

Gli SGLT2i: perché farmaci di prima scelta



Consensus tra esperti con il Metodo DELPHI

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

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Diapositiva preparata da ANDREA GIACCARI e ceduta alla 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
- 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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FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)



INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF*

CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age >55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVD)



If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa²
- TZD³
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- SU⁵

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population^{1,11}

+CKD

DRD and Albuminuria¹²

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

OR

SGLT2i with evidence of reducing CKD progression in CVDi¹³

OR

GLP-1 RA with proven CVD benefit¹ if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD¹⁴ (eGFR <60 mL/min/1.73 m²), thus at increased risk of complications

GLP-1 RA with proven CVD benefit¹

SGLT2i with proven CVD benefit¹

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



If A1C above target

If A1C above target

If A1C above target

If A1C above target

If A1C above target

Consider the addition of SU⁵ OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁴

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



If A1C above target

If A1C above target

If A1C above target

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of

• SU⁵ • TZD³ • Basal insulin

COST IS A MAJOR ISSUE¹¹⁻¹²



If A1C above target

If A1C above target

If A1C above target

Insulin therapy (basal insulin with lowest acquisition cost)

OR

Consider other therapies based on cost

1. Proven CVD benefit means it has robust indication of reducing CVD events
2. Low dose may be better tolerated through less well studied for CVD effects
3. Onglyres or aloglires have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labeling varies by region and individuals differ with regard to tolerated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVDi. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.

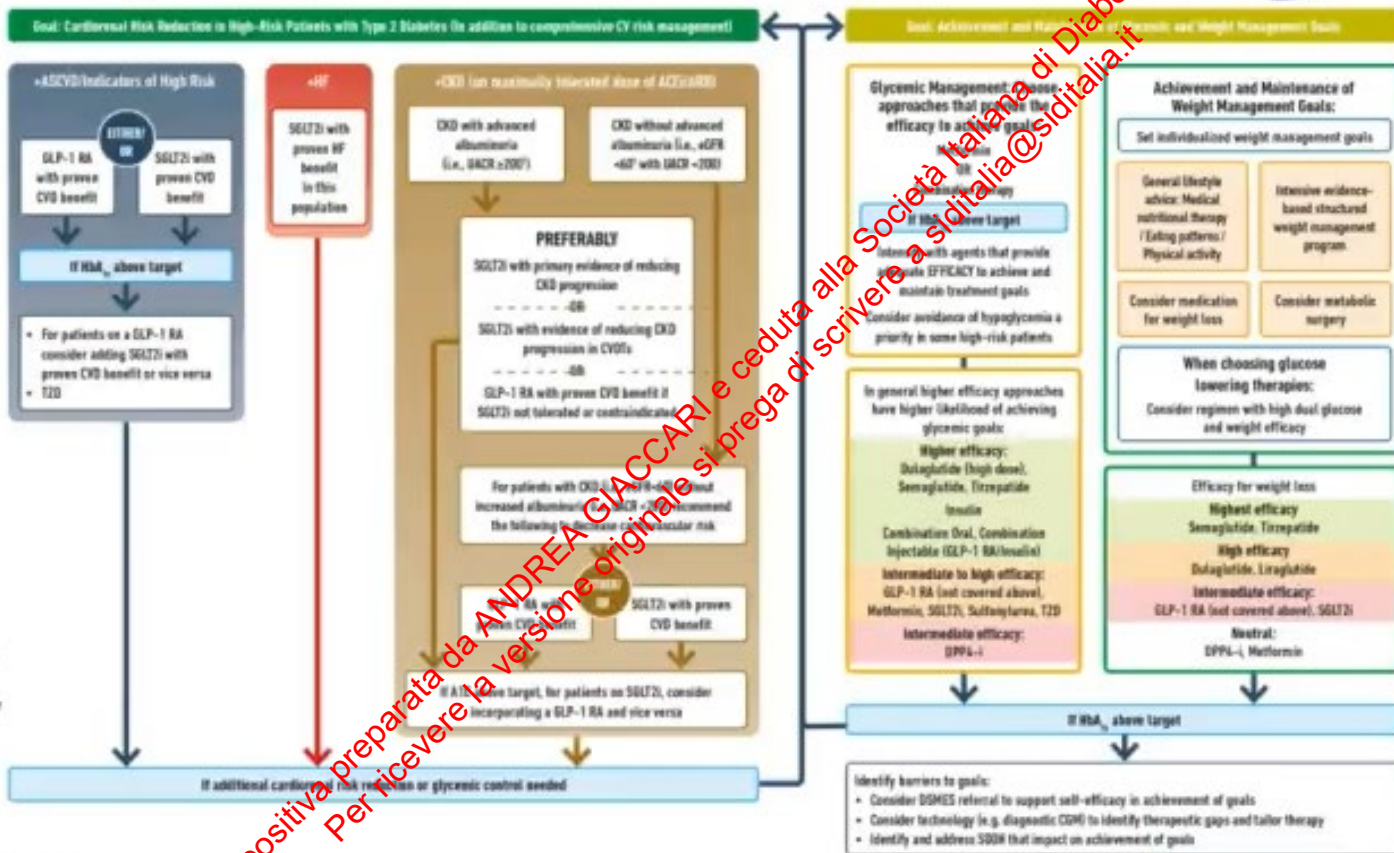
7. Proven benefit means it has robust indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Dapagliflozin, glimepiride, U-505 / delcort < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific considerations (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related considerations)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Antioxidant whenever these become new clinical considerations regardless of background glucose-lowering medications.
 ‡ Most patients involved in the relevant trials were on metformin at baseline as glucose-lowering therapy.

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Glucose lowering management of type 2 diabetes

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF MANAGEMENT, EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

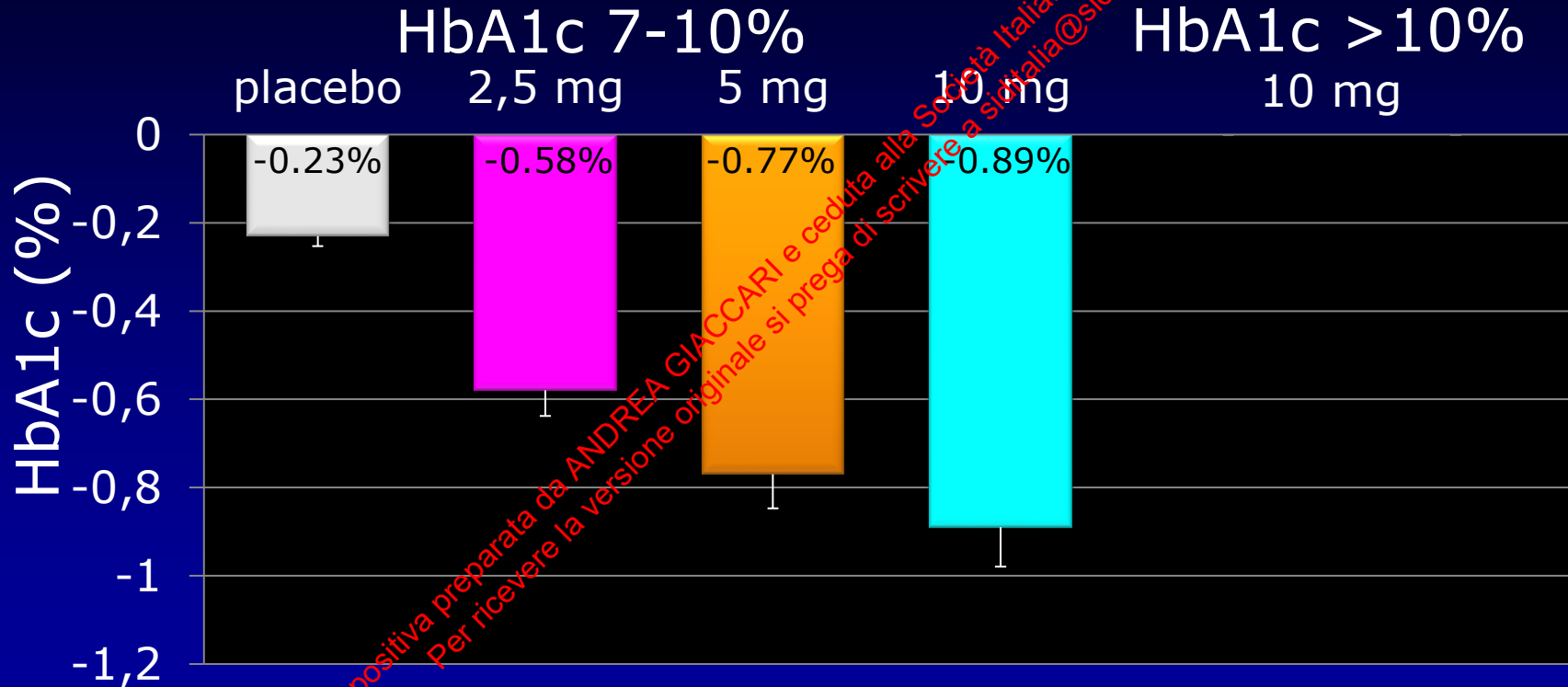


UAER = Urine albumin-to-creatinine ratio, with units as mg/g
 eGFR = estimated glomerular filtration rate, with units as mL/min/1.73m²
 CVOT = atherosclerotic cardiovascular disease
 TZD = thiazolidinedione; you follow region specific label for use of SGLT2i at lower eGFR levels



gliflozin (monotherapy)

