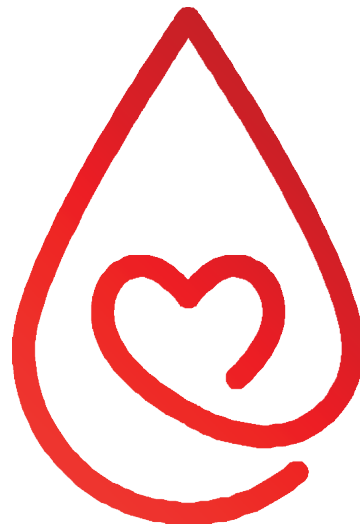


“Al
CUORE
del **DIABETE**”

A chi non prescrivere i farmaci innovativi
altri tipi di diabete
Andrea Giaccari

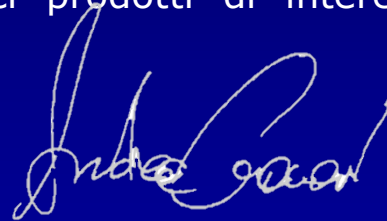


DICHIARAZIONE CONFLITTO D'INTERESSE DOCENTI

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

- Astra Zeneca
- Lilly
- Novo-Nordisk

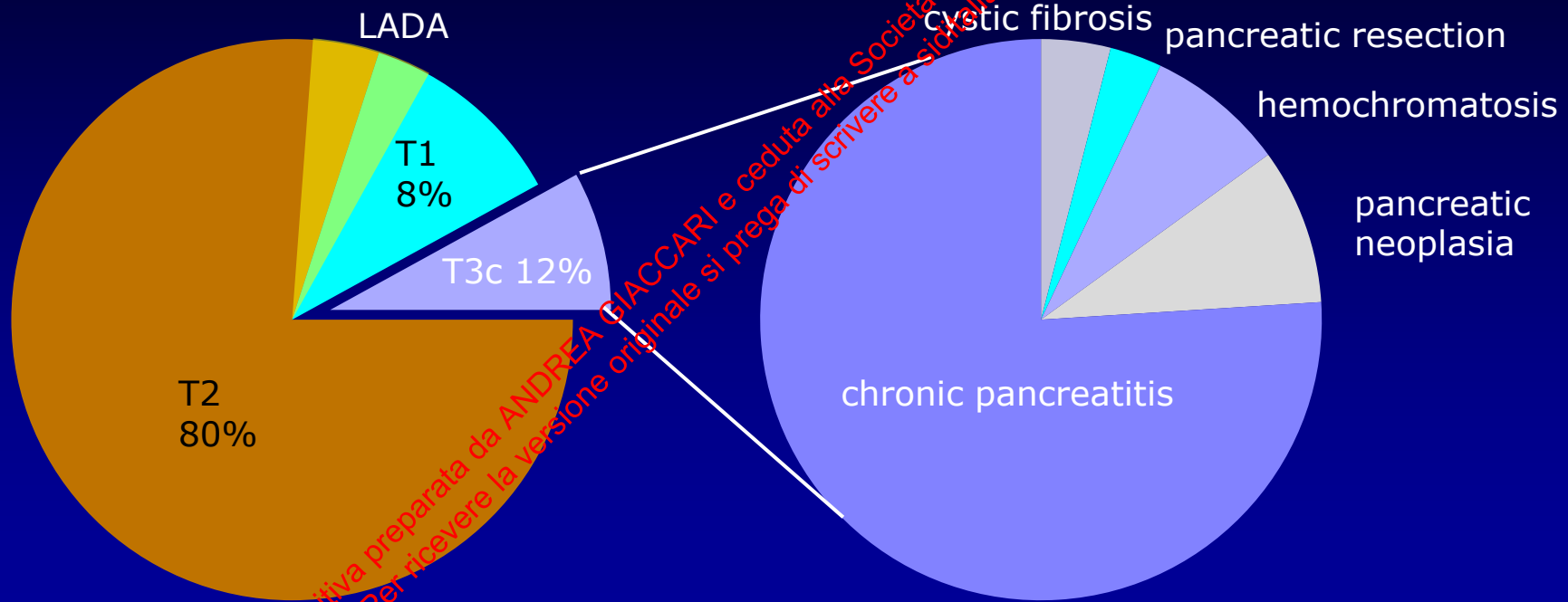
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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



Sponsor 3° G.Meta Forum:

