# Gli SGLT2i: perché farmaci di prima scelta


## IL GIUSTO POSTO DELLE GLIFLOZINE NEL TRATTAMENTO DEL DIABETE DI TIPO 2

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TEAM DIABETE

Gemelli

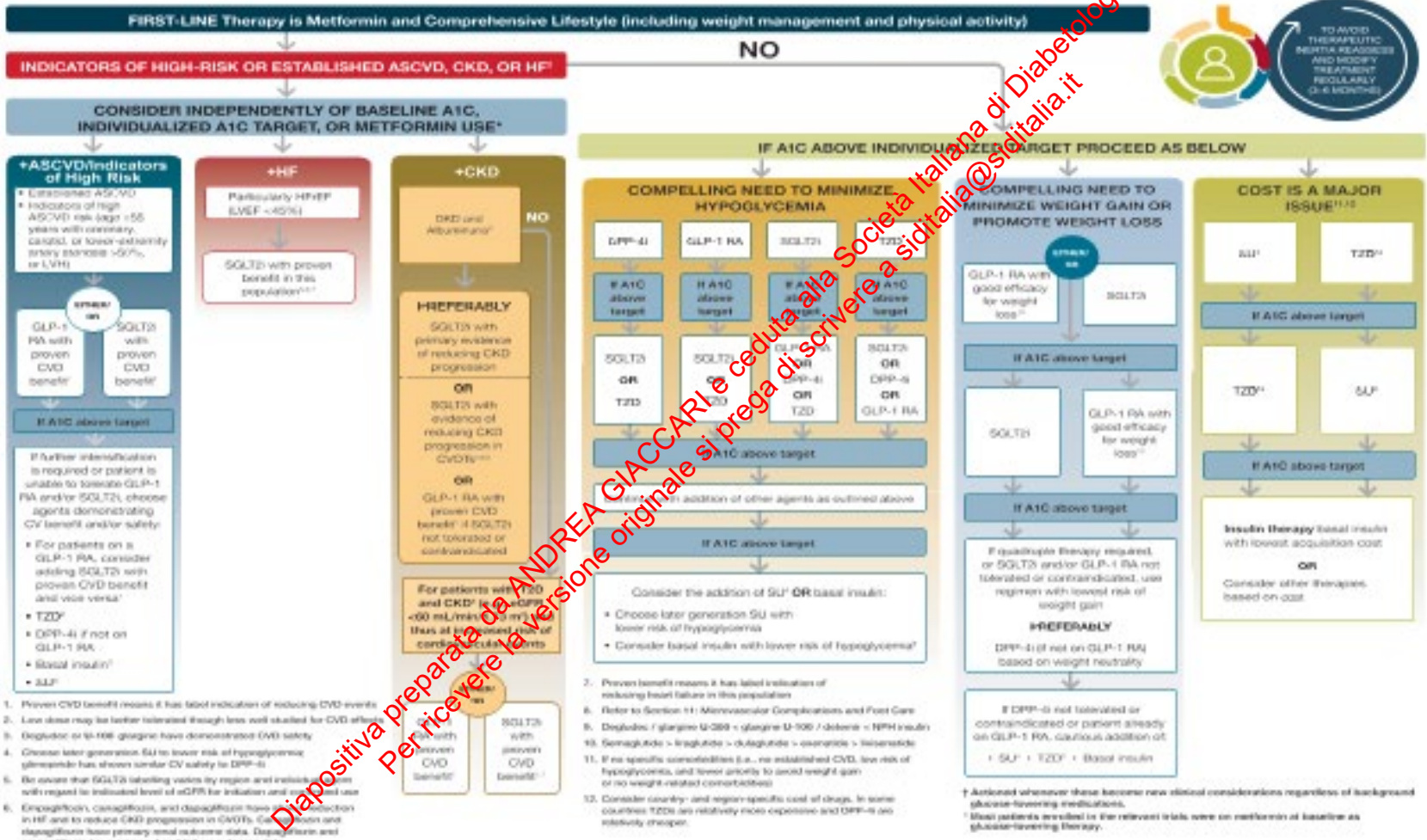
SID Società Italiana di Diabetologia

# DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

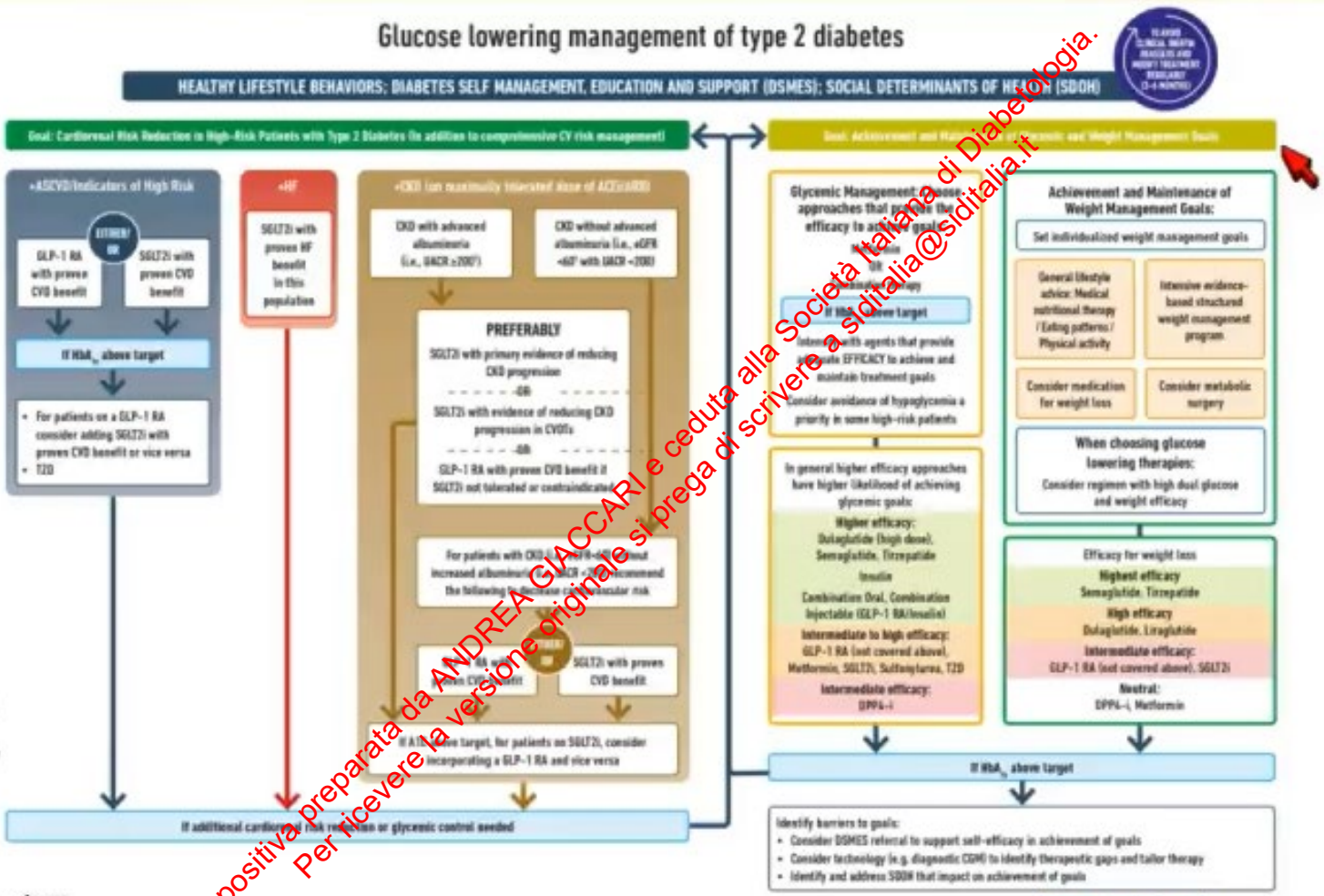
Il sottoscritto prof. Andrea Giaccari dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Eli-Lilly
- MSD
- 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.).



# Glucose lowering management of type 2 diabetes




UACR = Urine albumin-to-creatinine ratio, with units as mg/g
eGFR = estimated glomerular filtration rate, with units as mL/min/1.73m²
CVD = atherosclerotic cardiovascular disease
† = Ensure you follow region specific label for use of SGLT2i at lower eGFR levels



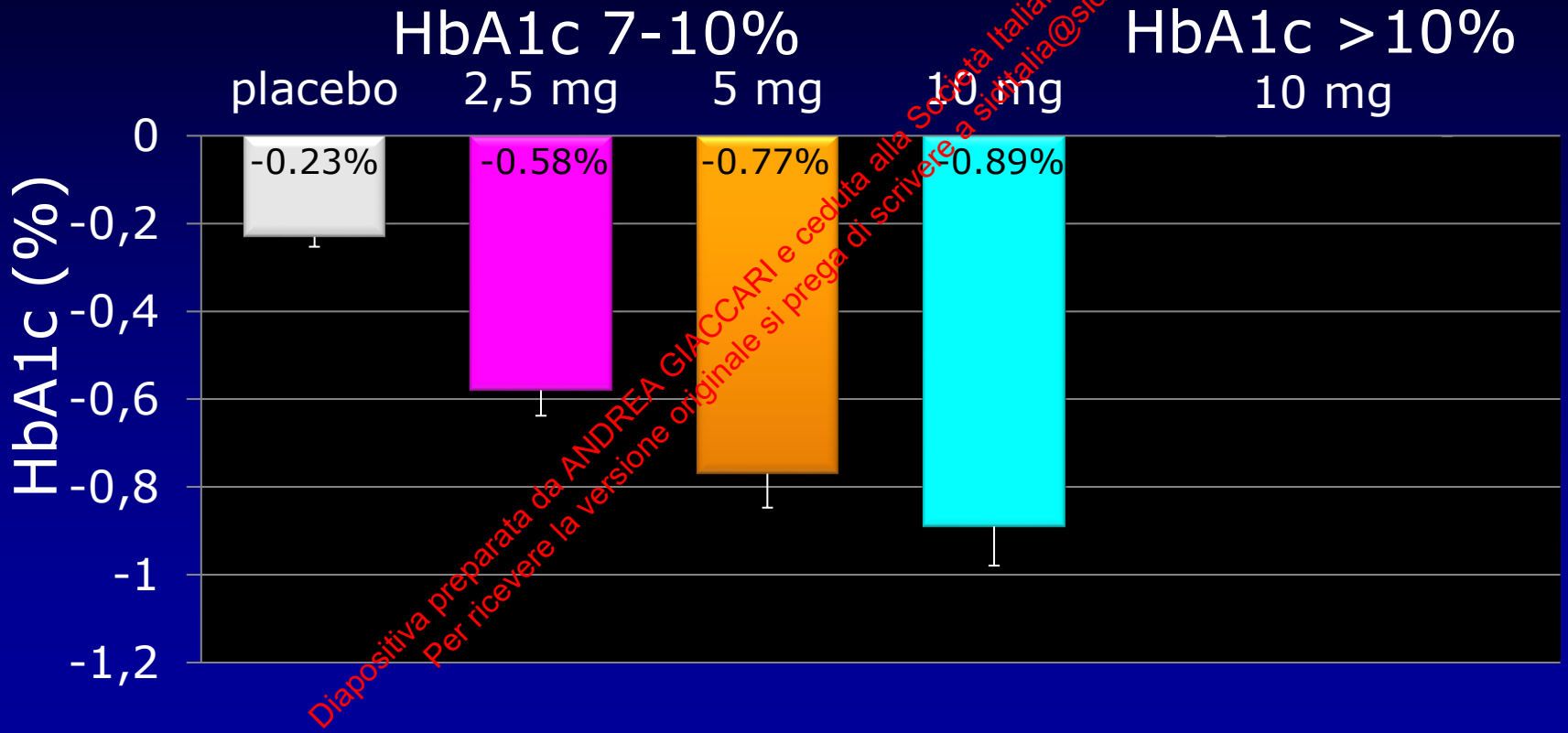


American Diabetes Association.