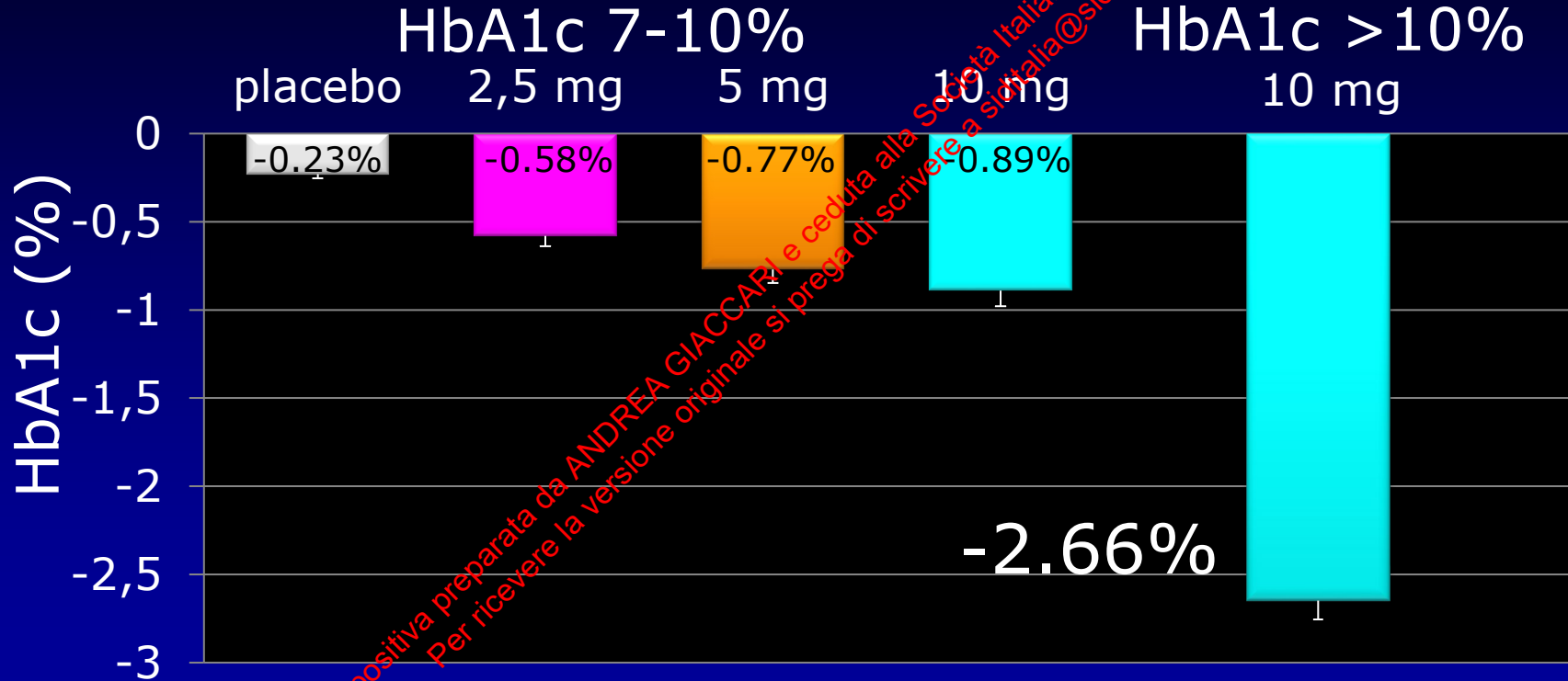
dapagliflozin - drug naïve patients



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gliflozin (monotherapy)

dapagliflozin - drug naïve patients



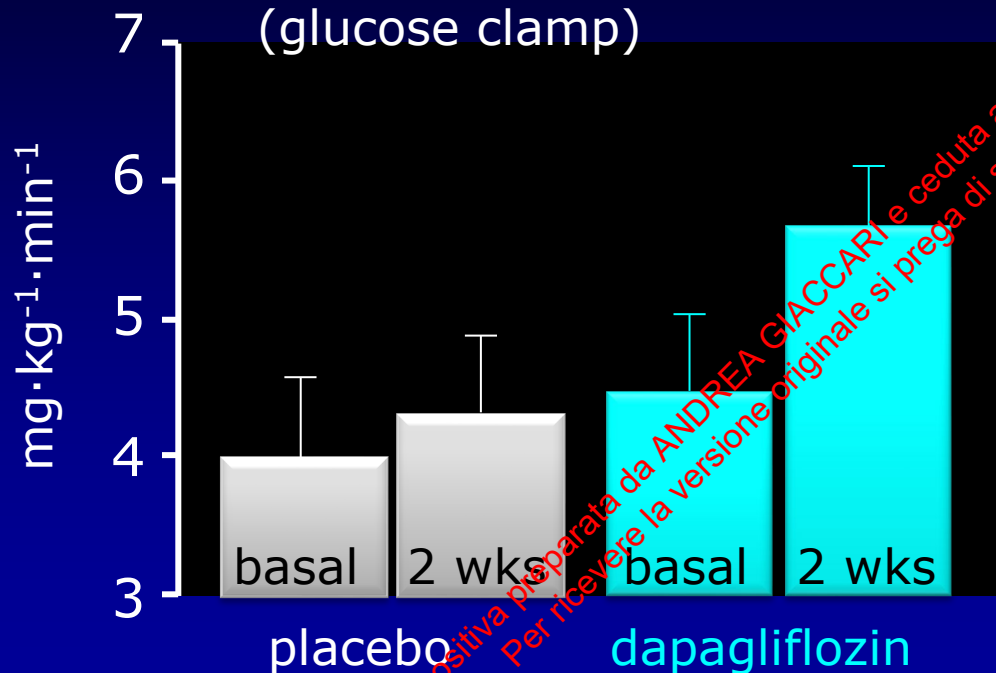
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gliflozins act on glucose toxicity

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

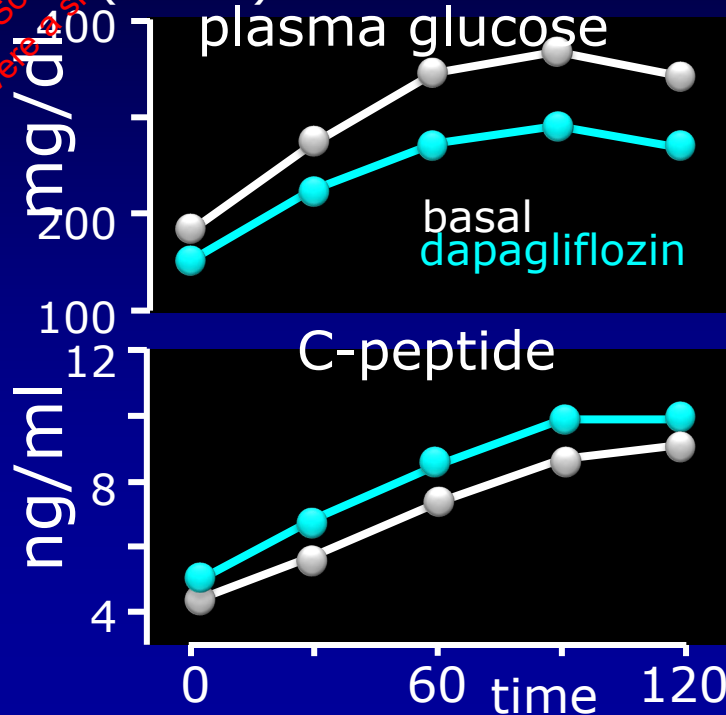
insulin sensitivity

(glucose clamp)



insulin secretion

(OGTT)