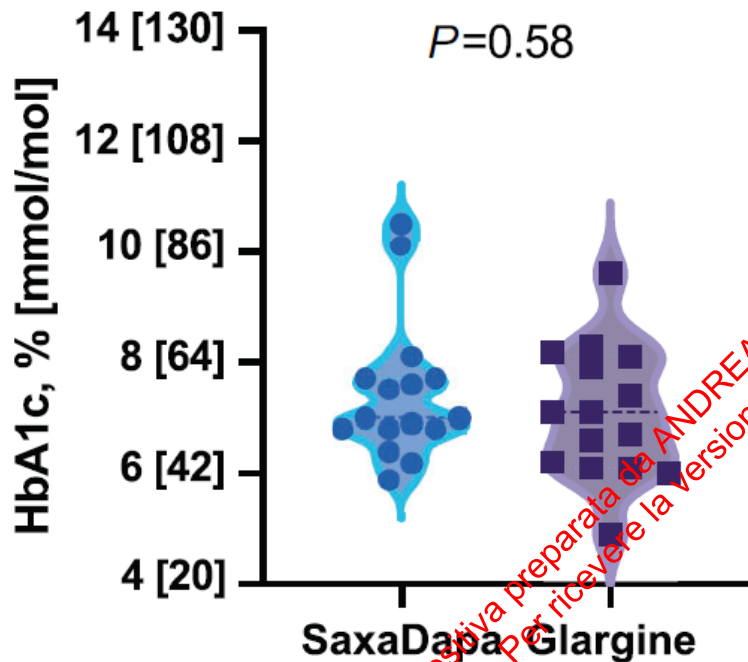
Novo-Nordisk, AstraZeneca, Boehringer-Ingelheim Lilly, Lilly, Guidotti, Novartis, Sanofi, Amgen, Amarin, MSD, Bayer

prevalence of types of diabetes

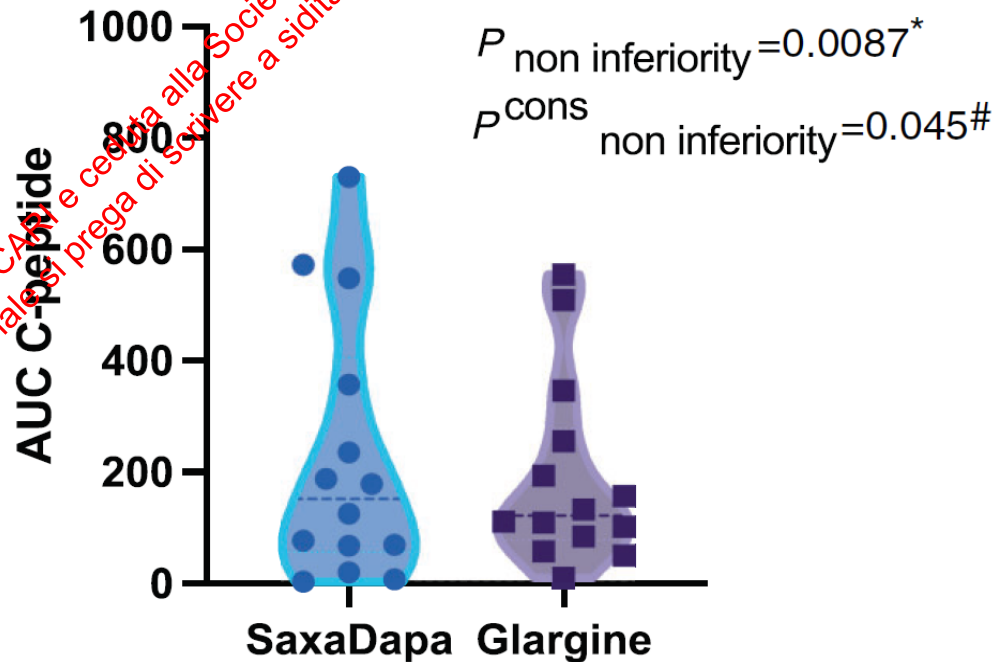


DPP-4i+SGLT-2i vs glargine in LADA

(A) HbA1c at 12 months



(C) AUC C-peptide at 12 months



repaglinide (?) in patients with cystic fibrosis T3c diabetes



Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial

Manfred Ballmann, Dominique Hubert, Barouk M Assael, Doris Schab, Alexandra Hebestreit, Lutz Naehrlich, Tanja Nickolay, Nicole Prinz, Reinhard W Holl, CFRD Study Group*