EASD European Association for the Study of Diabetes

# gliflozin (monotherapy)

## dapagliflozin - drug naïve patients






*Ferrannini E Diabetes Care 33:2217, 2010*

# gliflozin (monotherapy)

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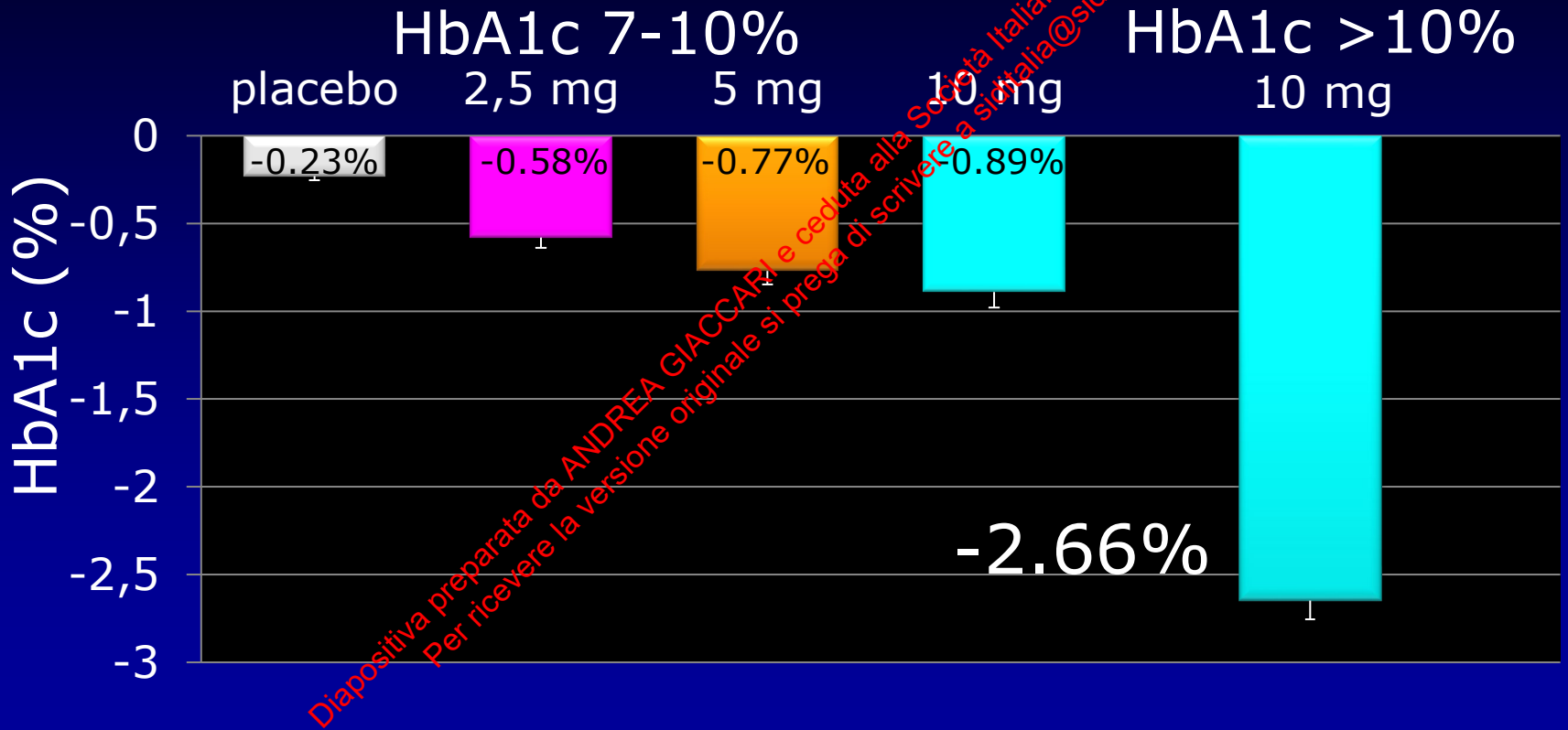




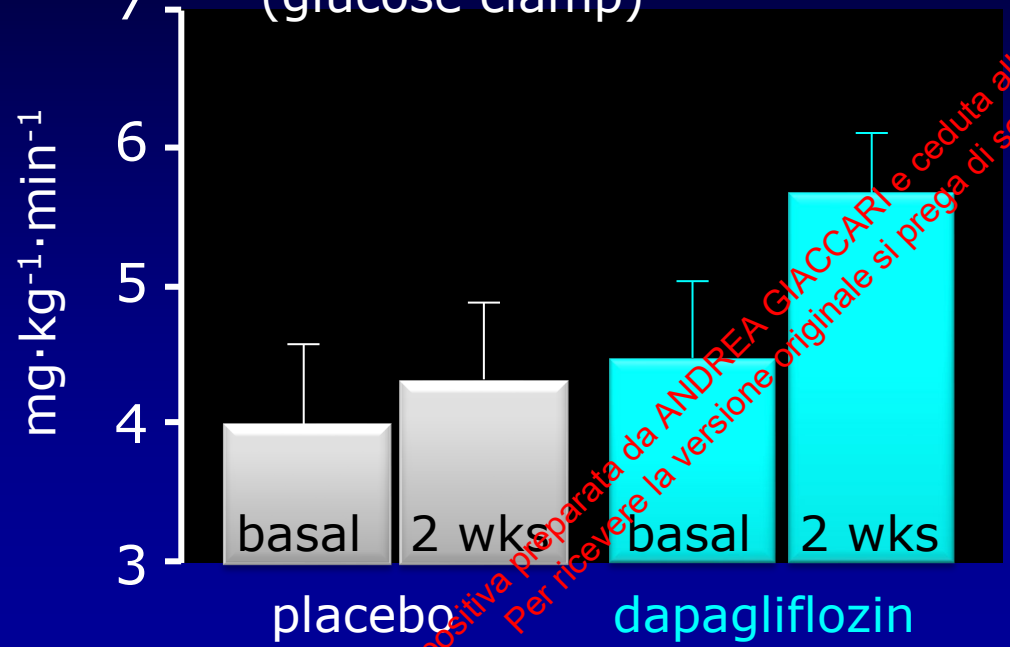

*Ferrannini E Diabetes Care 33:2217, 2010*

# gliflozins act on glucose toxicity

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

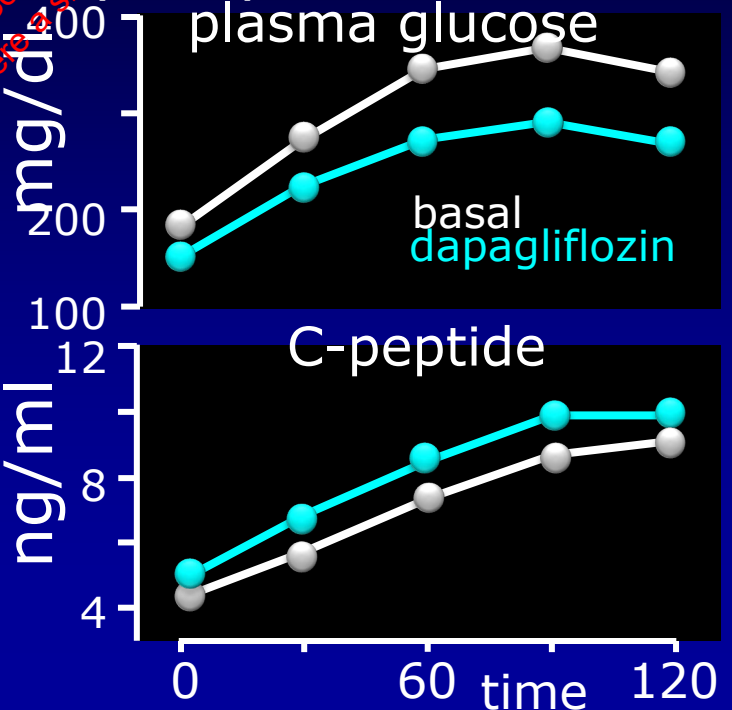
## insulin sensitivity

(glucose clamp)




## insulin secretion

(OGTT)

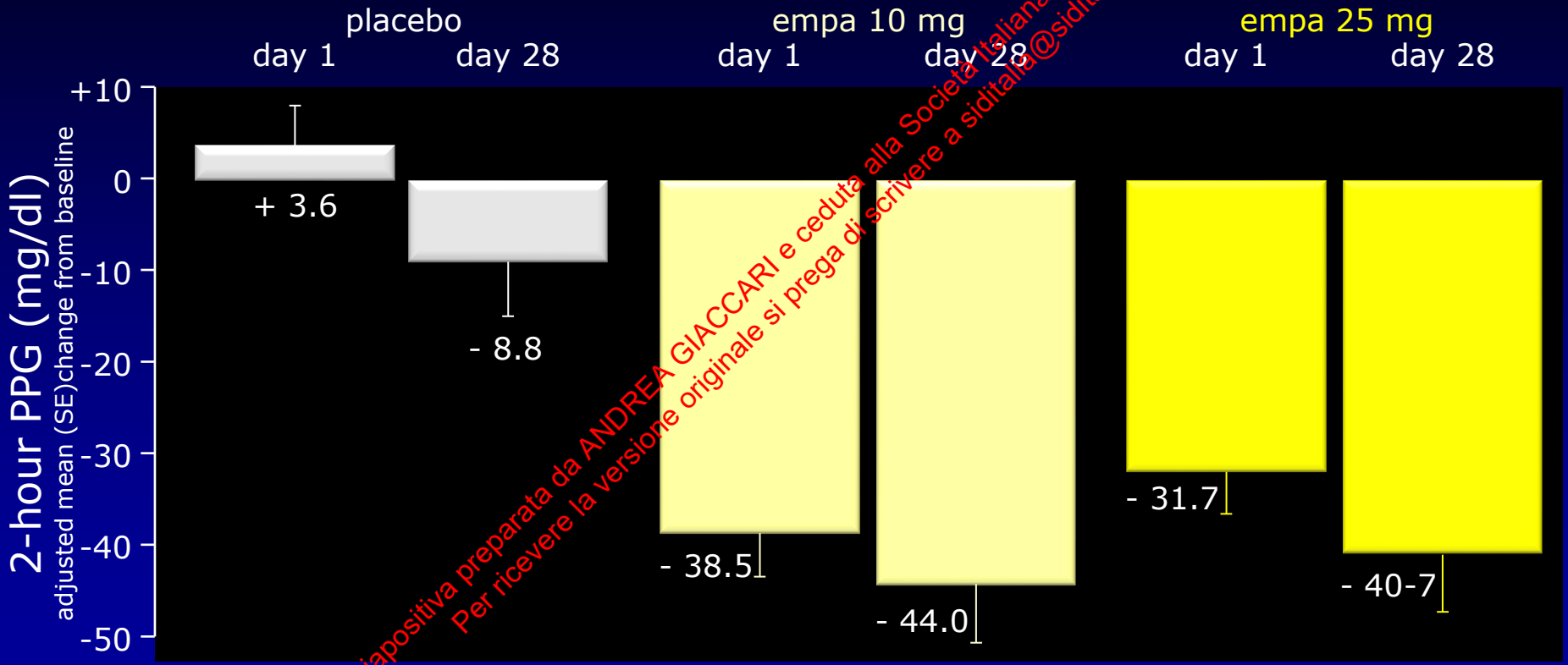





*Merovci A et al.: JCI 124: 509; 2014*
*Merovci A et al.: JCEM 100:1927; 2015*

# SGLT-2is improve post-prandial glucose

glucose concentration 2h after breakfast - 1 and 28 days of empagliflozin treatment