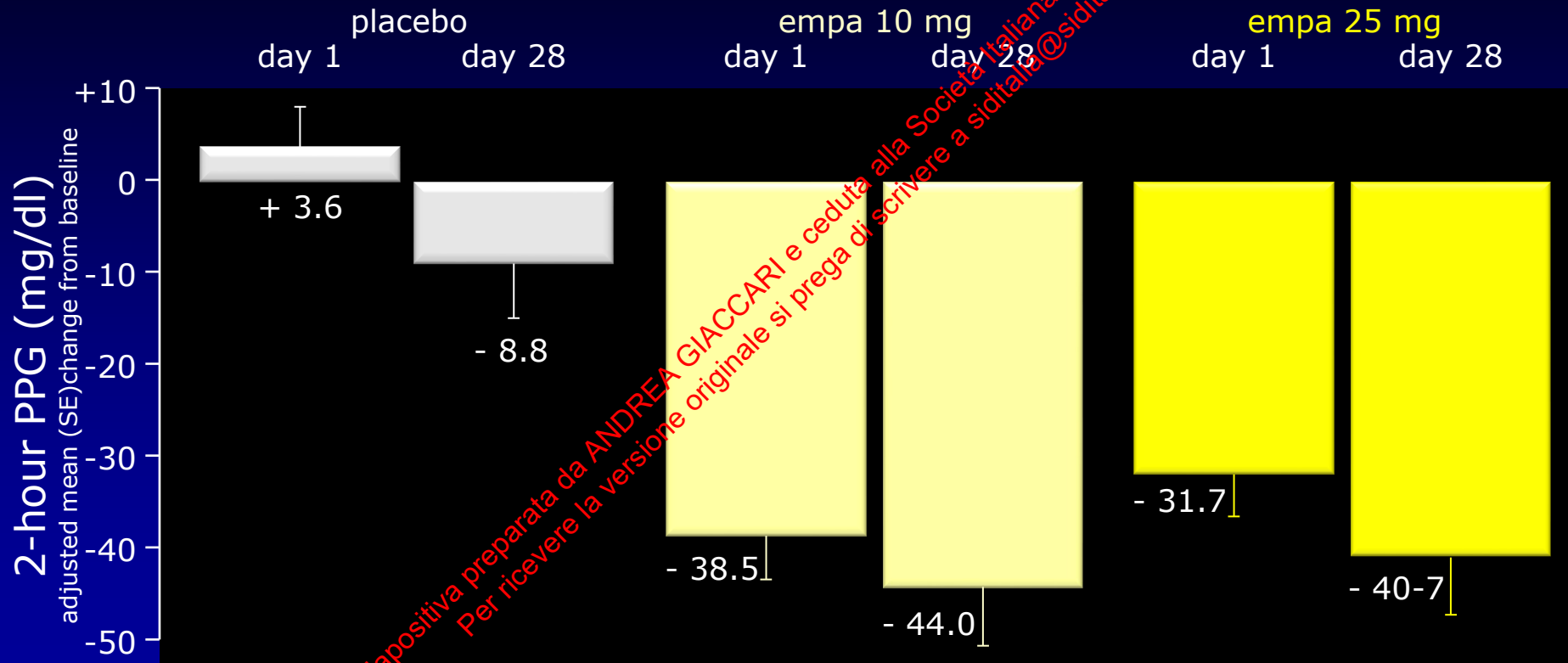


Merovci A et al.: JCI 124: 509; 2014

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

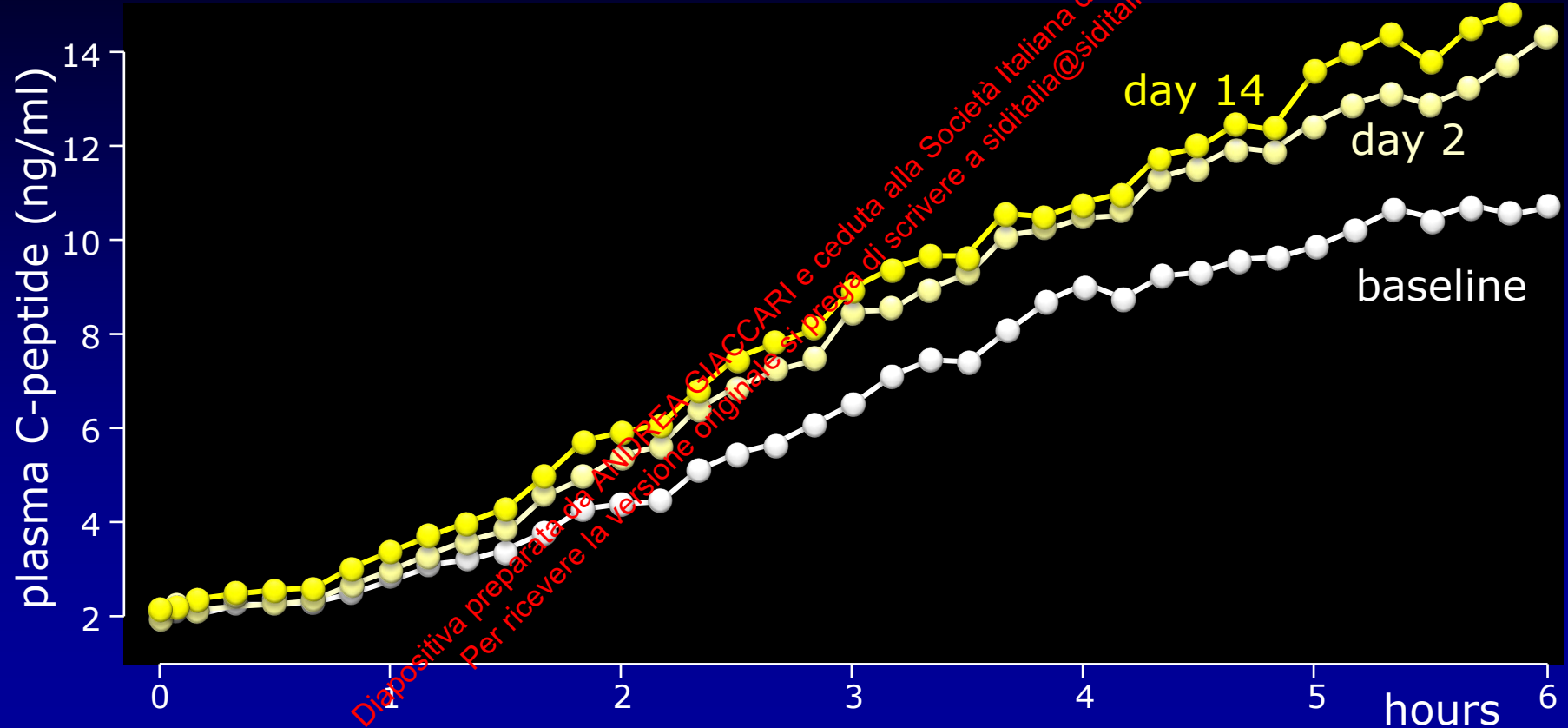
SGLT-2is improve post-prandial glucose

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

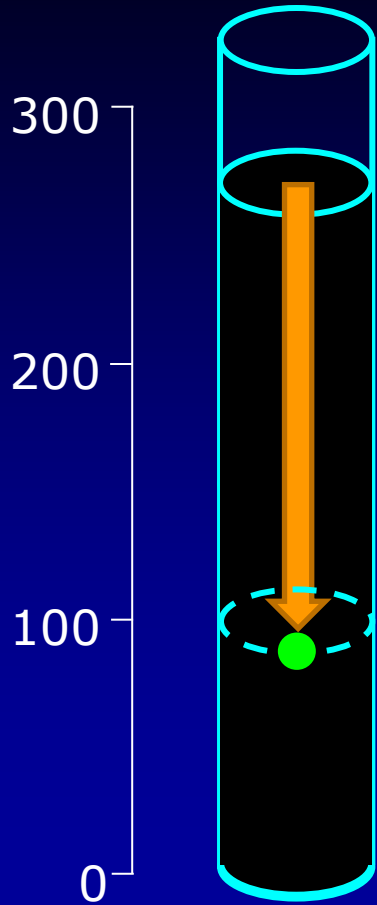


SGLT-2is improve insulin secretion

step-wise hyperglycemic clamp after empagliflozin



flux in glycosuria



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

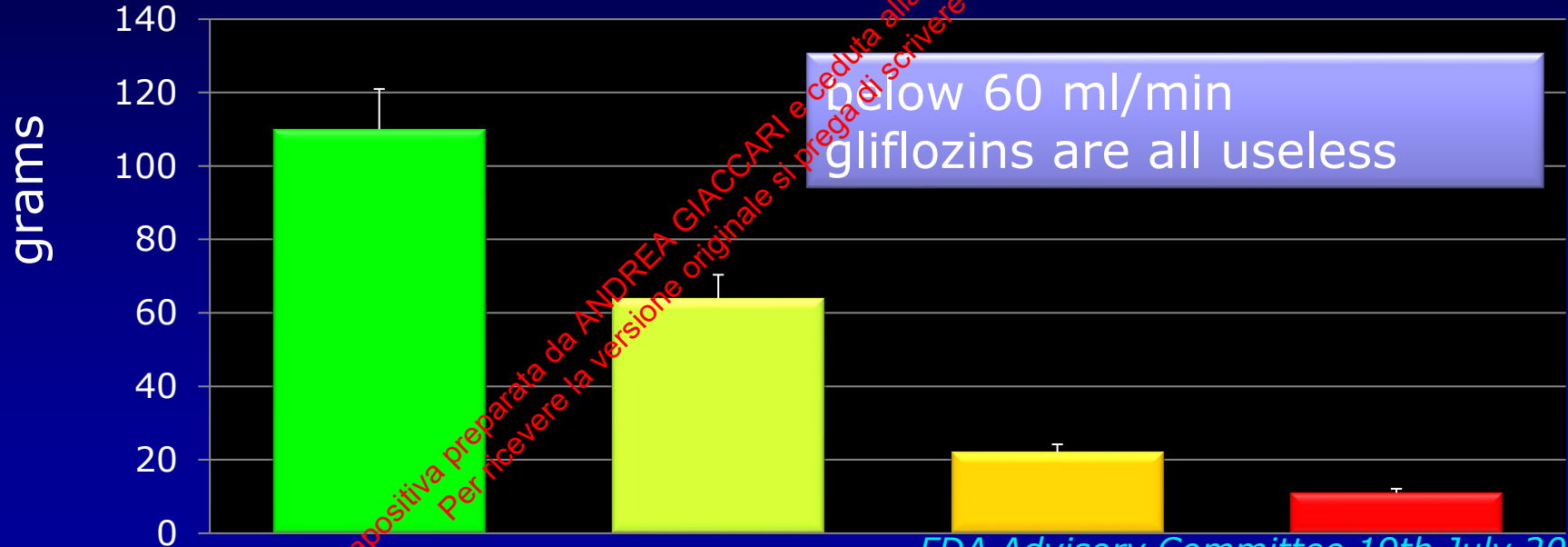
1. glycaemia
2. renal function (eGFR)