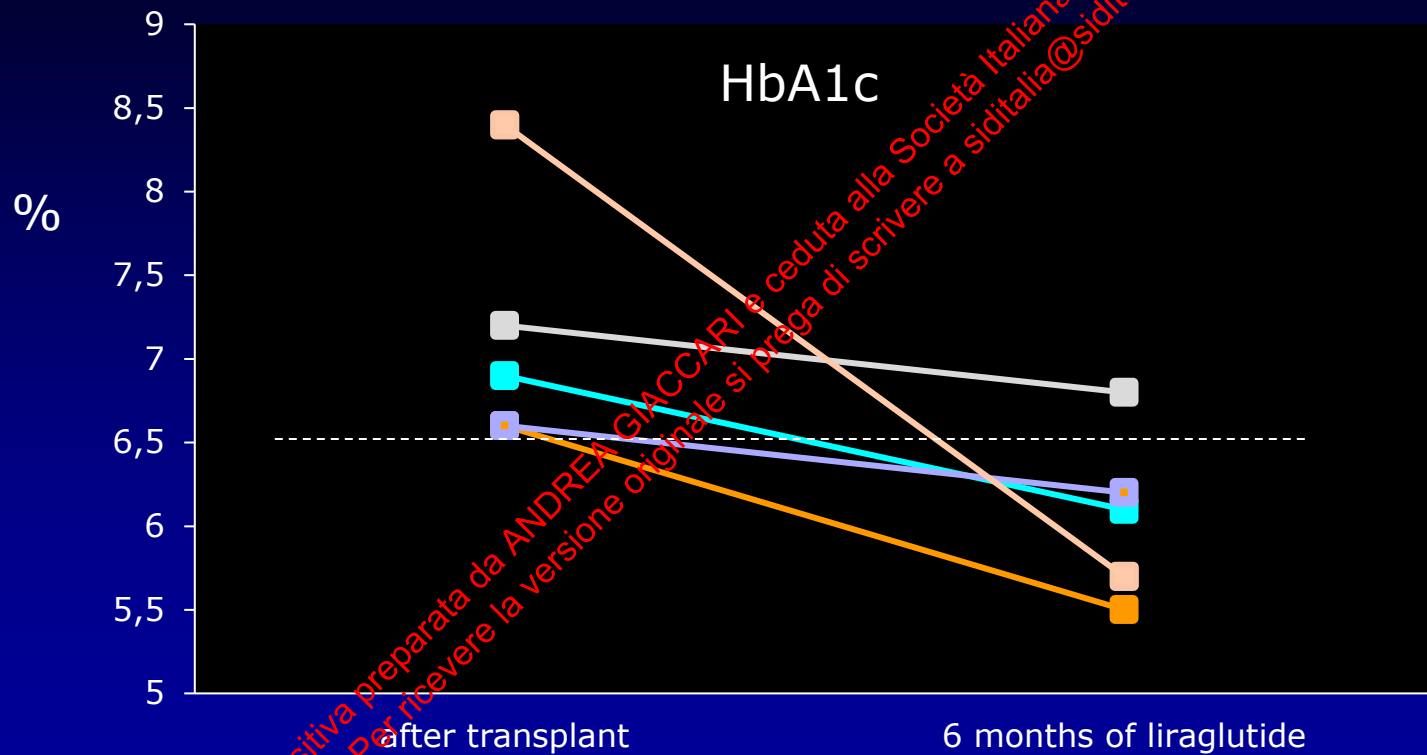
Summary

Lancet Diabetes Endocrinol 2018: **Background** As survival among patients with cystic fibrosis has improved in recent decades, complications have