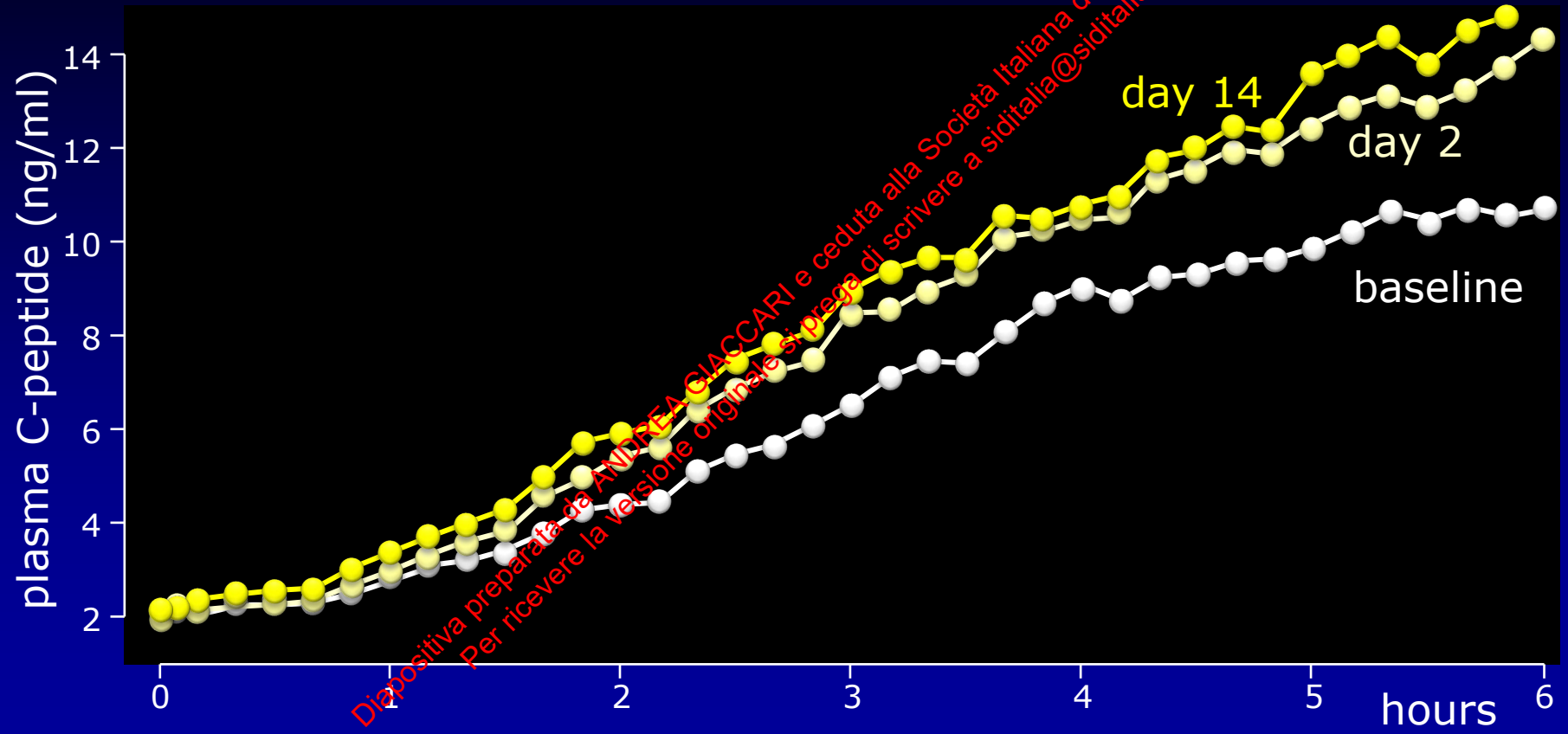





*Nishimura r. et al. Cardiovascular Diabetology 14:11, 2015 doi: 10.1186/s12933-014-0169-9*

# SGLT-2is improve insulin secretion

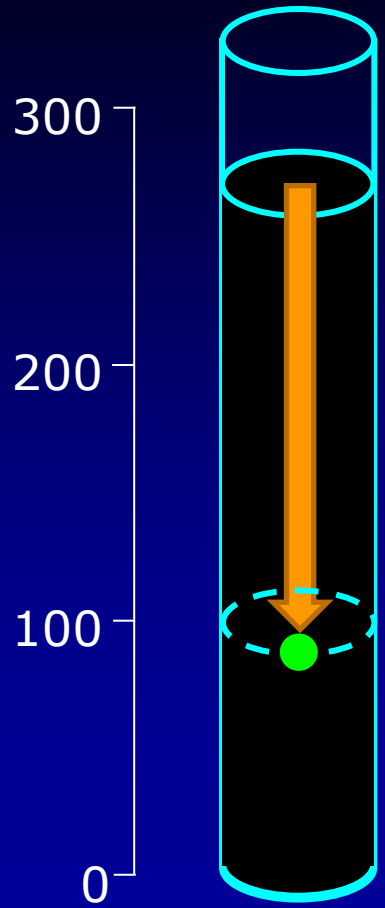
step-wise hyperglycemic clamp after empagliflozin






*Hussein Al Jobori H et al.: JCEM 103:1402, 2018. doi: 10.1210/jc.2017-01838*

# flux in glycosuria




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

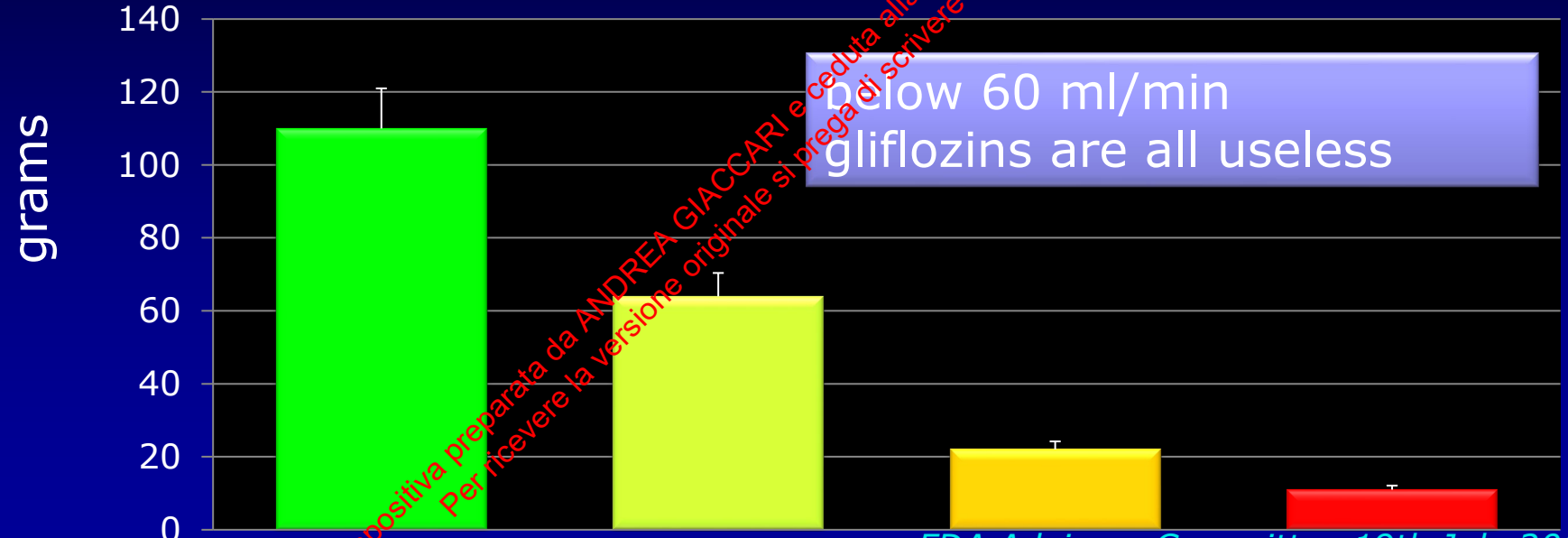
1. glycaemia
2. renal function (eGFR)

when blood glucose reaches normal values glycosuria is compensated by endogenous glucose production

