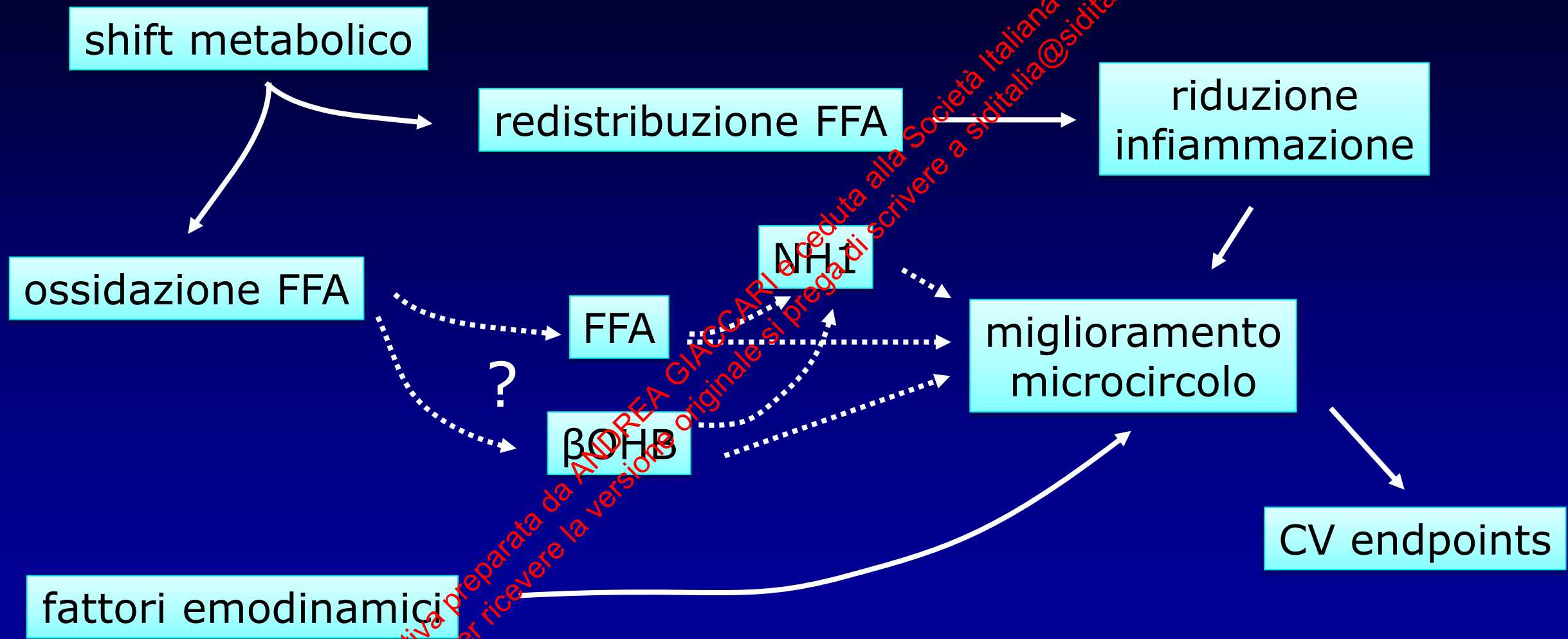
resting MBF



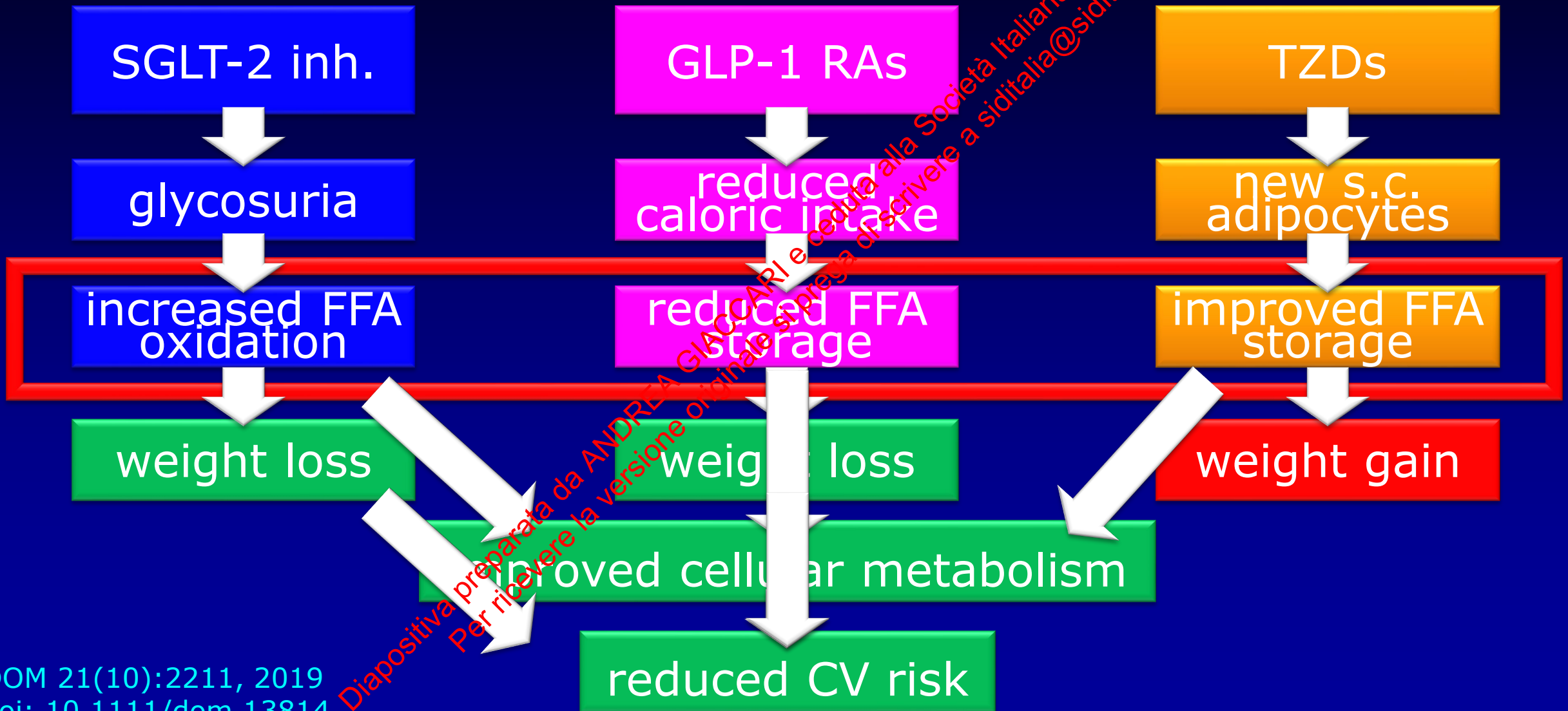
SGLT-2i modify adipose tissue metabolism



possibili meccanismi



reduced caloric overflow (fasting) to improve CV risk



Umberto

Valentina

Simona

Francesca

Flavia

Ilaria

Erminia

Gianfranco

Teresa

Serena

Chiara

Gea



Gemelli



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