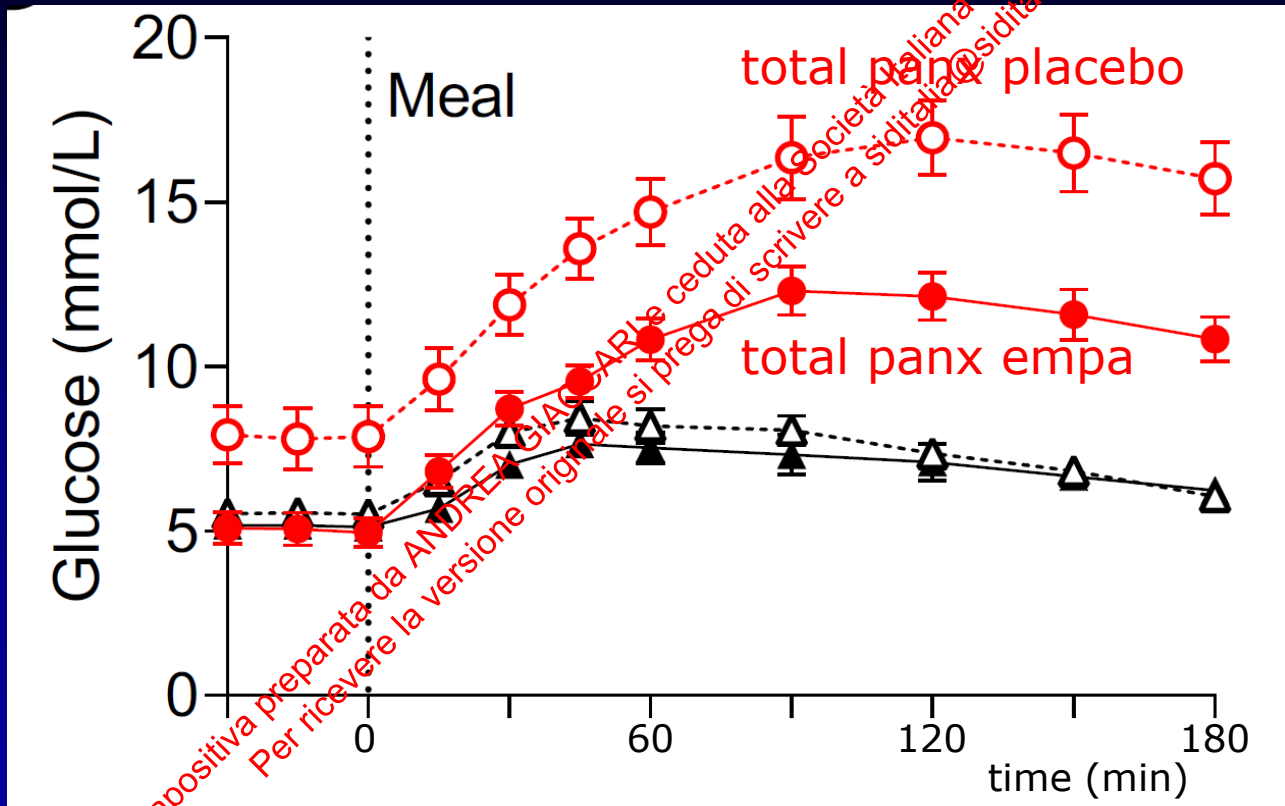
	Repaglinide group	Insulin group	Mean group difference (95% CI)	p value*
HbA_{1c} concentration				
Baseline	6.4 (0.9), 46.0 (9.9)	6.6 (0.7), 48.6 (7.1)	..	..
At 12 months (% , mmol/mol)	6.2 (0.8), 44.2 (8.9)	6.7 (1.4), 49.7 (15.1)	..	..
Change from baseline to 12 months (% , mmol/mol)	0.2 (0.6), 2.1 (7.0)	-0.1 (1.2), -1.1 (13.5)	-0.3 (-0.8 to 0.2), -3.2 (-9.0 to 2.6)	0.26
At 24 months (% , mmol/mol)	6.2 (0.7), 43.9 (7.3)	6.8 (1.4), 51.0 (15.5)	..	..
Change from baseline to 24 months (% , mmol/mol)	0.2 (0.7), 1.7 (8.1)	-0.2 (1.3), -2.7 (14.5)	-0.4 (-1.1 to 0.2), -4.4 (-11.5 to 2.7)	0.15