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

gliflozins in CKD

24 h glycosuria according to eGFR

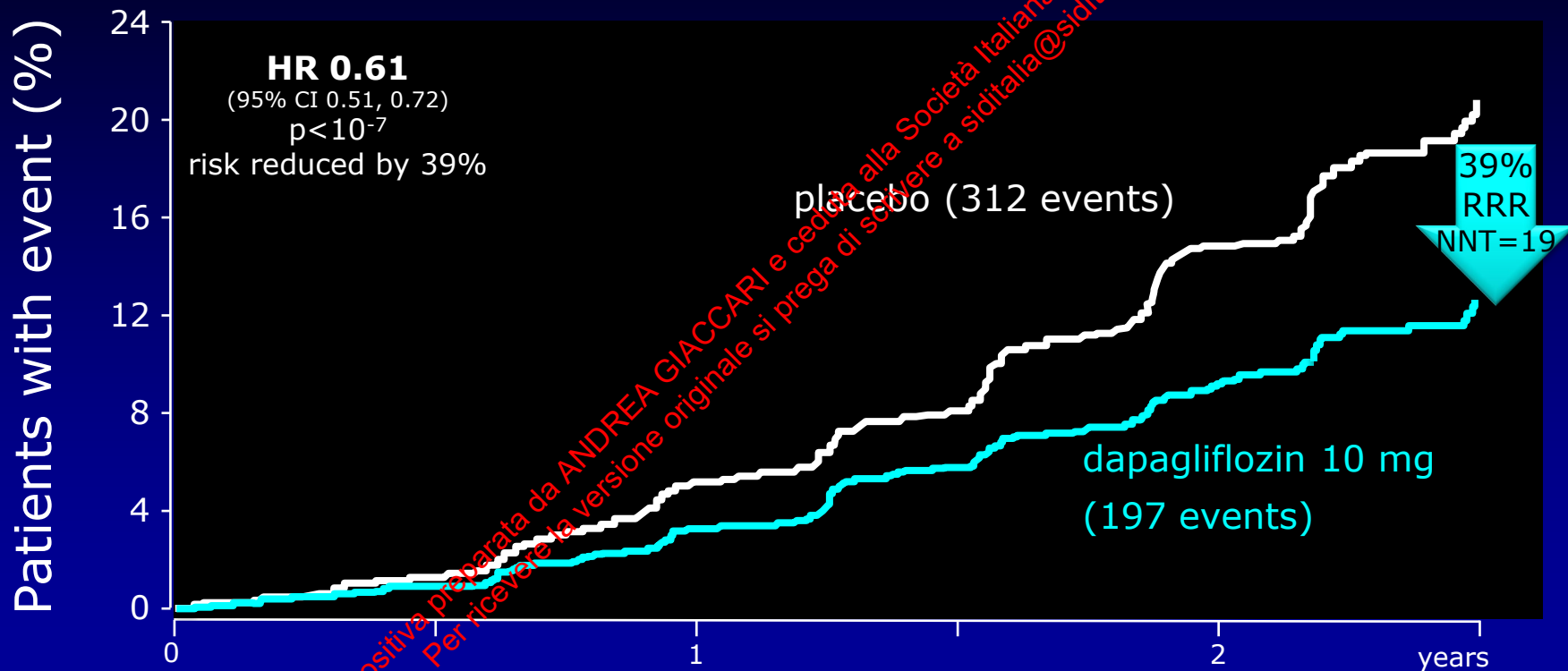
eGFR: > 90 60-90 30-59 < 30



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

DAPA-CKD: primary composite renal

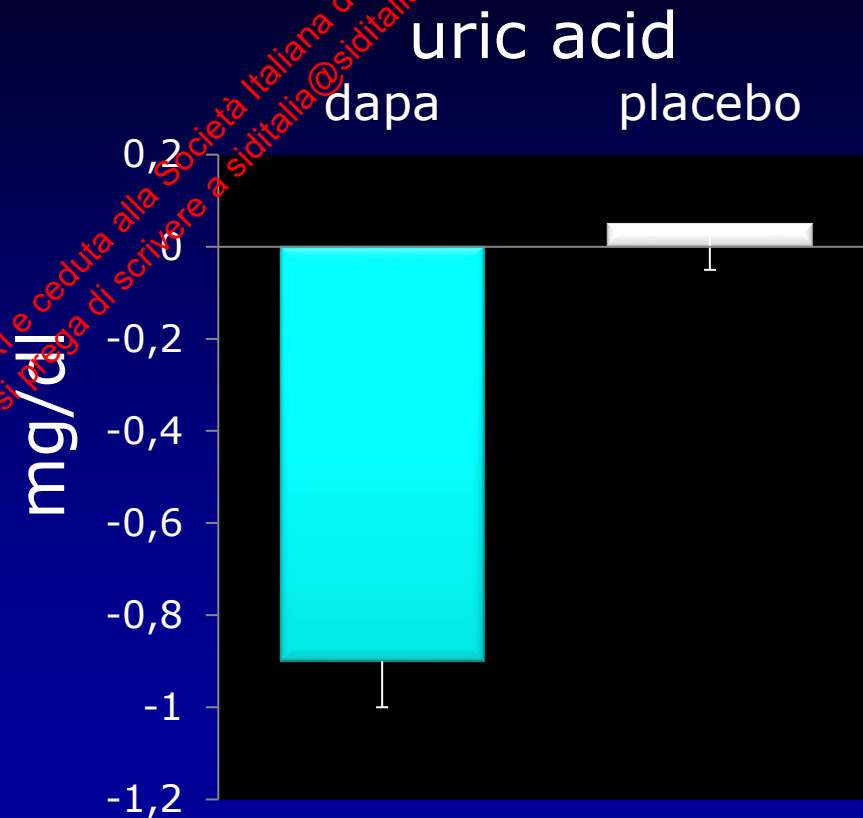
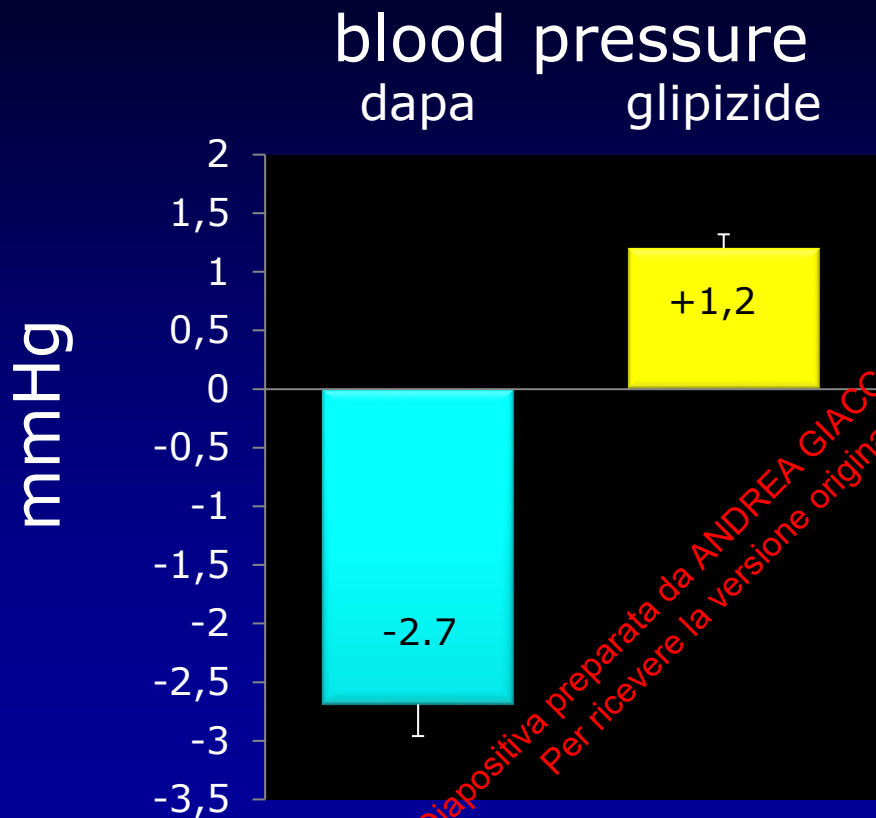
Sustained $\geq 50\%$ eGFR Decline, ESKD, Renal or CV Death*



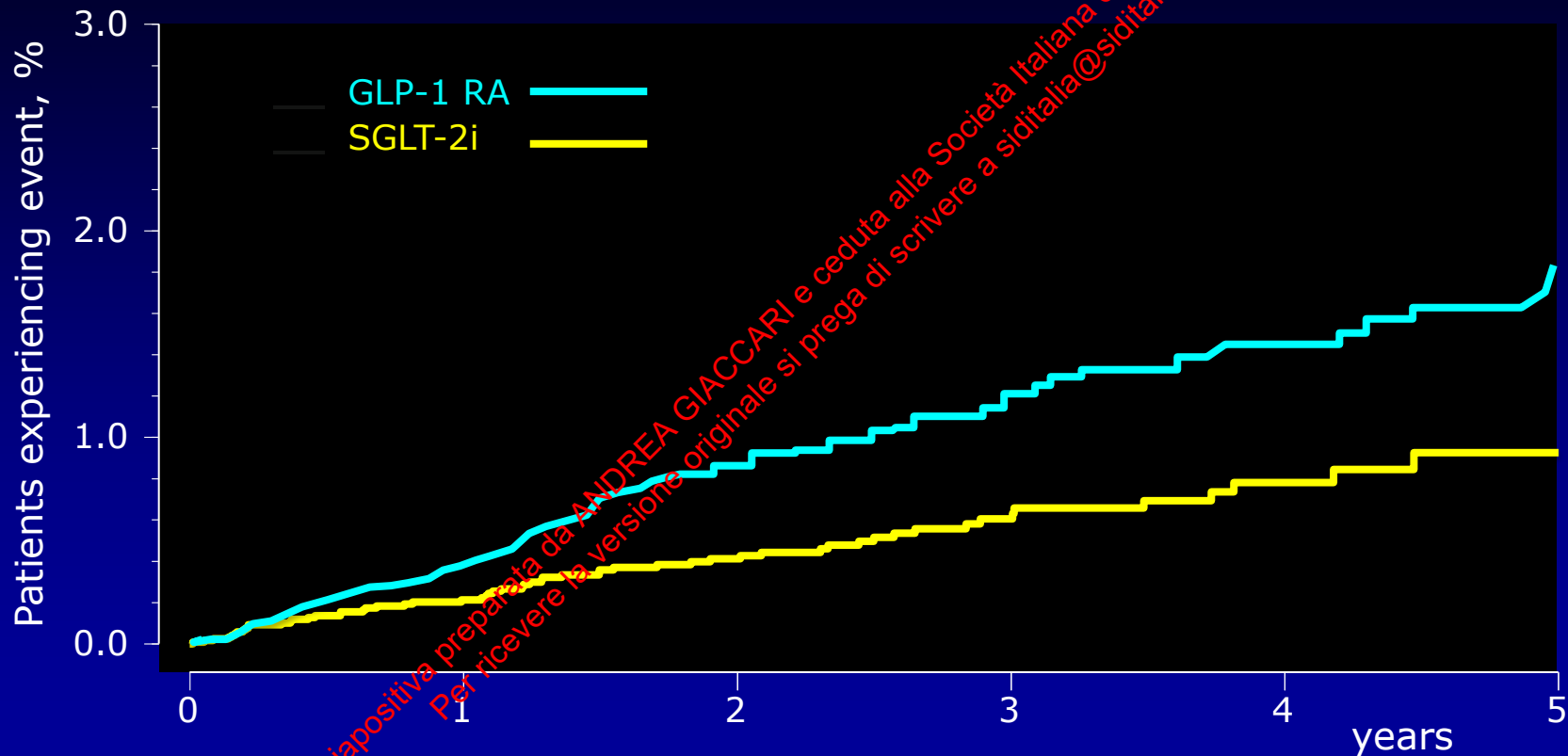
*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR $< 15 \text{ mL/min/1.73 m}^2$ for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld

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

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

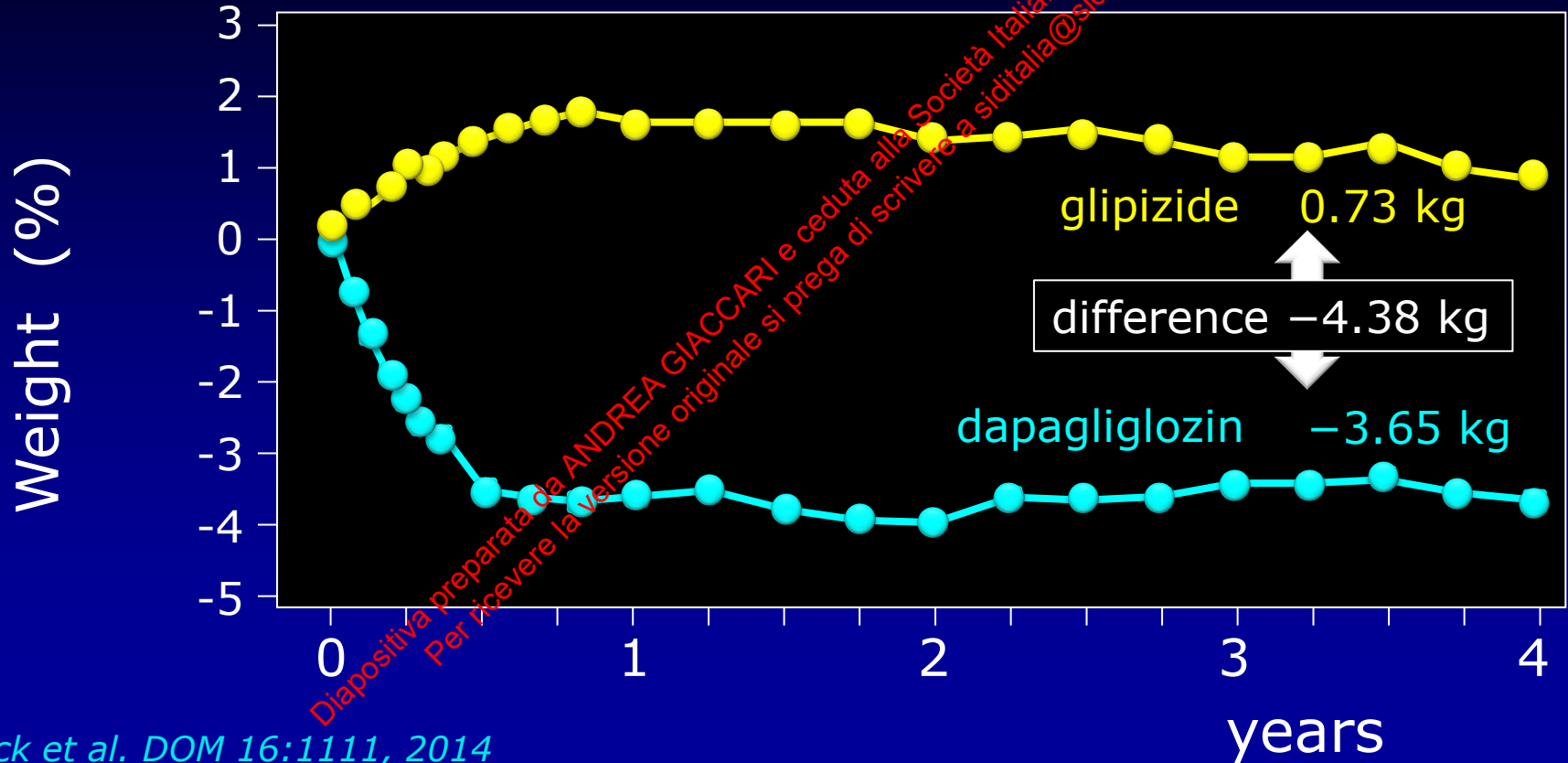


SGLT-2is reduce nephrolitis



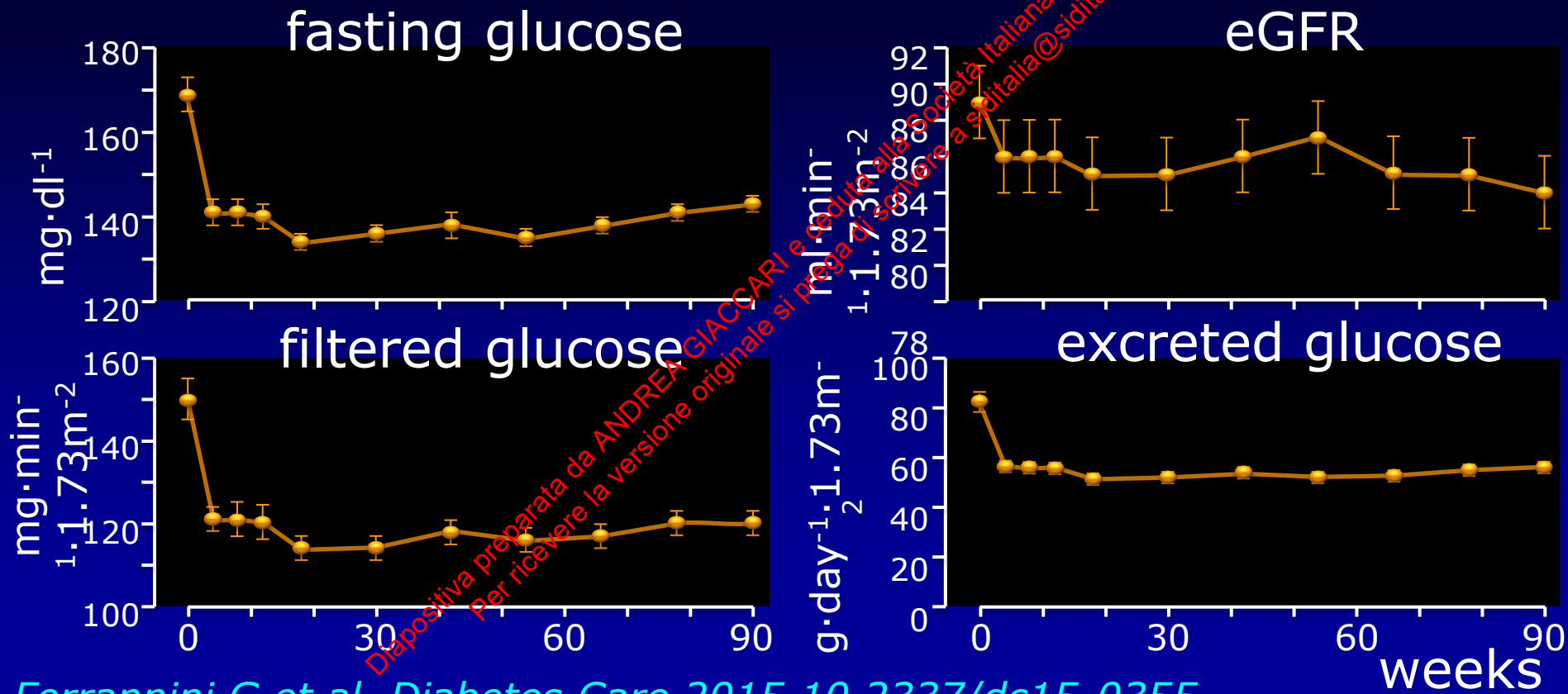
gliflozins induce stable weight loss

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



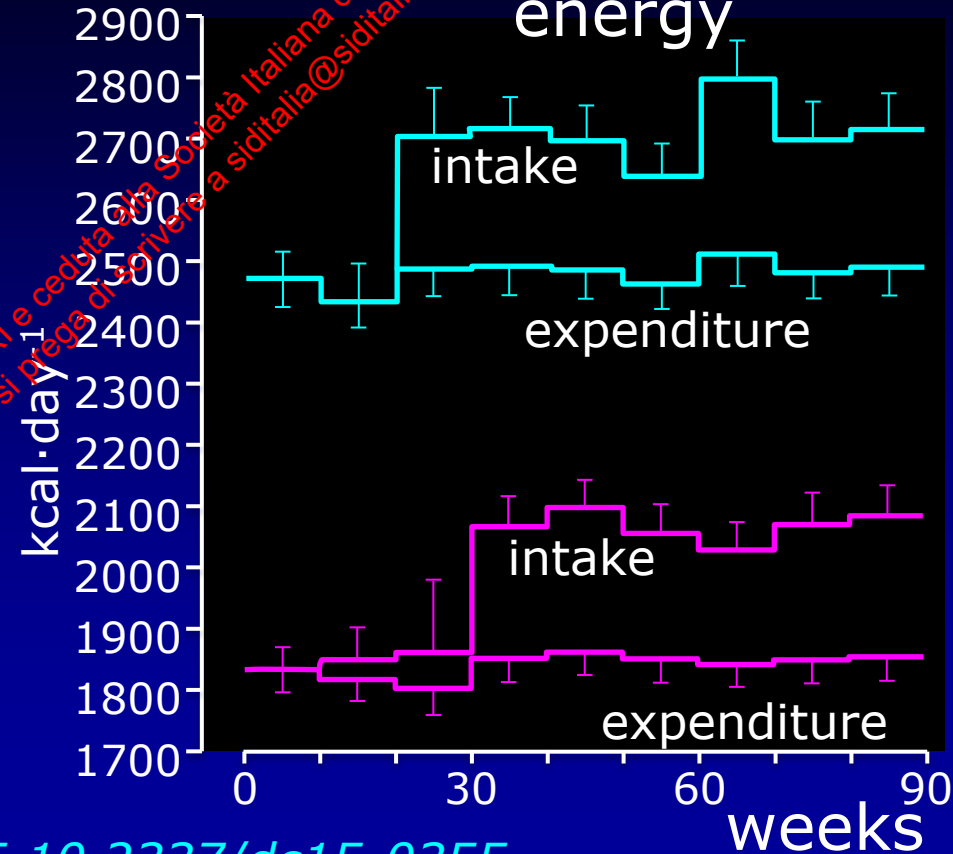
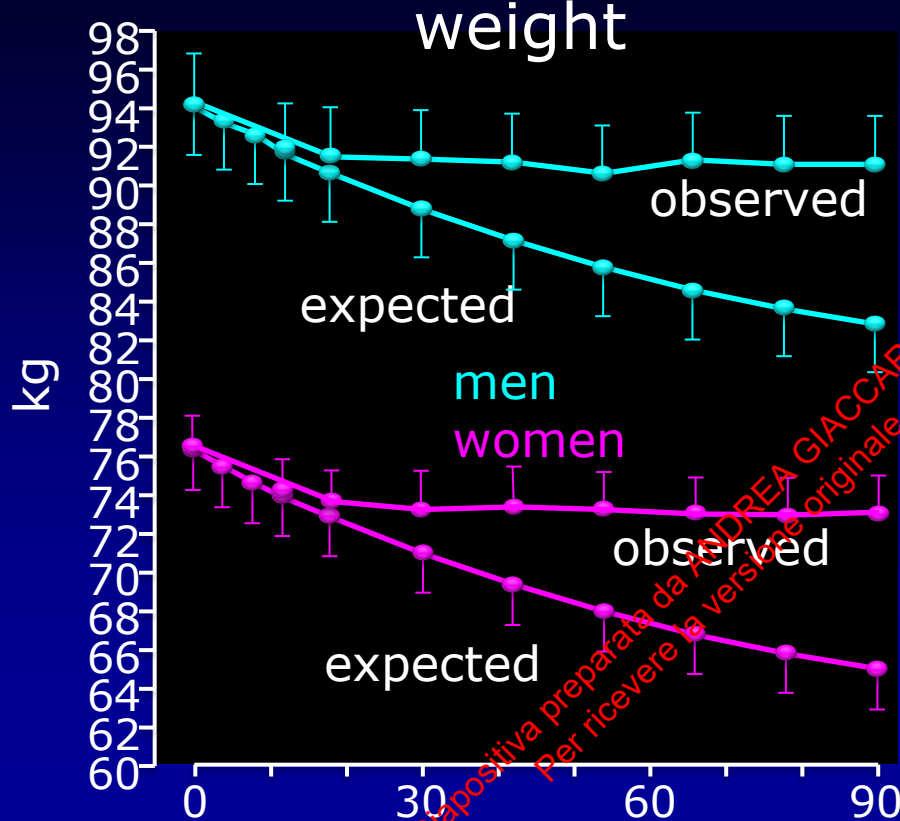
estimated glucose loss with SGLT2i