# gliflozins in CKD

## 24 h glycosuria according to eGFR

eGFR: > 90 60-90 30-59 < 30

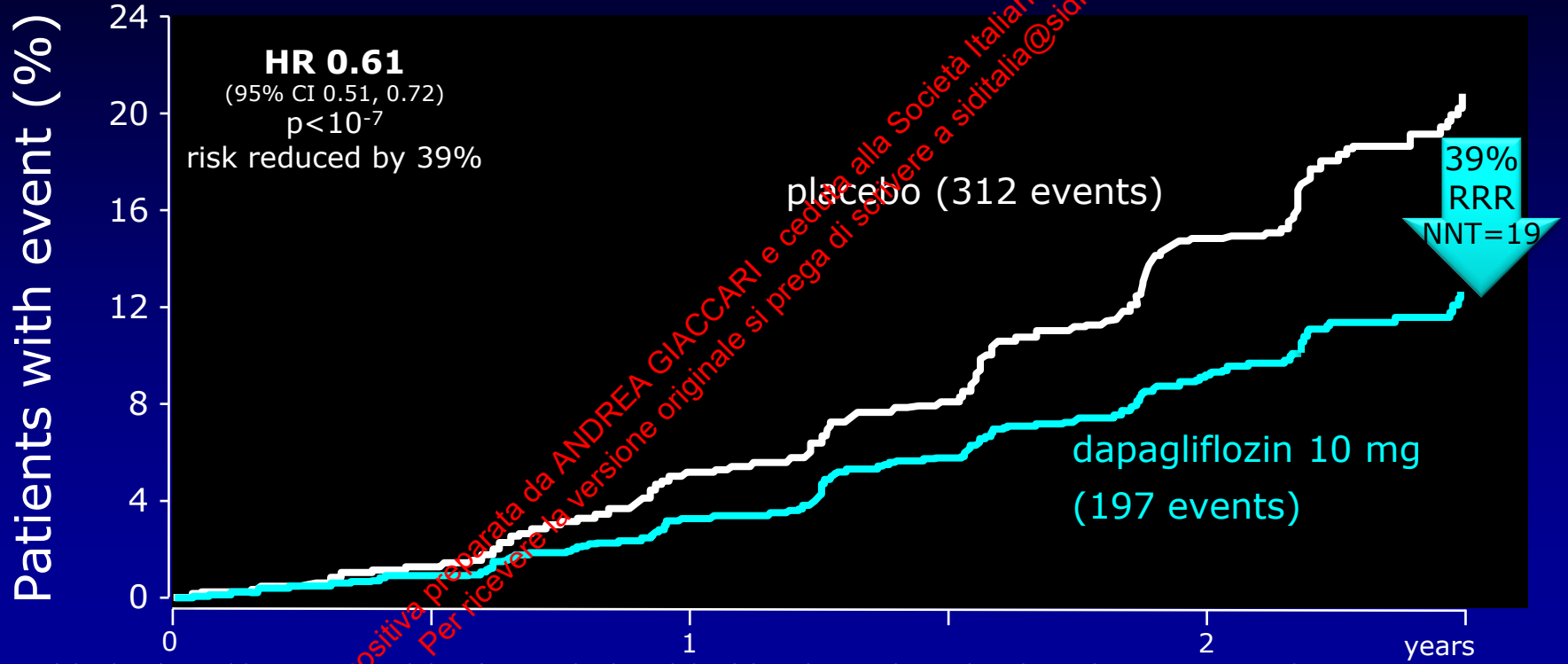





*FDA Advisory Committee 19th July 2011:*
*http://www.fda.gov*

# DAPA-CKD: primary composite renal

## Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death*

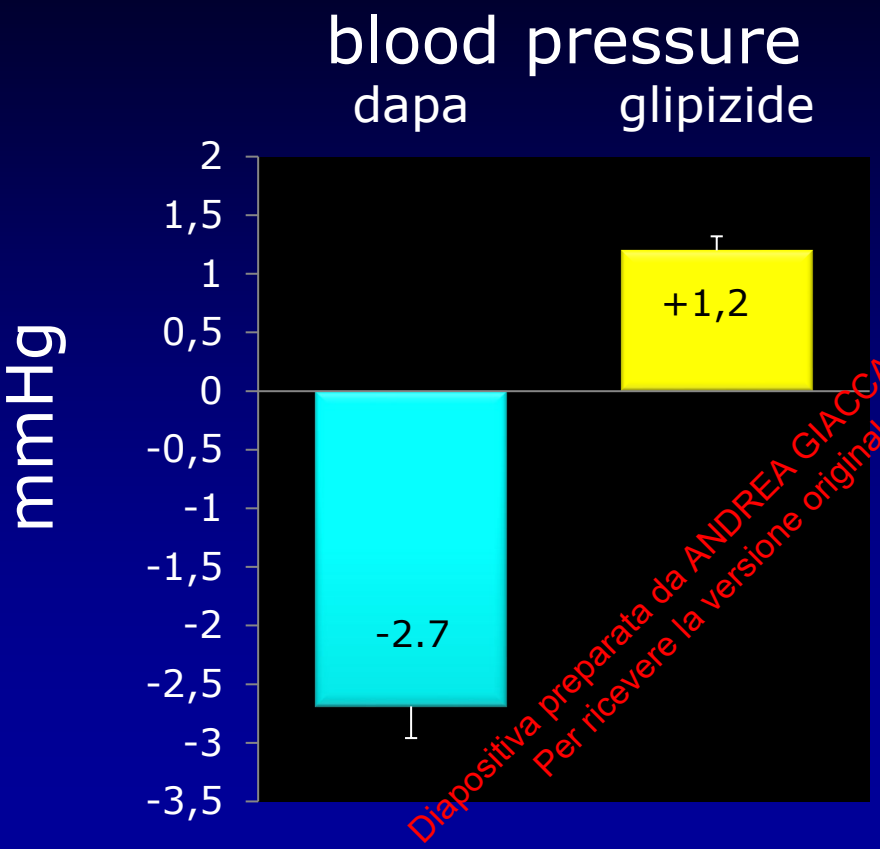


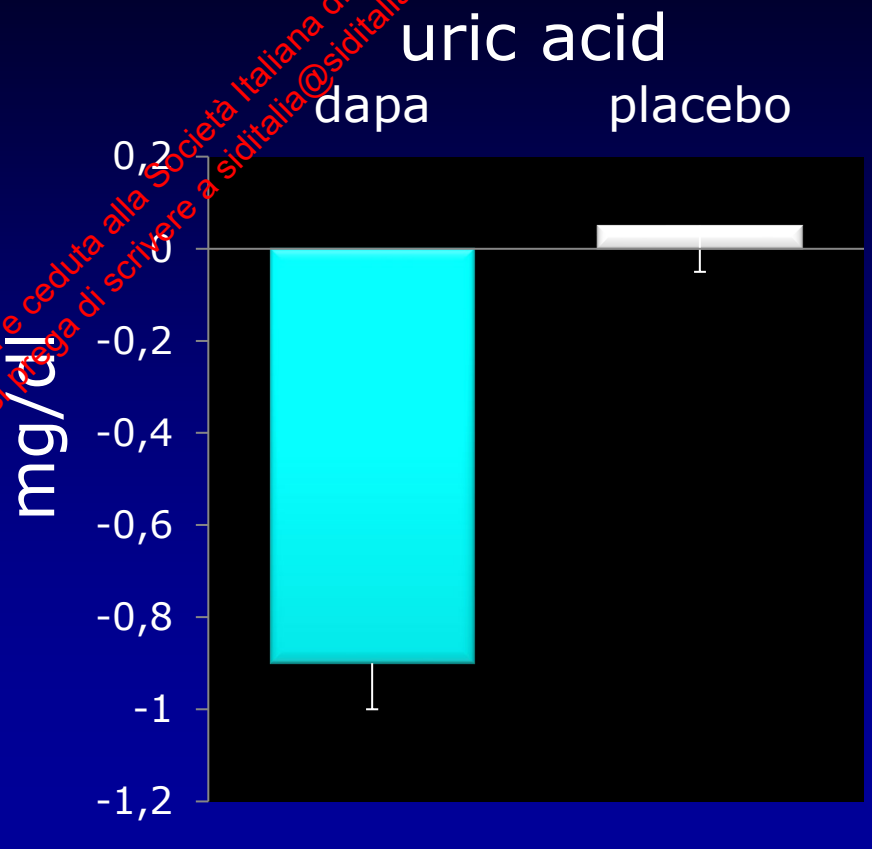



*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld

*Heerspink HJL et al.: Nephrol Dial Transplant. 35:274, 2020*

# SGLT-is: effect on Blood Pressure and Uric Ac.

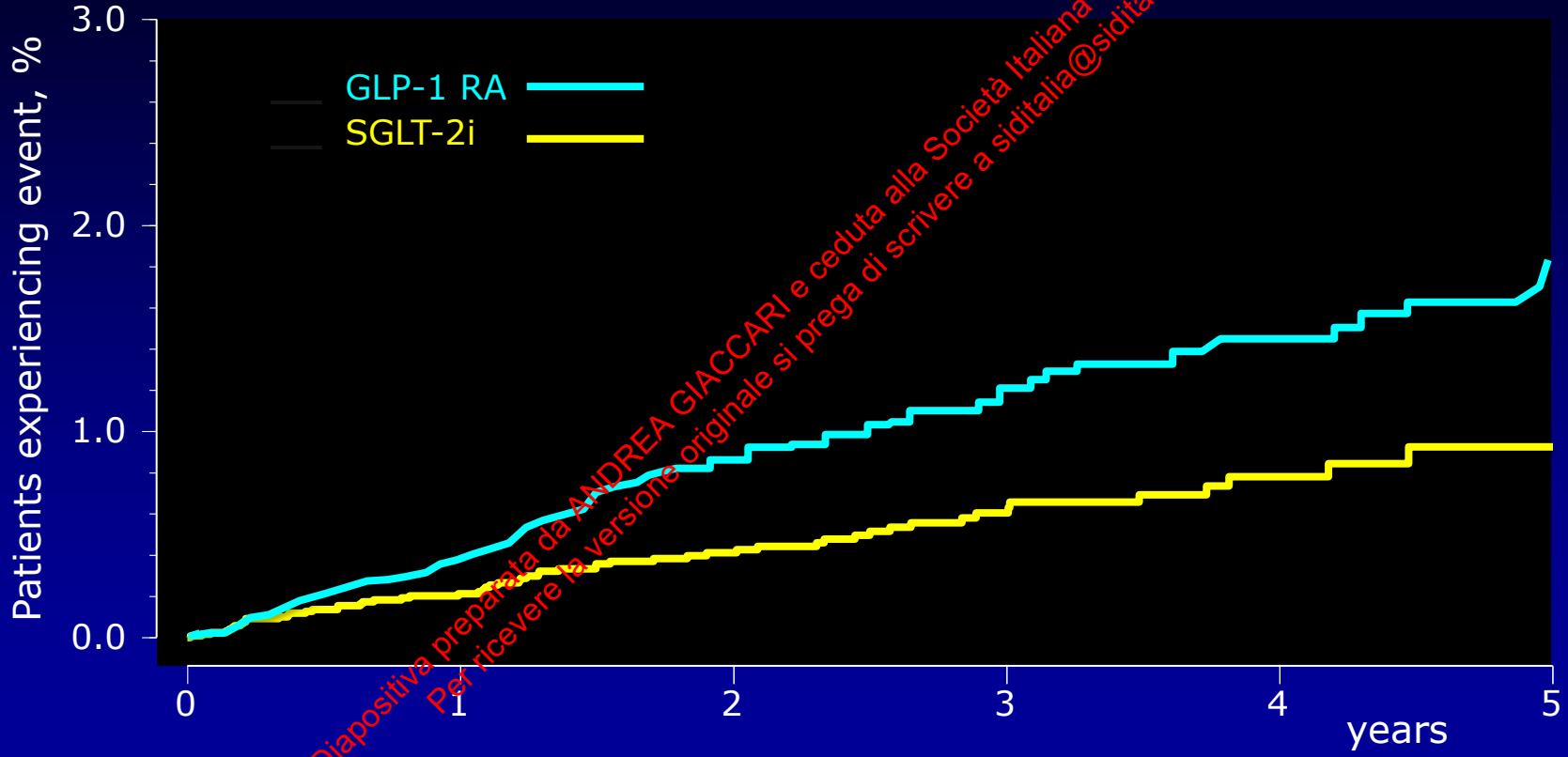





*Nauck et al. DOM 16:1111, 2014*

# SGLT-2is reduce nephrolitiasis

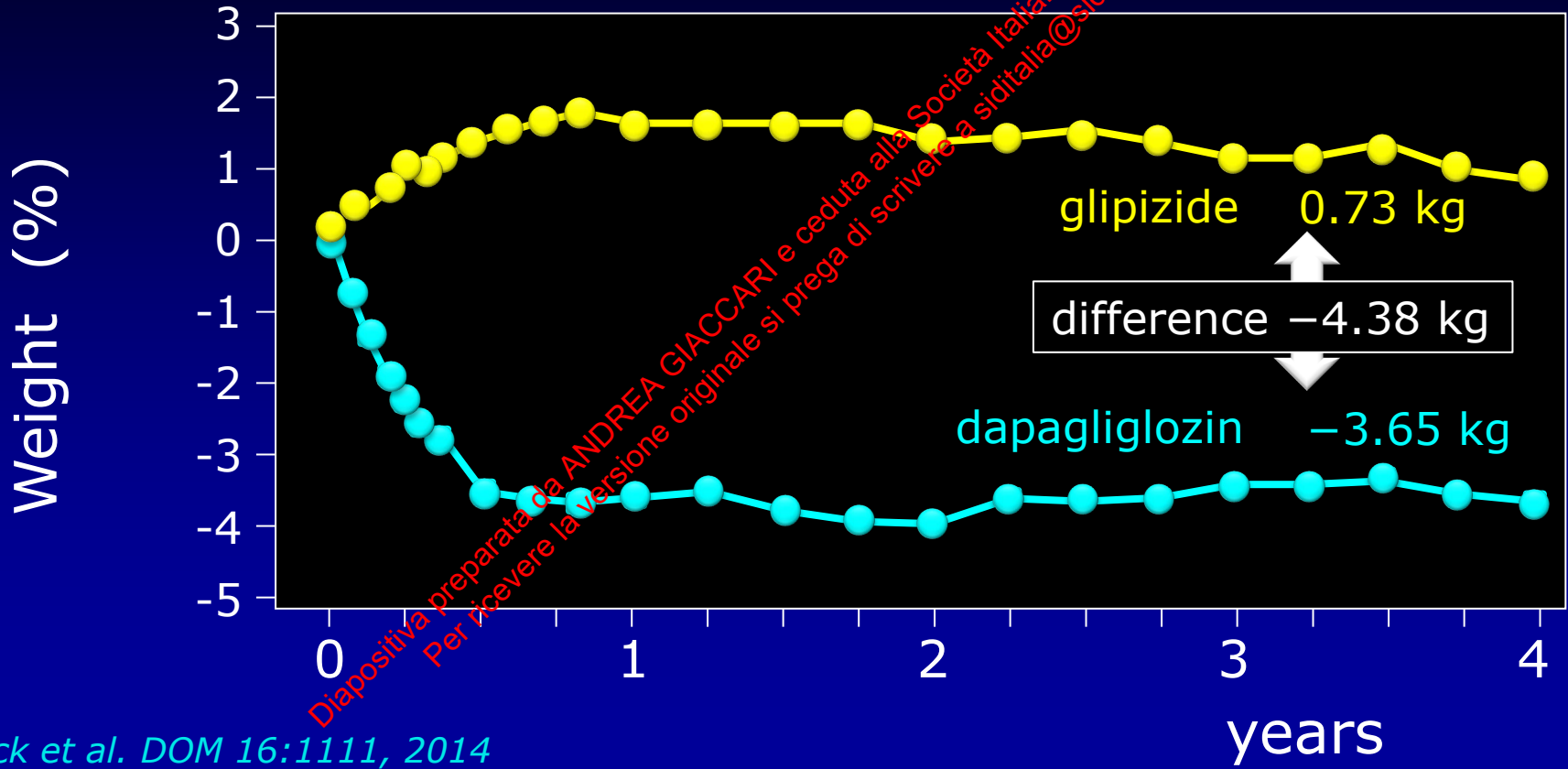





*Kristensen KB et al.: Diabetologia 64:1563, 2021 doi: 10.1007/s00125-021-05424-4*