liraglutide in whole-pancreas transplant patients

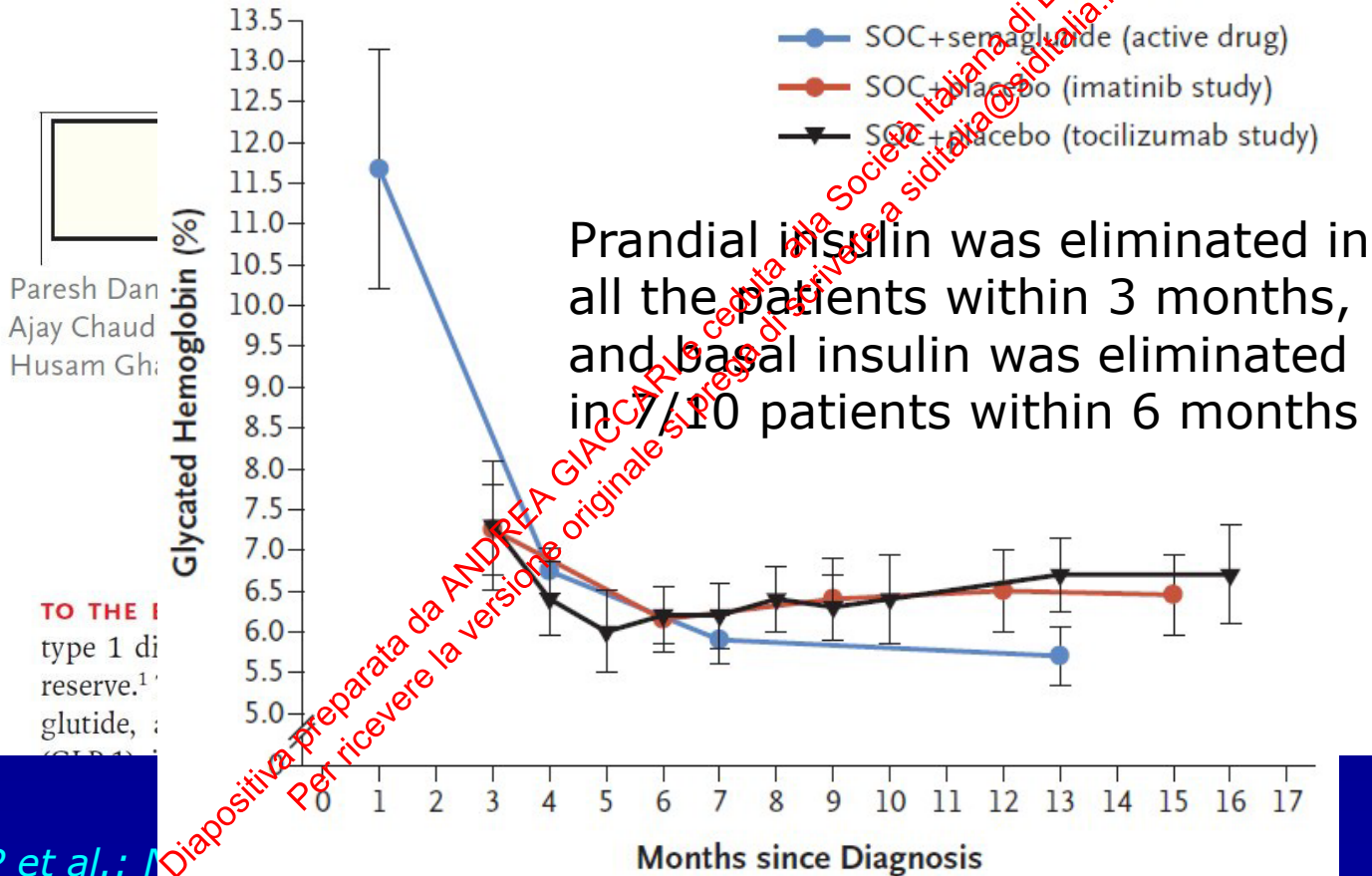
five patients transplanted after 25-48 years of type 1 diabetes



SGLT-2i normalizes fasting hyperglycemia and improves postprandial glucose tolerance in totally pancreatectomized patients

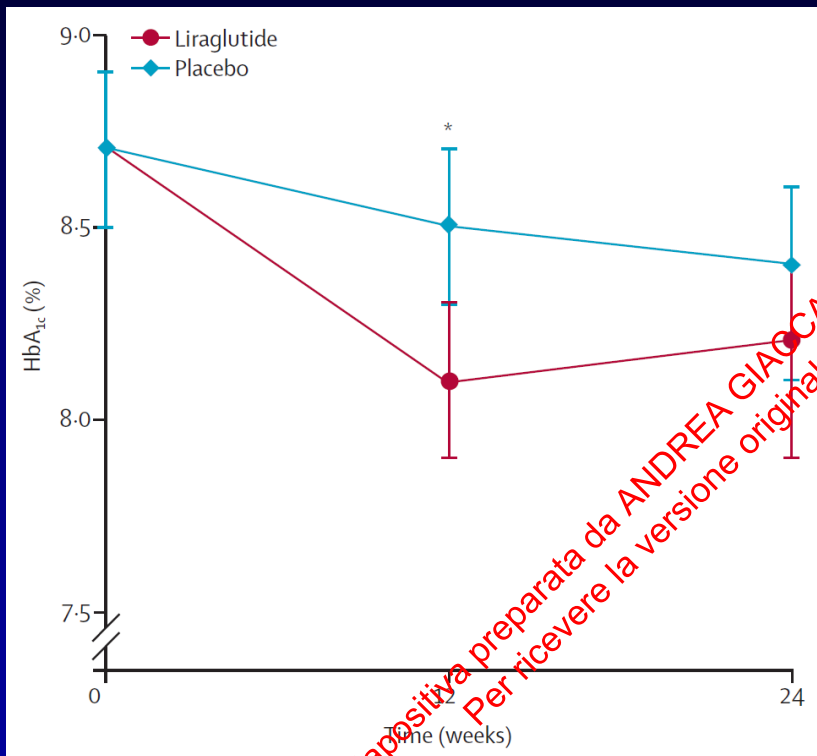


semaglutide in early type 1 diabetes (?)