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

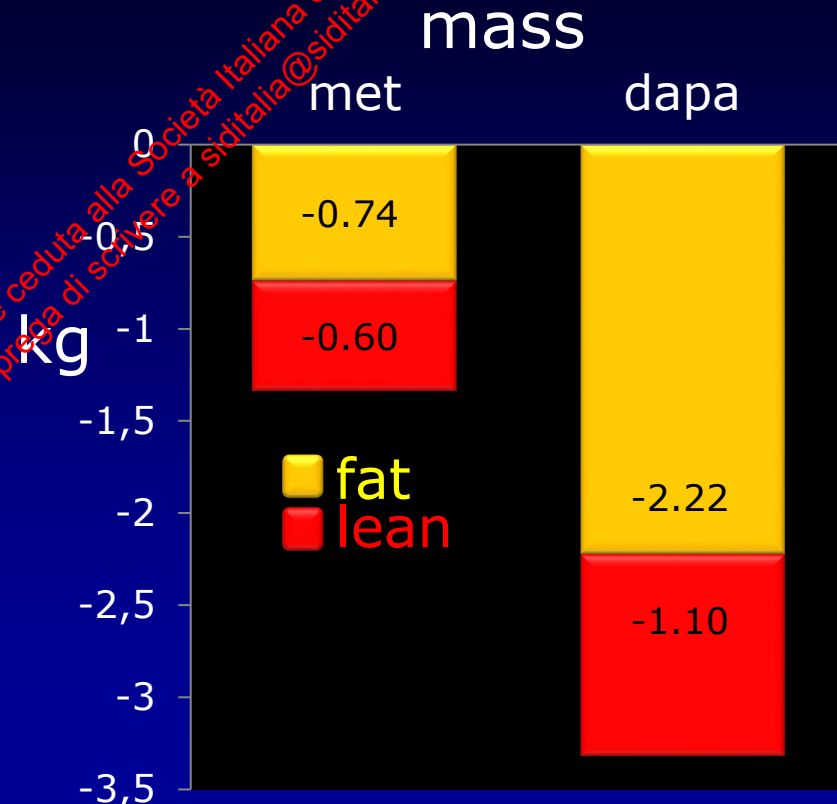
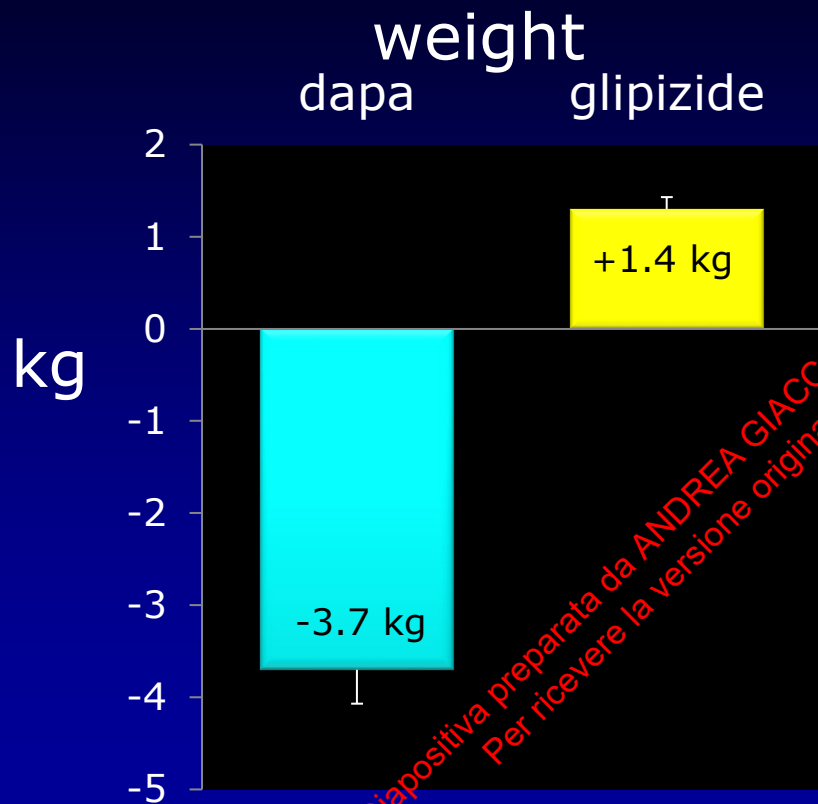