# gliflozins induce stable weight loss

(met ≥ 1.500 mg, dapa ≤ 10 mg, glipizide ≤ 20 mg)

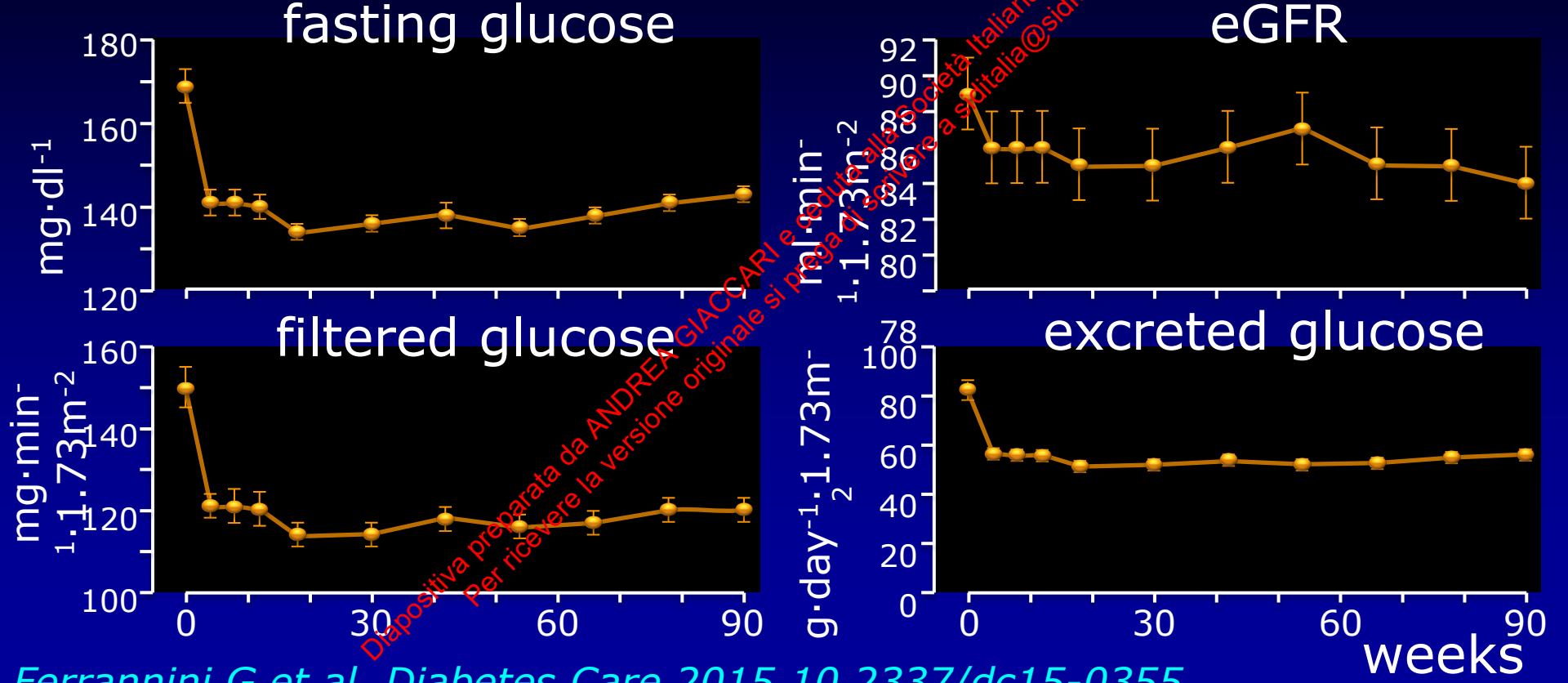





*Nauck et al. DOM 16:1111, 2014*

# estimated glucose loss with SGLT2i

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

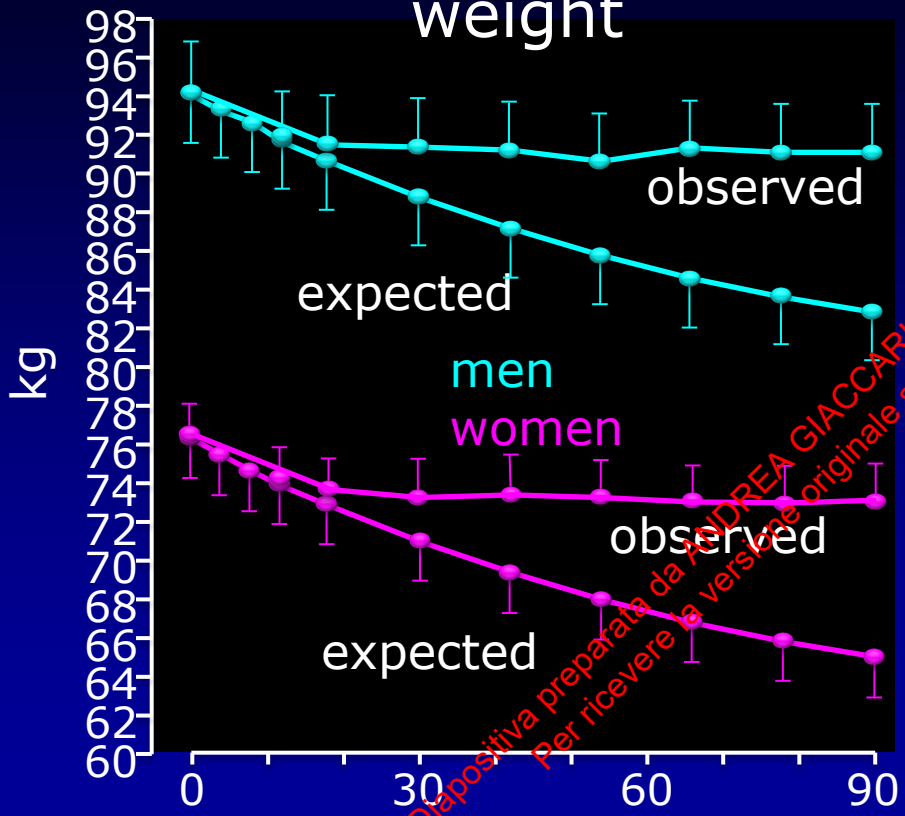


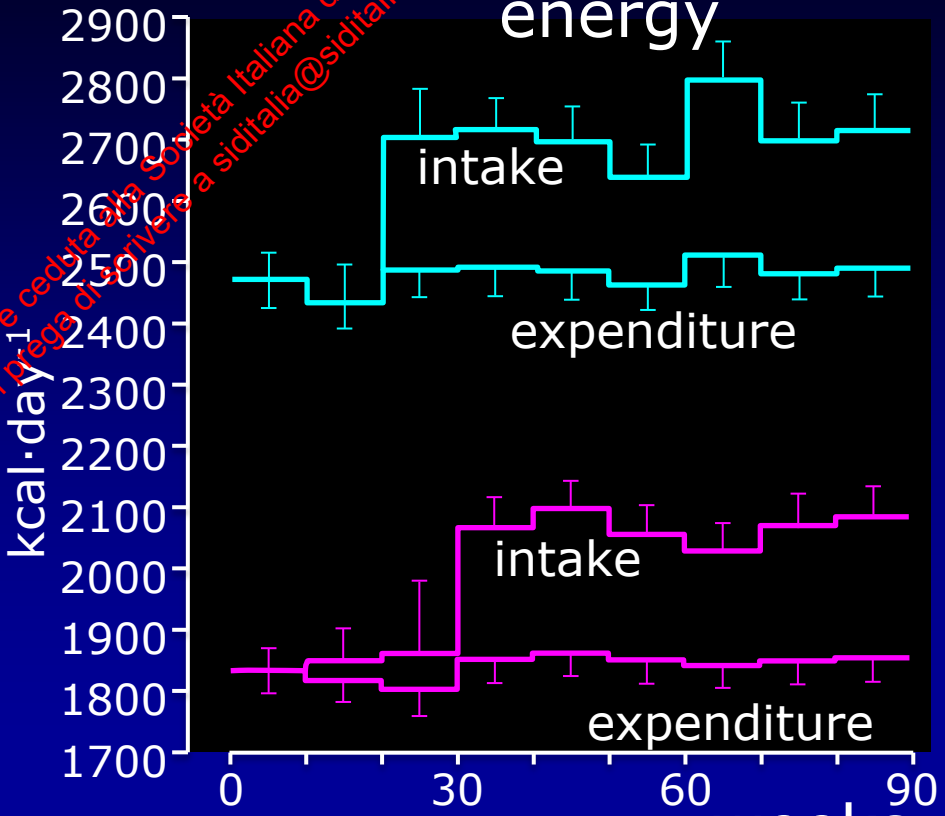



*Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355*

# energy balance with SGLT2i

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