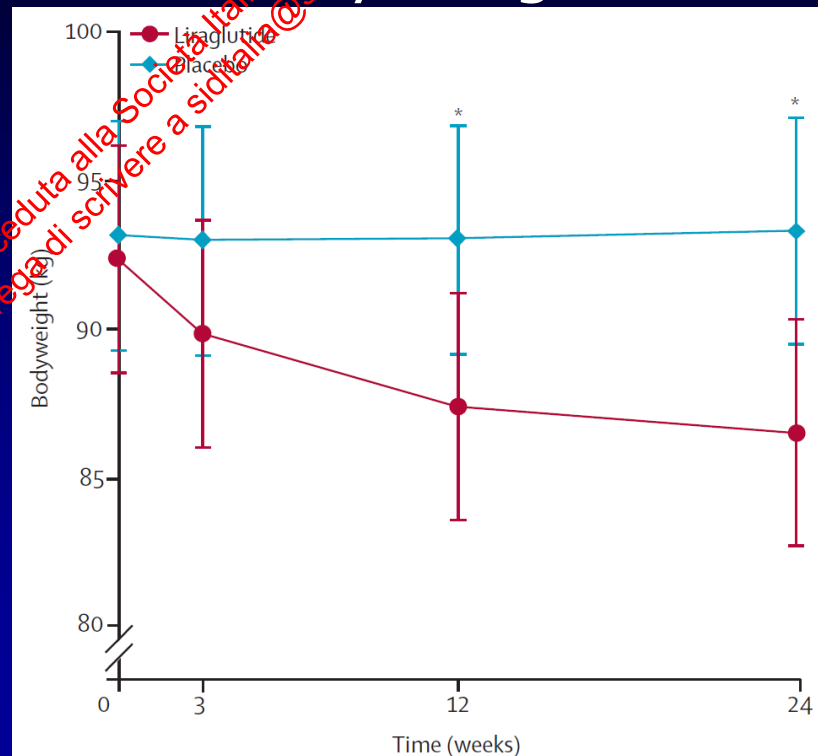


Lira-1: liraglutide in obese type 1 diabetes

HbA_{1c}

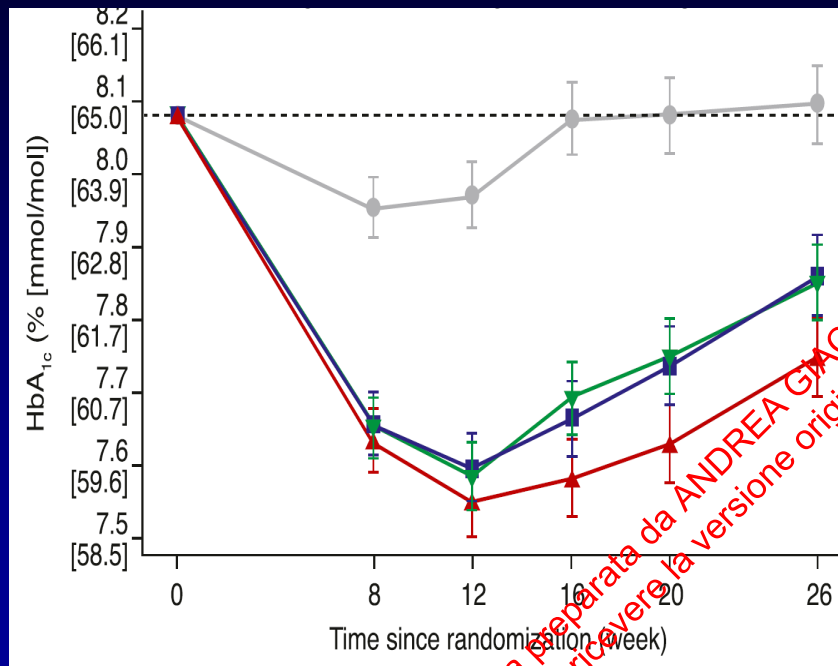


body weight

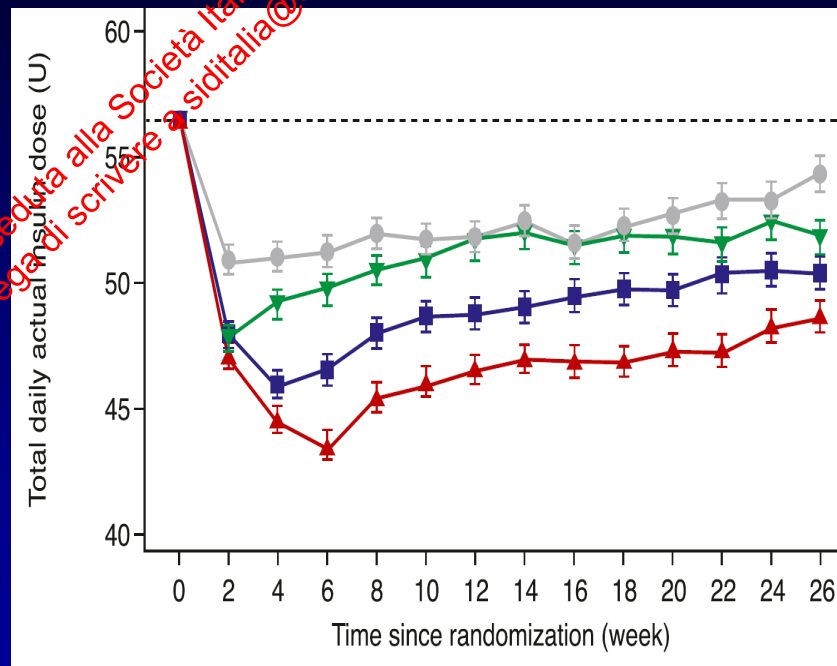


ADJUNCT TWO: liraglutide in type 1 diabetes