energy balance with SGLT2i

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



SGLT-is mostly reduce fat mass



intracellular metabolism

lower glucose with same
insulin reduces glucose
oxidation

glycolysis

fasting-
mimicking state

pyruvate

4 ATP

PDH PC

oxalacetate

Ac-CoA

β -ox

protons

5 ATP

12 ATP

protons

WEIGHT
LOSS

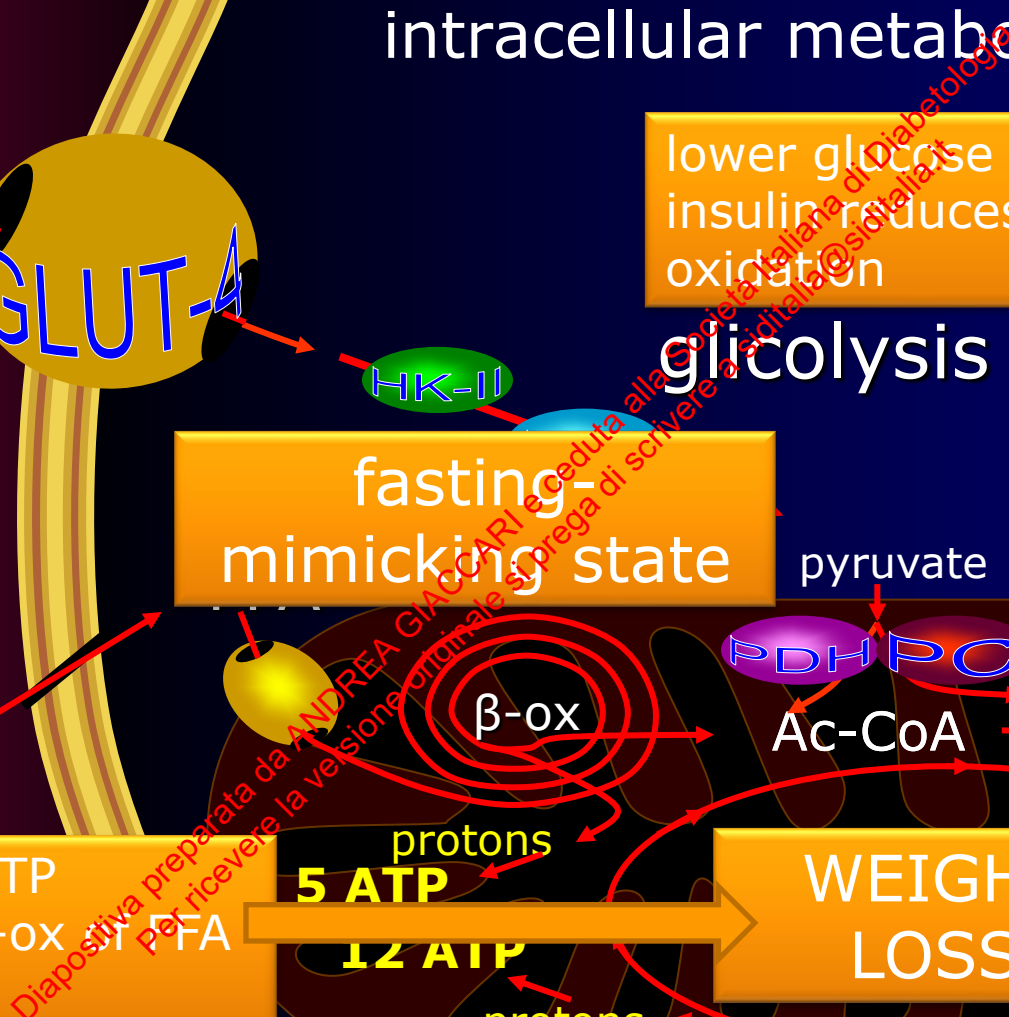
glucose

GLUT-4

HK-II

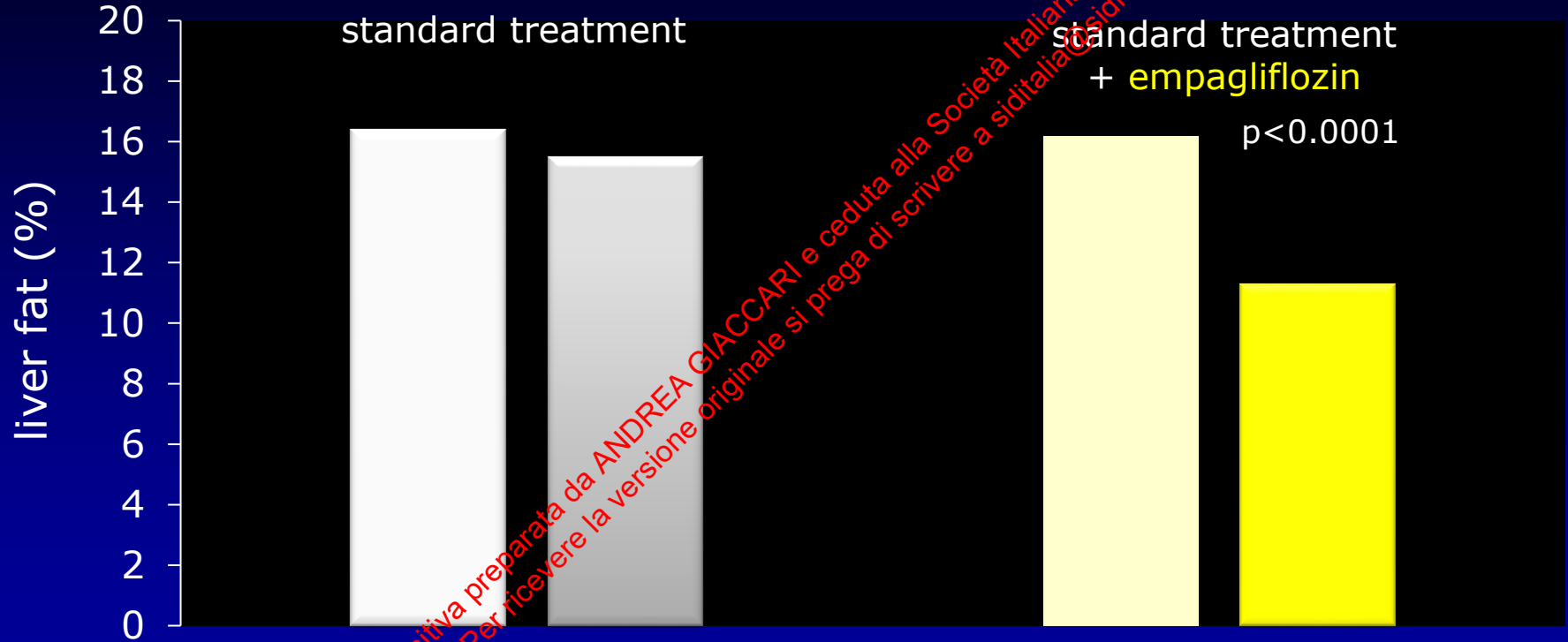
FFA

to maintain ATP
production β -ox or FFA
increases



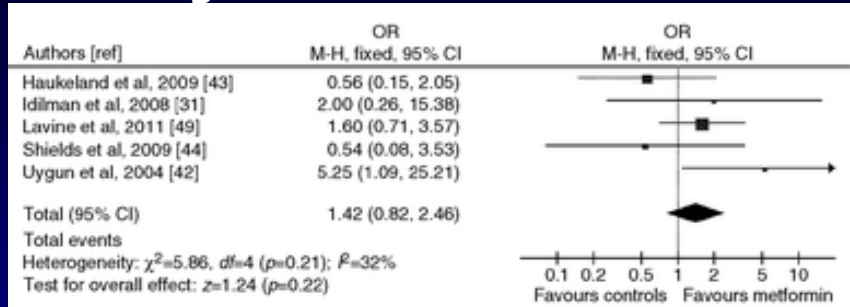
SGLT-2is reduce liver fat

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

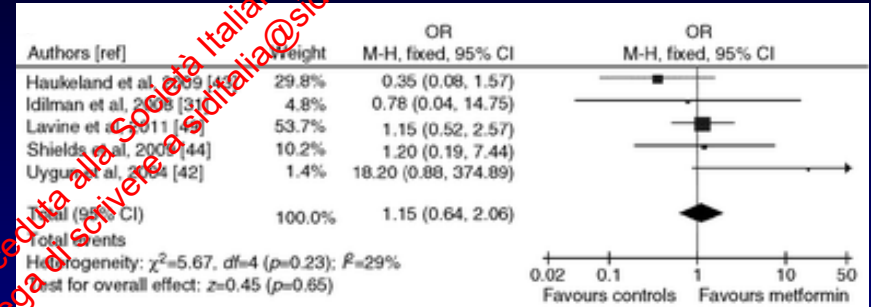


metformin and NASH

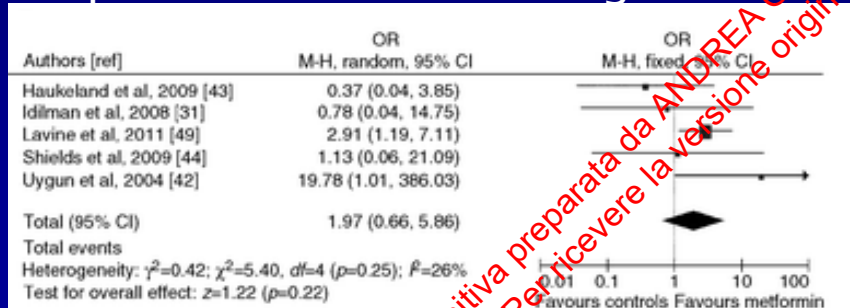
histological steatosis



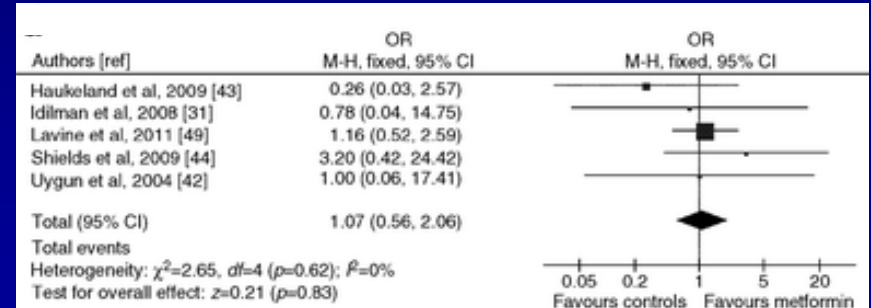
lobular inflammation



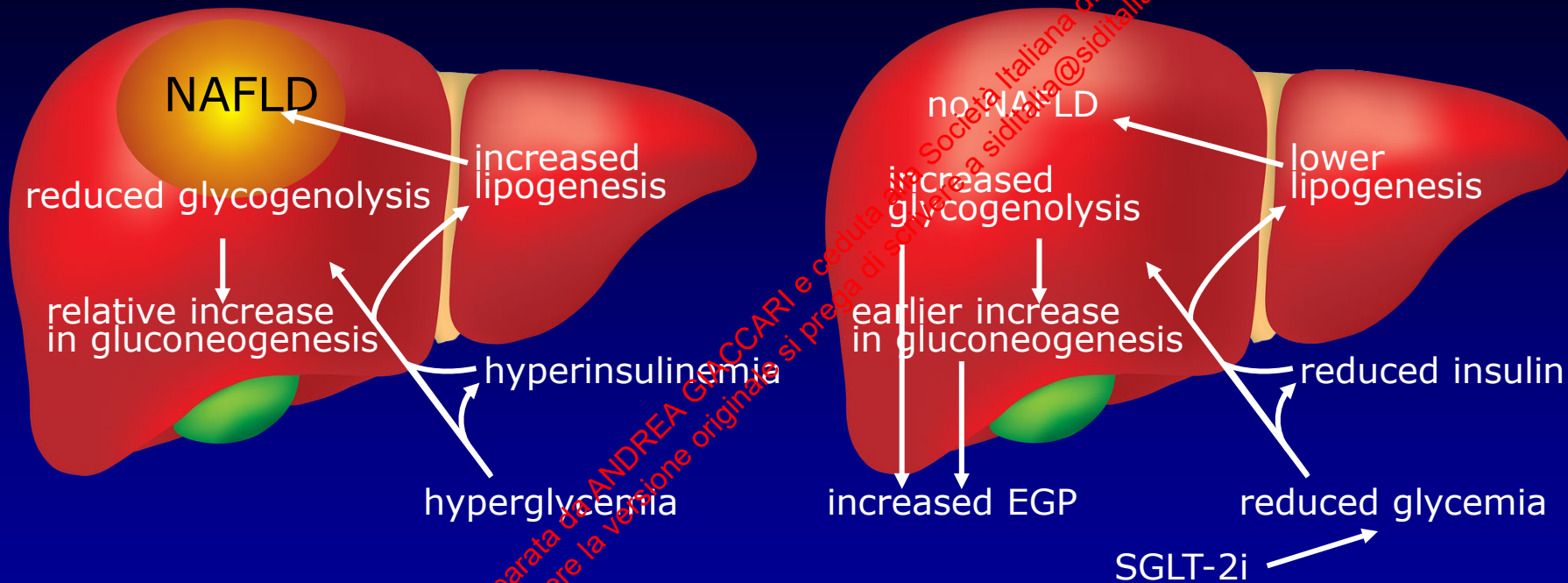
hepatocellular ballooning



fibrosis

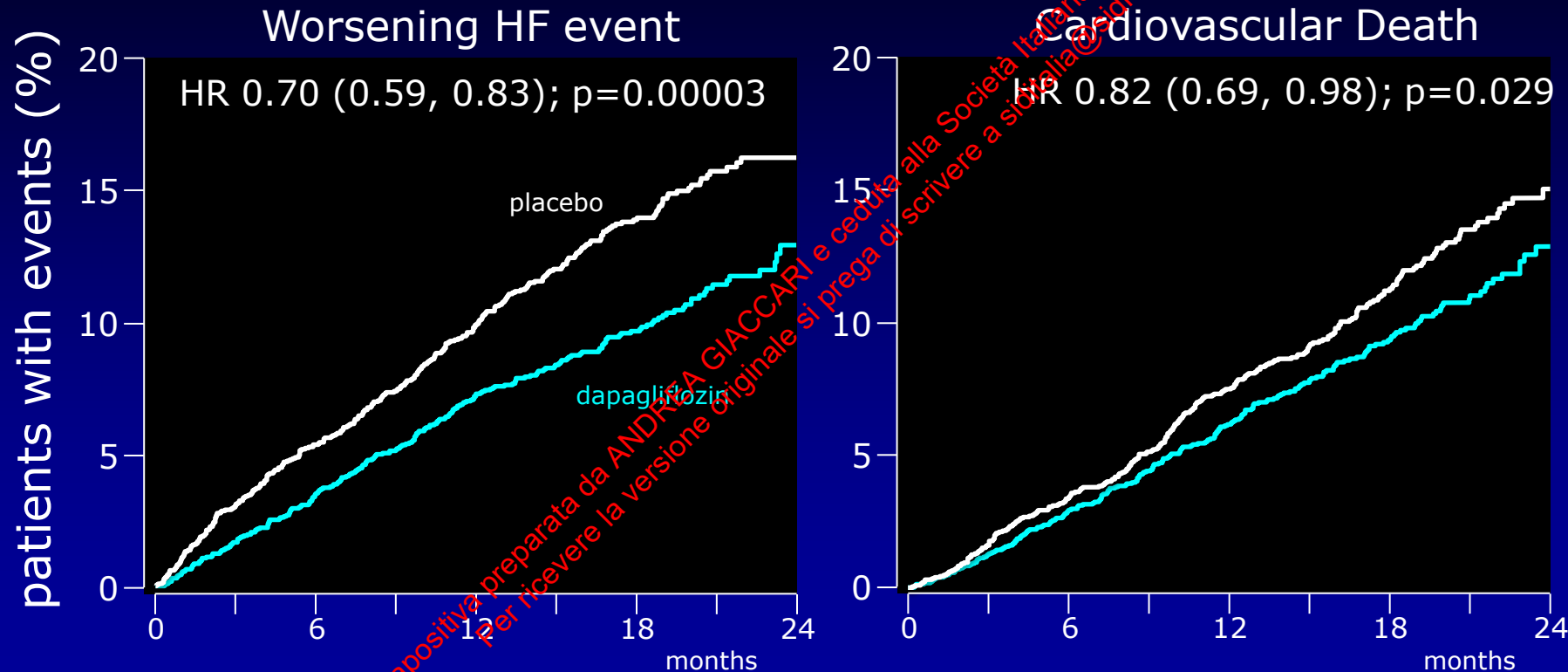


increased EGP with SGLT-2i is a positive effect

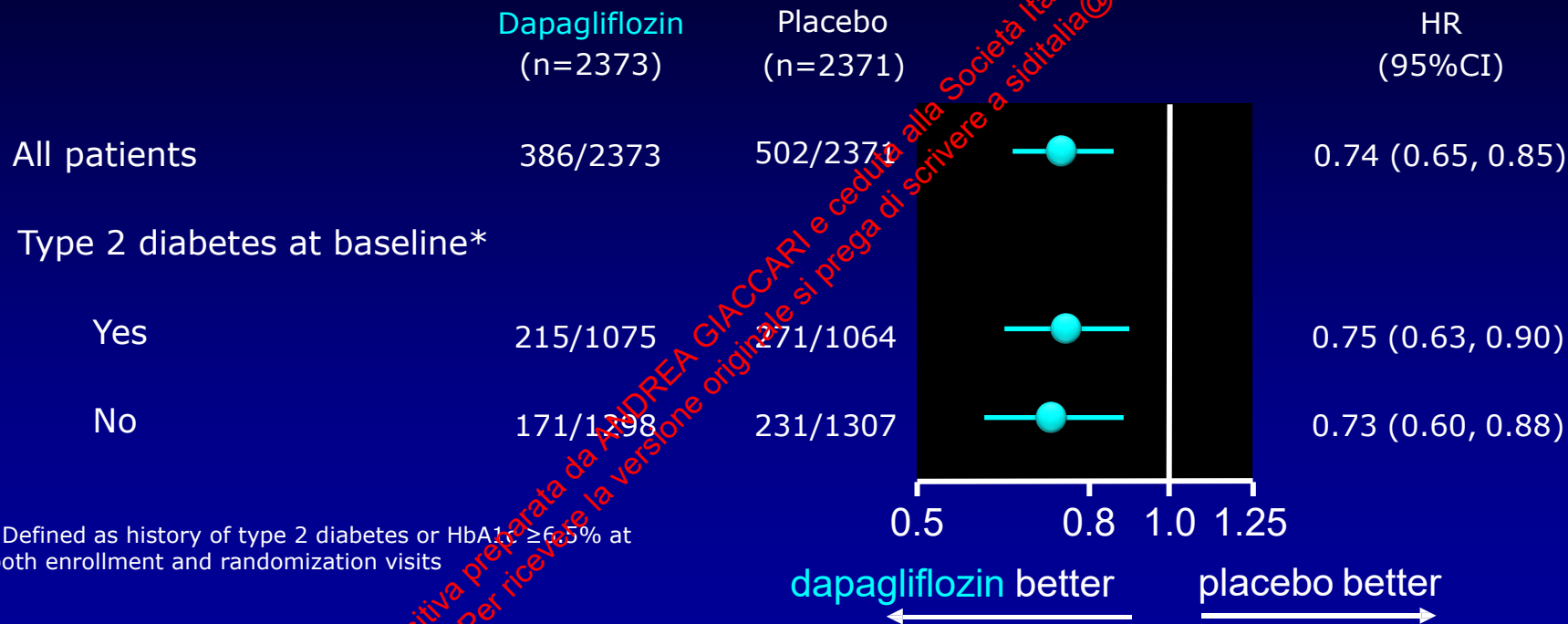