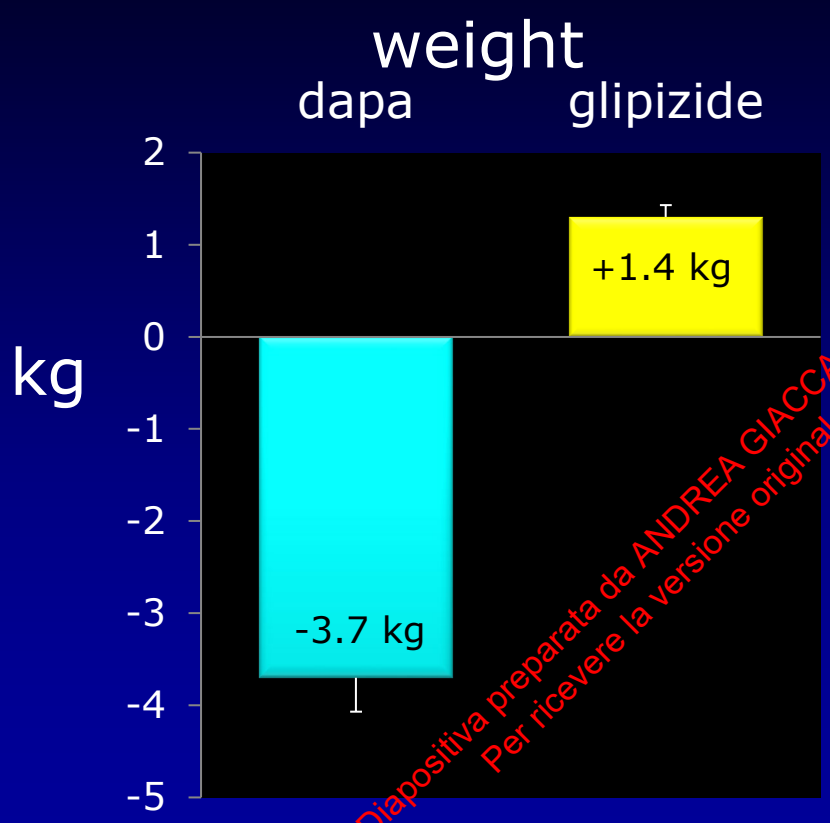


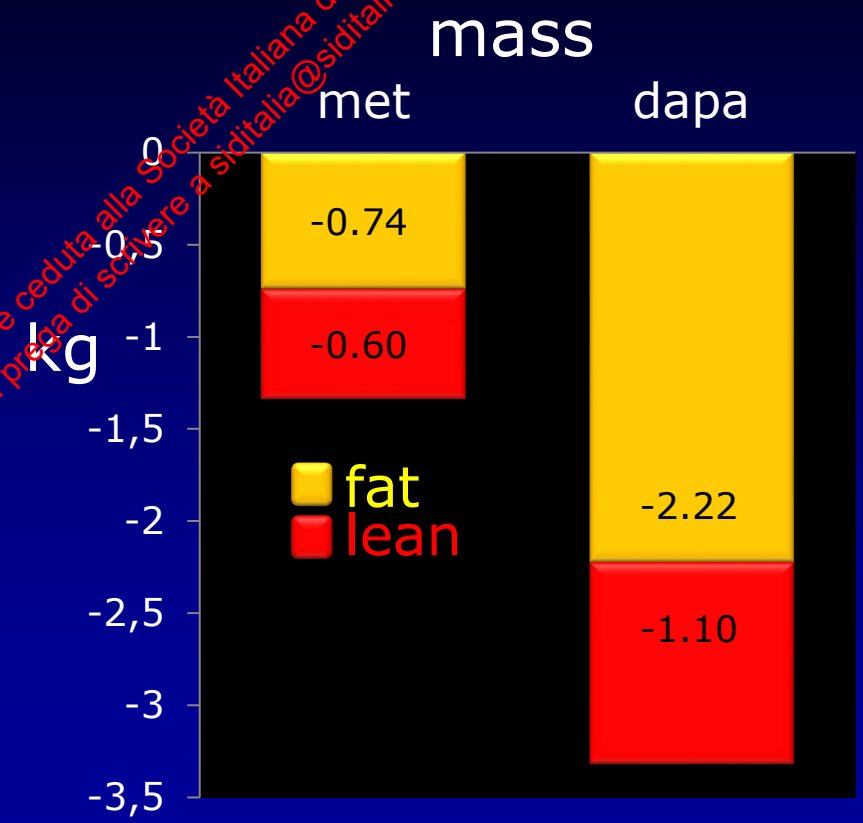






*Ferrannini G et al, Diabetes Care 2015 10.2337/dc15-0355*

# SGLT-is mostly reduce fat mass

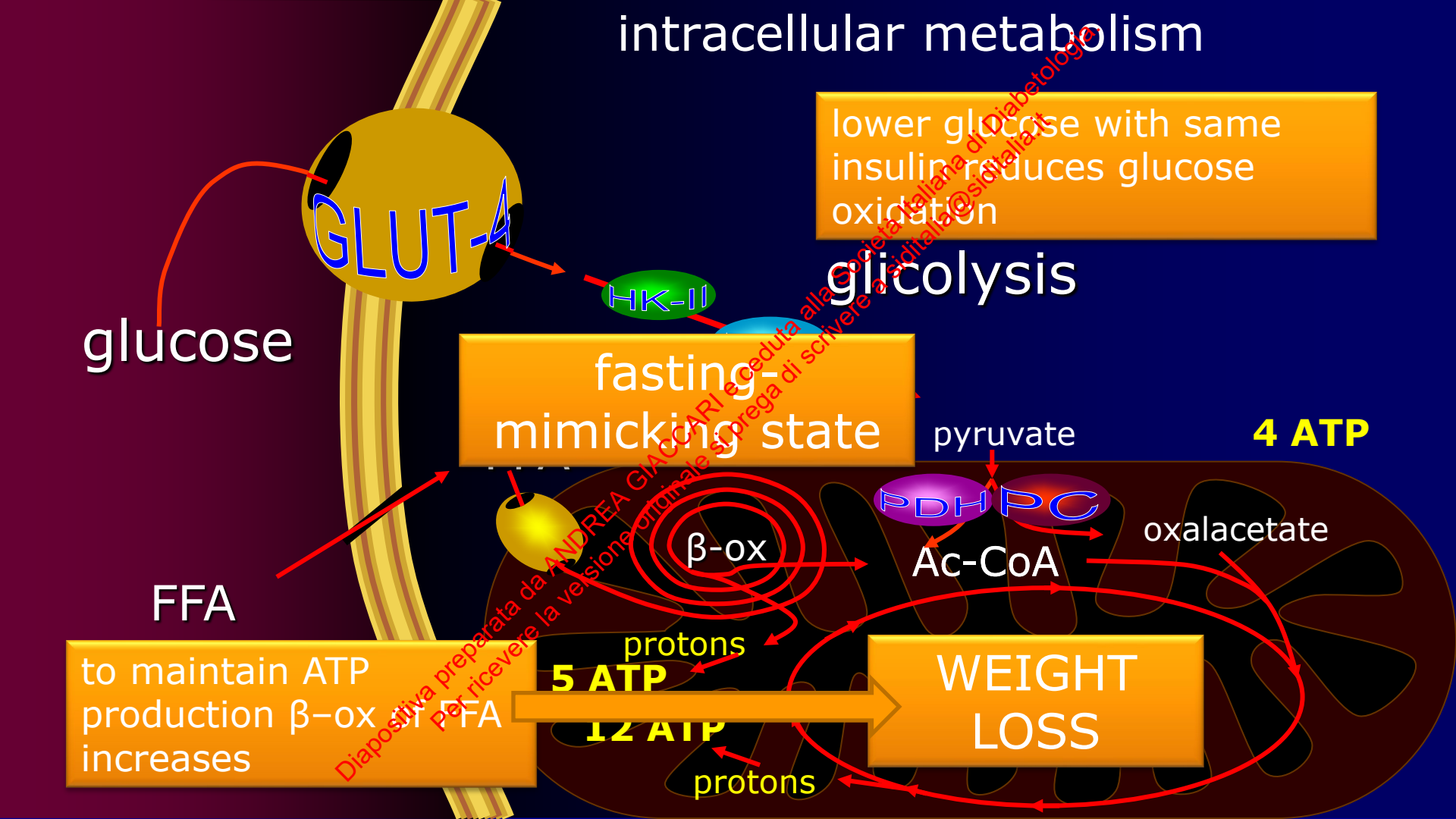




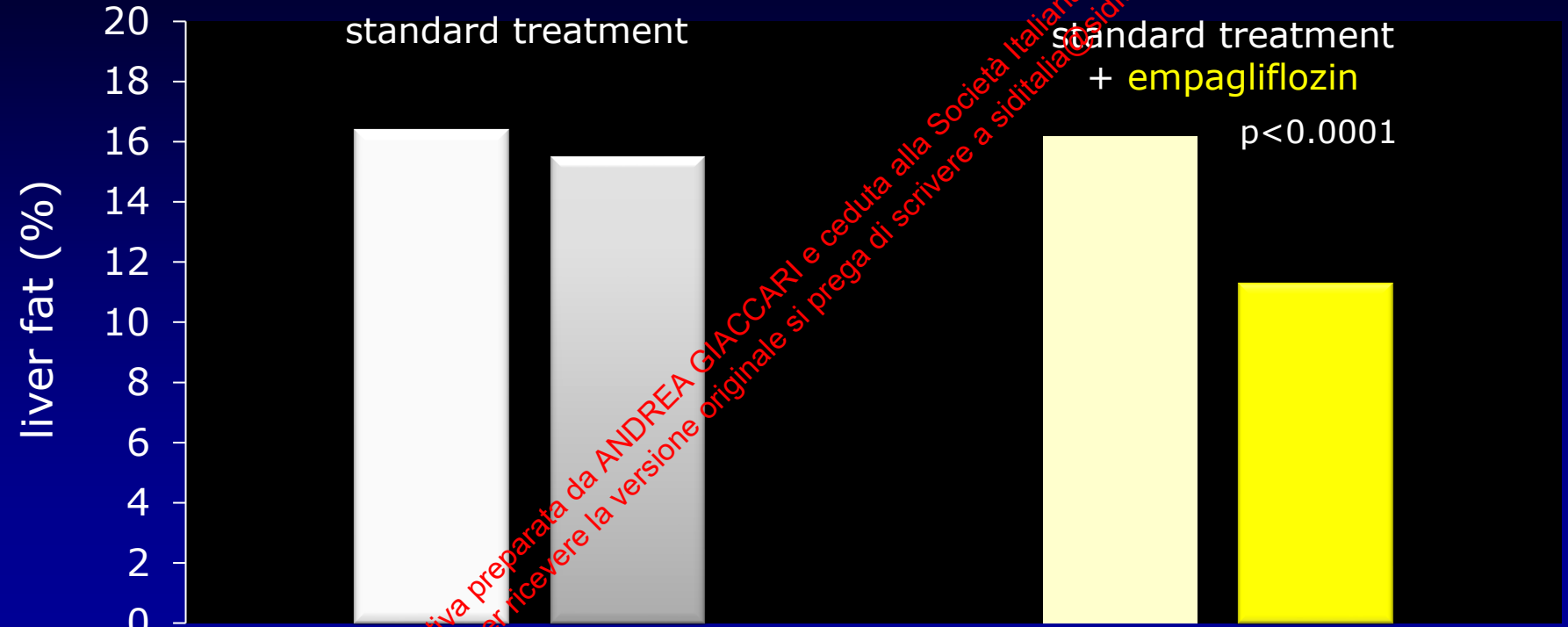

*Nauck et al. DOM 16:1111, 2014*

*Bolinder et al JCEM 97:1020, 2012*


intracellular metabolism
lower glucose with same insulin reduces glucose oxidation
glycolysis
GLUT-4
HK-II
glucose
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 scrivere a sidit@sidit.it