HbA_{1c}



daily insulin dose



▲ Lira 1.8 mg ■ Lira 1.2 mg ▼ Lira 0.6 mg ● Placebo

prime considerazioni

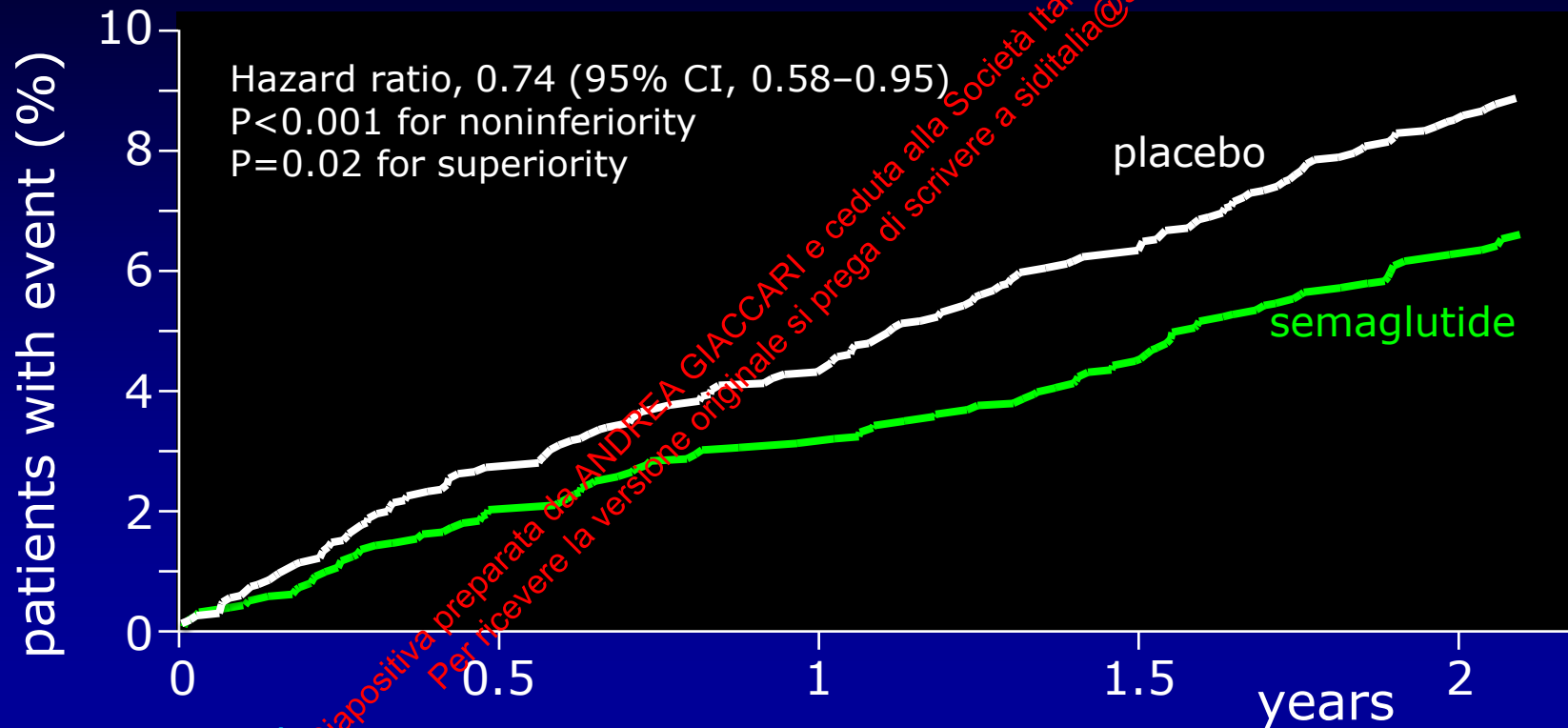
esistono numerose evidenze di efficacia di SGLT-2i e GLP-1 RA in pazienti con diabete NON di tipo 2