DAPA-HF: components of primary outcome

Patients with Heart Failure and Reduced Ejection Fraction



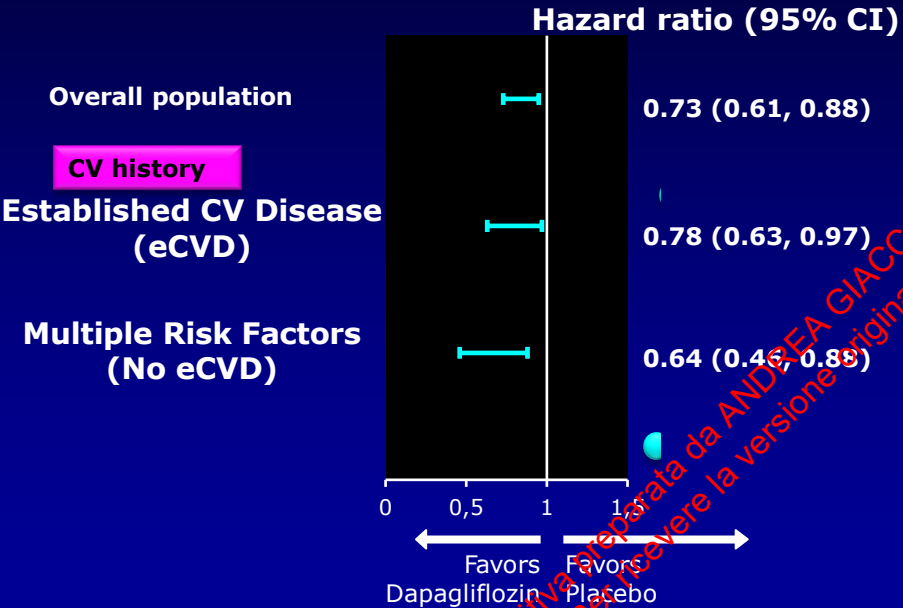
DAPA-HF No diabetes/diabetes subgroup in Primary endpoint



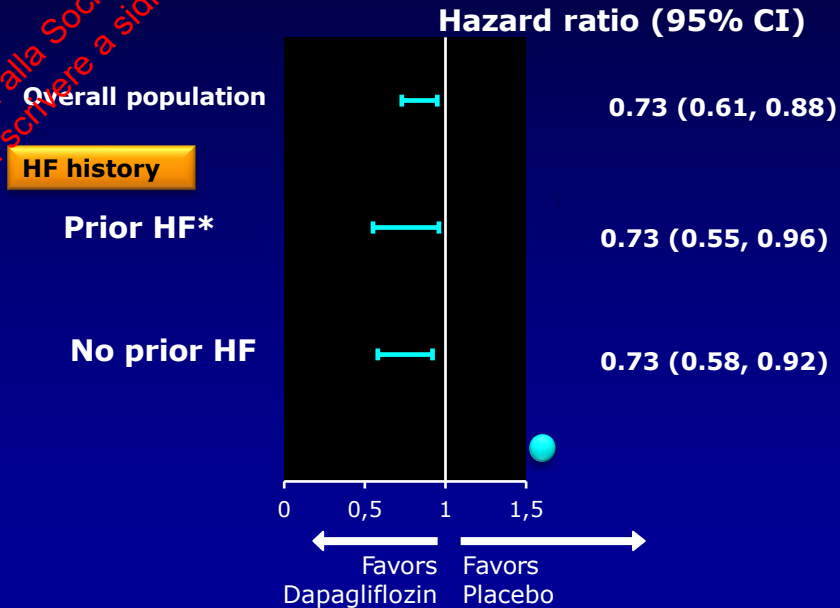
*Defined as history of type 2 diabetes or HbA1c $\geq 6.5\%$ at both enrollment and randomization visits

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

hHF per **CV** history



hHF per **HF** history

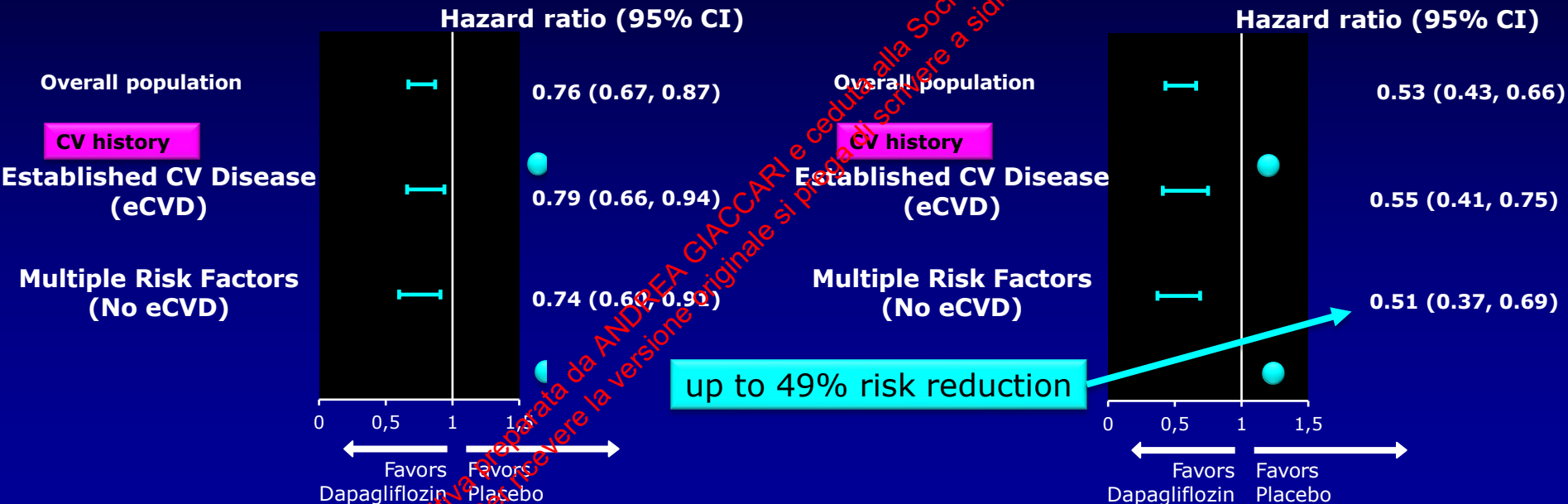


*10% of patients in DECLARE had prior HF

DECLARE: prevention of CKD regardless of history of eCVD

composite Renal & CV death

composite Renal



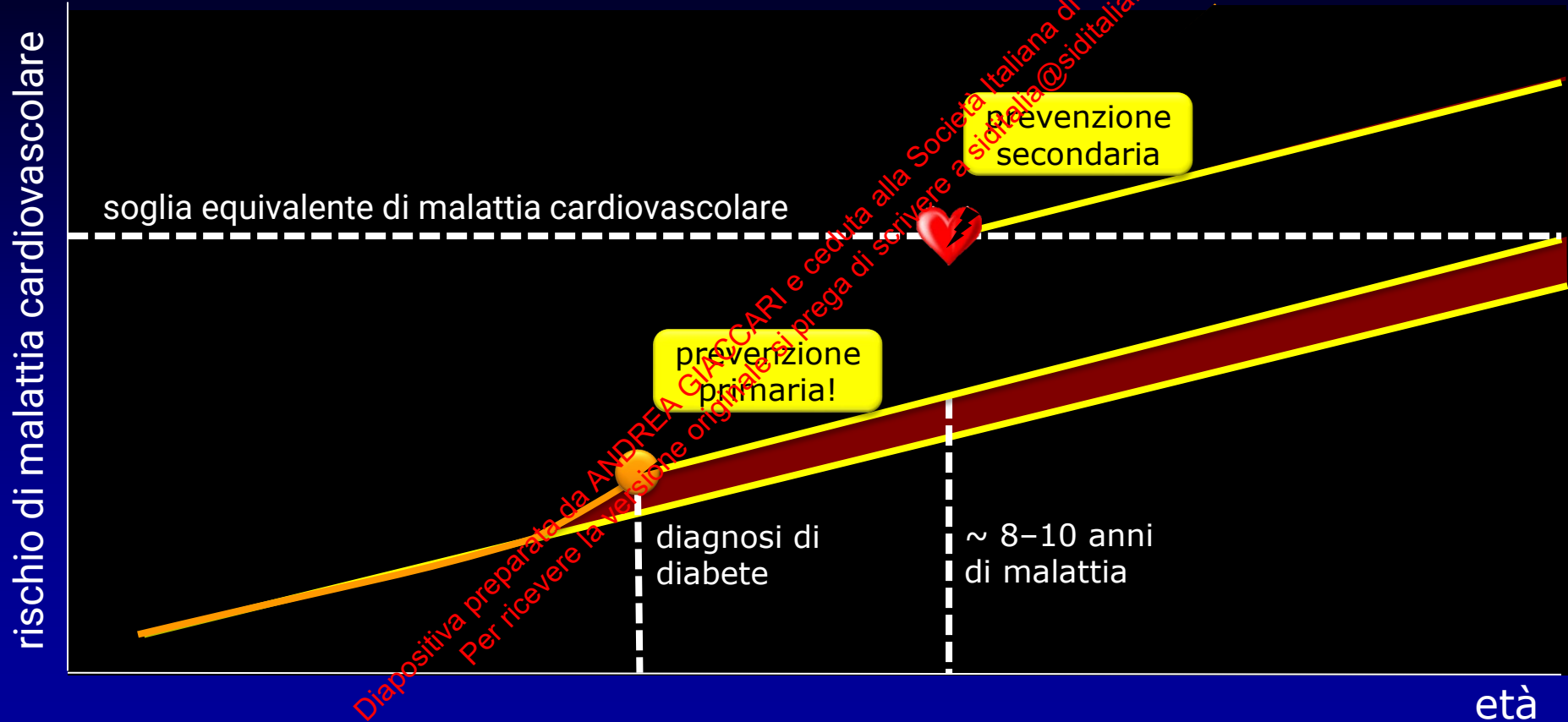
composite Renal: composite of $\geq 40\%$ decrease in eGFRa to <60 mL/min/1.73 m², ESRD, or renal death

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



Umberto

Valentina

Simona

Francesca

Flavia

Ilaria

Erminia

Gianfranco

Maria

Teresa

Chiara

Serena



Gemelli



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