# SGLT-2is reduce liver fat

change in liver fat relative to baseline as assessed by MRI-PDFF in T2DM

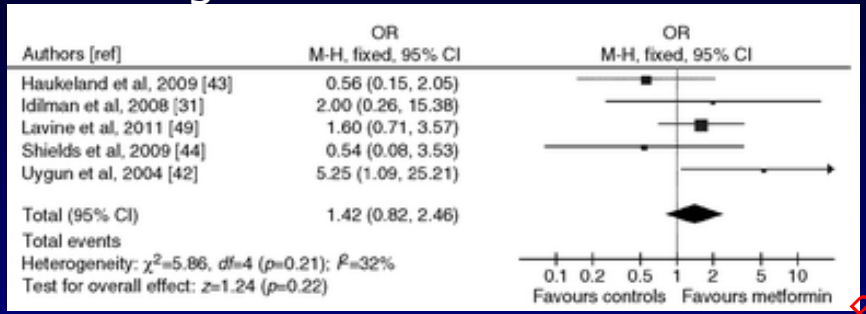




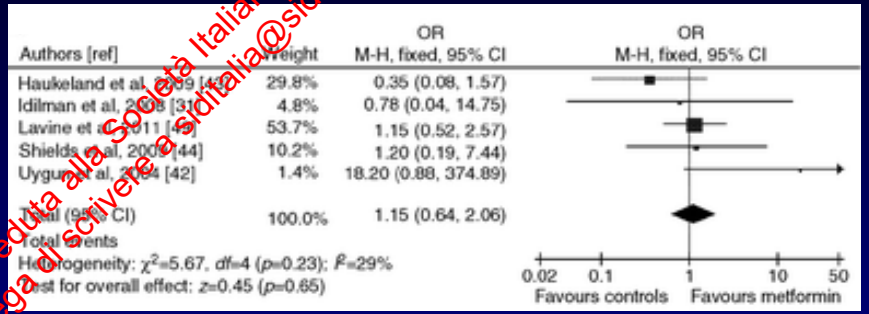

*Shafi Kuchay M. et al.: Diabetes Care 41:1801, 2018 doi: 10.2337/dc18-0165*

# metformin and NASH

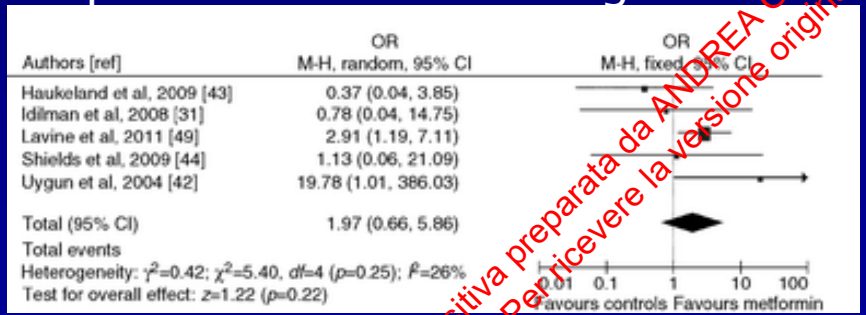
## histological steatosis



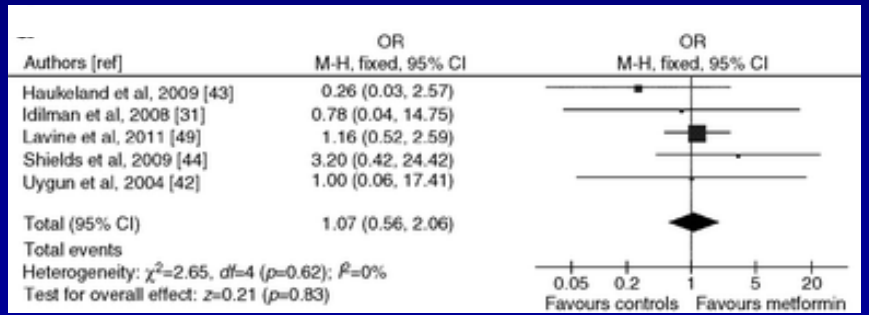

## lobular inflammation




## hepatocellular ballooning



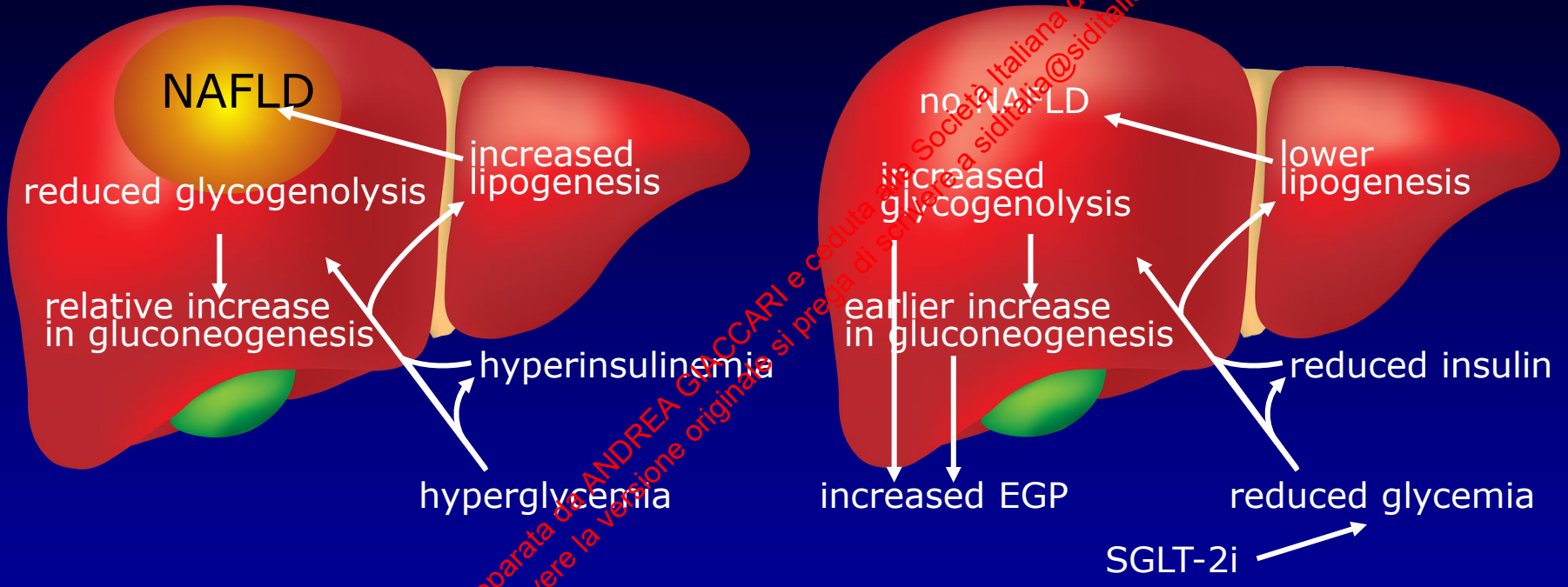

## fibrosis






*Musso G et al.: Diabetologia. 55:885, 2012 doi: 10.1007/s00125-011-2446-4*

# increaased EGP with SGLT-2i is a positive effect

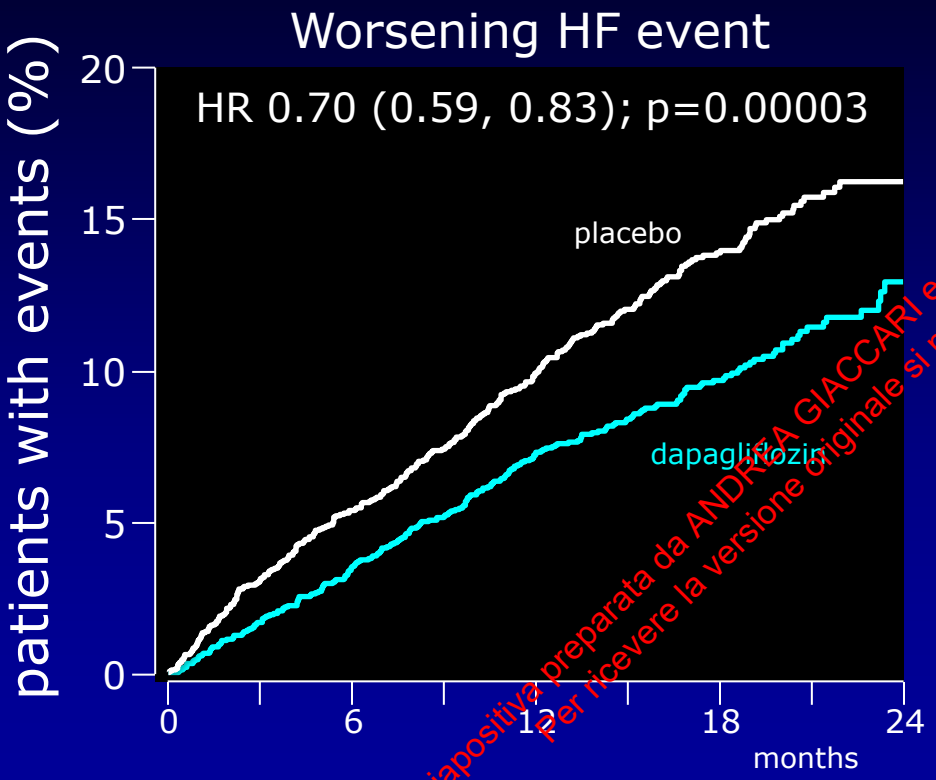


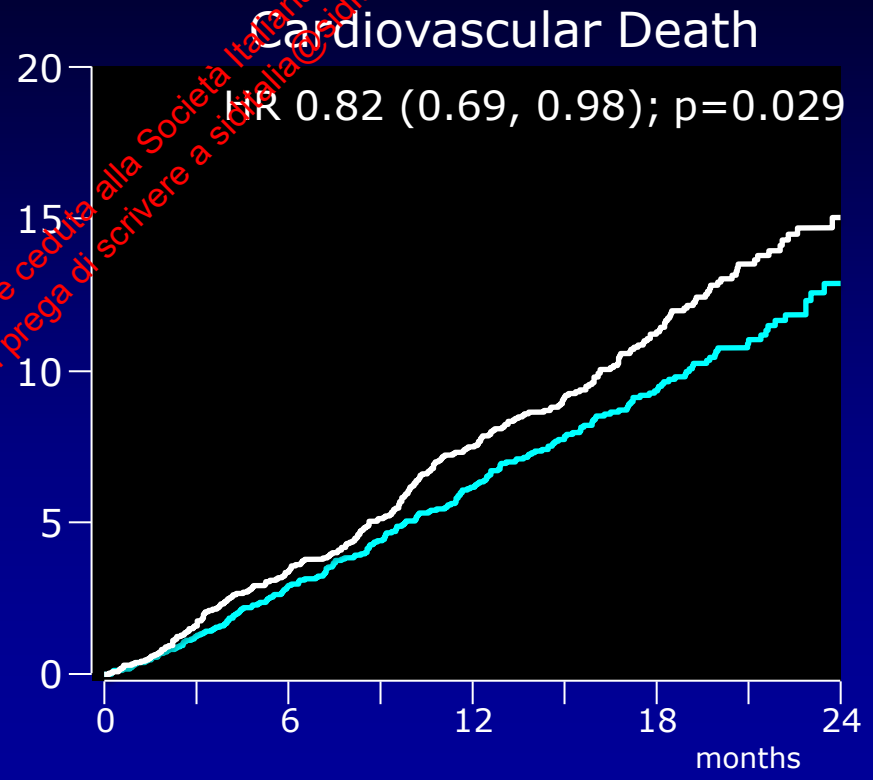



*Giaccari A. Diabetes Care 45:1301, 2022 doi: 10.2337/dci22-0010*

# DAPA-HF: components of primary outcome

## Patients with Heart Failure and Reduced Ejection Fraction



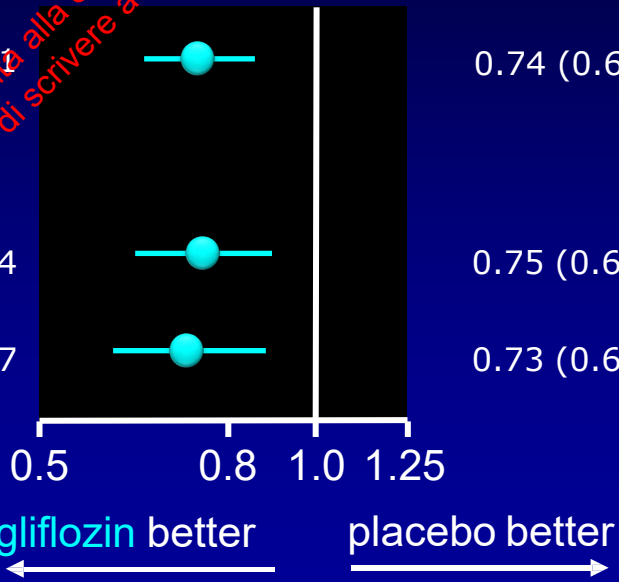






*McMurray JJV et al.: NEJM 2019 Sep 19. doi: 10.1056/NEJMoa1911303*

# DAPA-HF No diabetes/diabetes subgroup in Primary endpoint

| | Dapagliflozin (n=2373) | Placebo (n=2371) | HR (95%CI) |
|---|---|---|---|
| All patients | 386/2373 | 502/2371 | 0.74 (0.65, 0.85) |
| Type 2 diabetes at baseline* | | | |
| Yes | 215/1075 | 271/1064 | 0.75 (0.63, 0.90) |
| No | 171/1298 | 231/1307 | 0.73 (0.60, 0.88) |




*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits

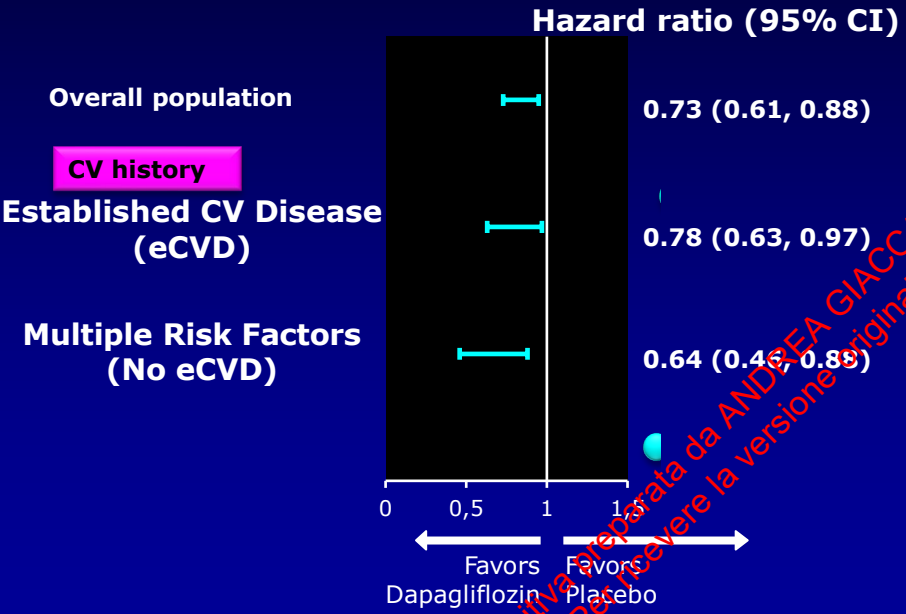


*McMurray JJV et al.: NEJM 2019 Sep 19. doi: 10.1056/NEJMoa1911303*

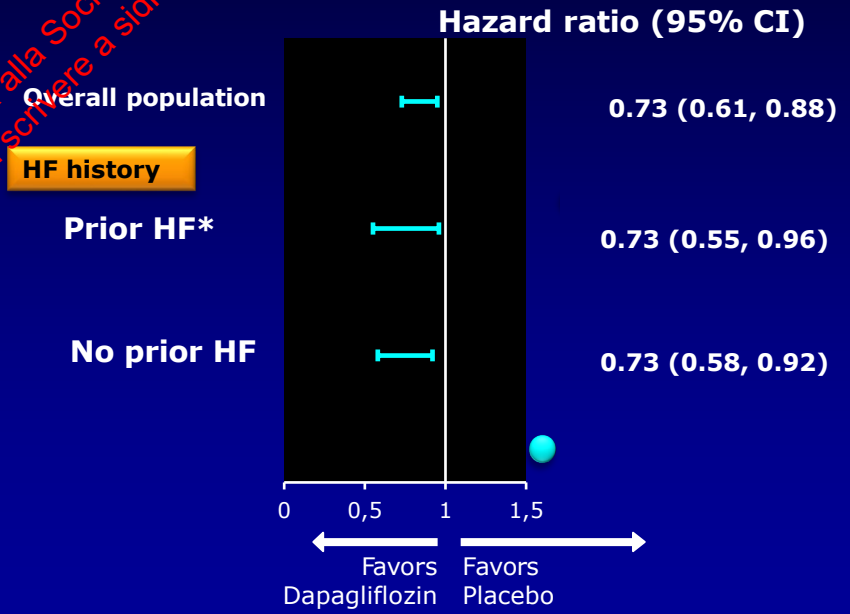
# DECLARE: prevention of hHF
## regardless of history of eCVD or HF



### hHF per **CV** history




### hHF per **HF** history



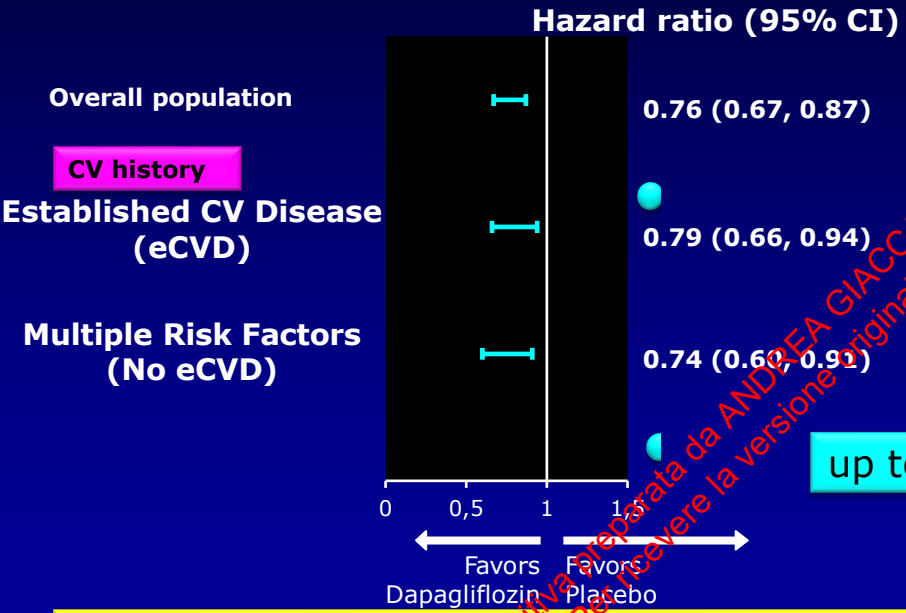

***10% of patients in DECLARE had prior HF**

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

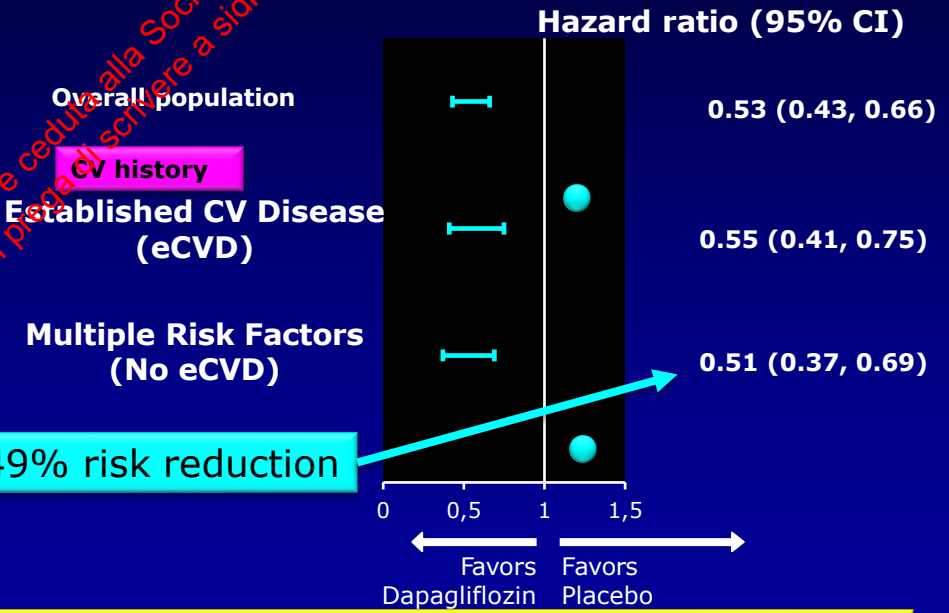
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

# DECLARE: prevention of CKD
## regardless of history of eCVD

composite Renal & CV death




composite Renal




up to 49% risk reduction

composite Renal: composite of ≥40% decrease in eGFRa to <60 mL/min/1.73 m2, ESRD, or renal death

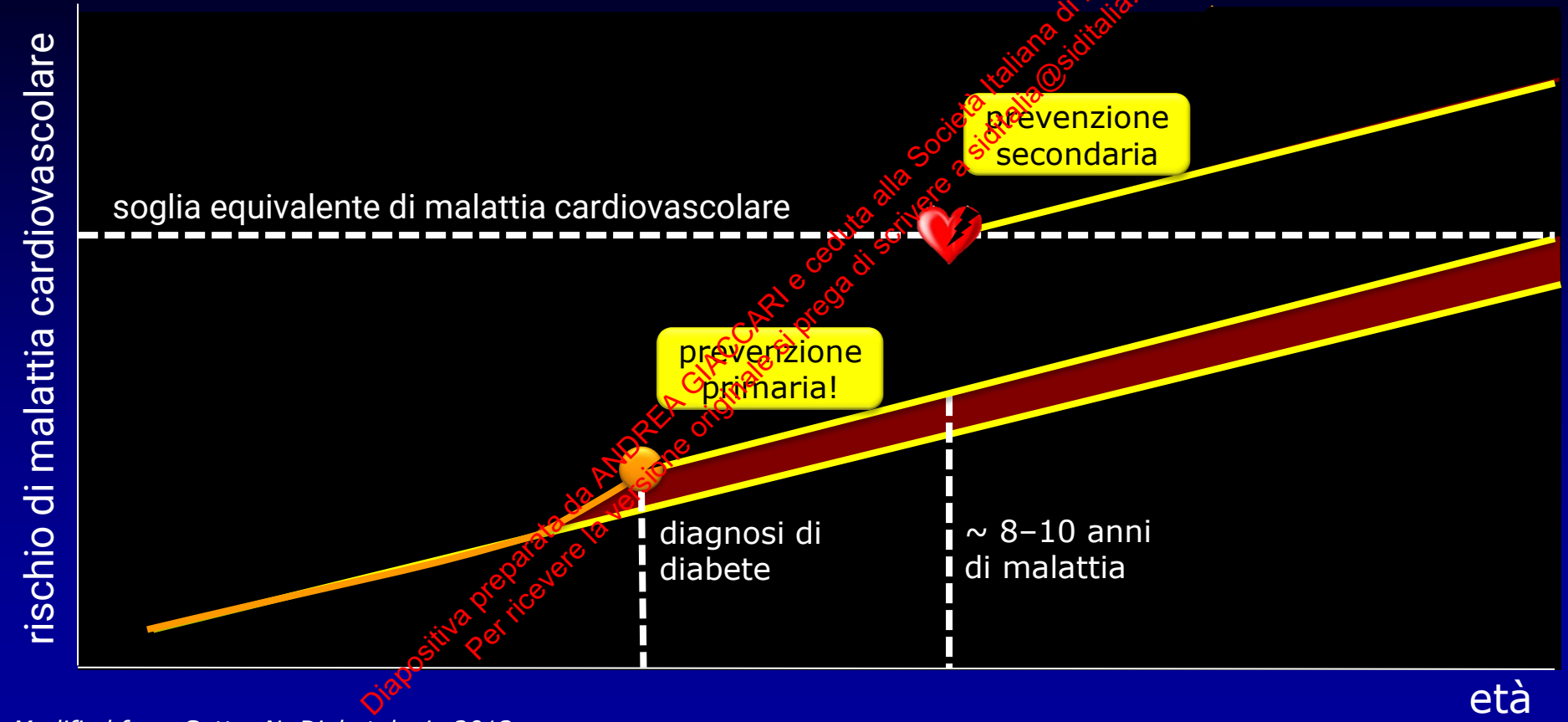
CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

# confronto (indiretto) fra SGLT-2i e metformina

| | metformina | SGLT-2i |
|---|---|---|
| efficacia | +++ | ++ |
| calo ponderale | ++ | ++ |
| gluco-tossicità | + | + |
| insulino-resistenza | ++ | ++ |
| secrezione di insulina | + | + |
| tollerabilità | +/- (GI) | + (Inf. Gen.) |
| aderenza | + | ++ |
| NAFLD | - | ++ |
| prevenzione MACE | +? | + |
| prevenzione HF | - | +++ (primaria) |
| prevenzione CKD | ? | +++ (primaria) |

# Rischio CV prima e durante il decorso del diabete di tipo 2






*Modified from Sattar N, Diabetologia 2013*