ma SGLT-2i e GLP-1 RA sono utili solo per efficacia sul controllo del diabete?

Diapositiva preparata da ANDREA GIACCARI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale, prega di scrivere a siditalia@siditalia.it

SUSTAIN 6: primary outcome: 3-point MACE

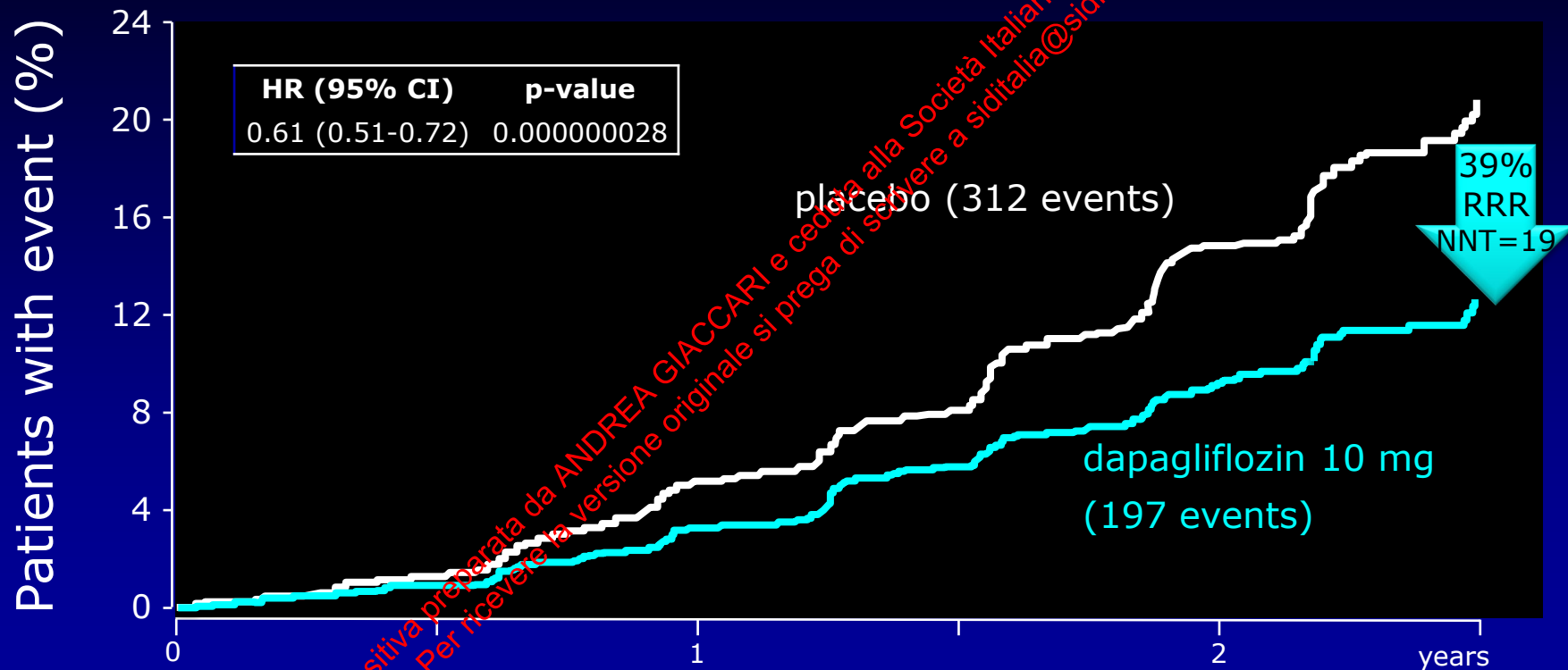
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



Marso SP et al.: NEJM 375:1834, 2016

DAPA-CKD: primary composite renal

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

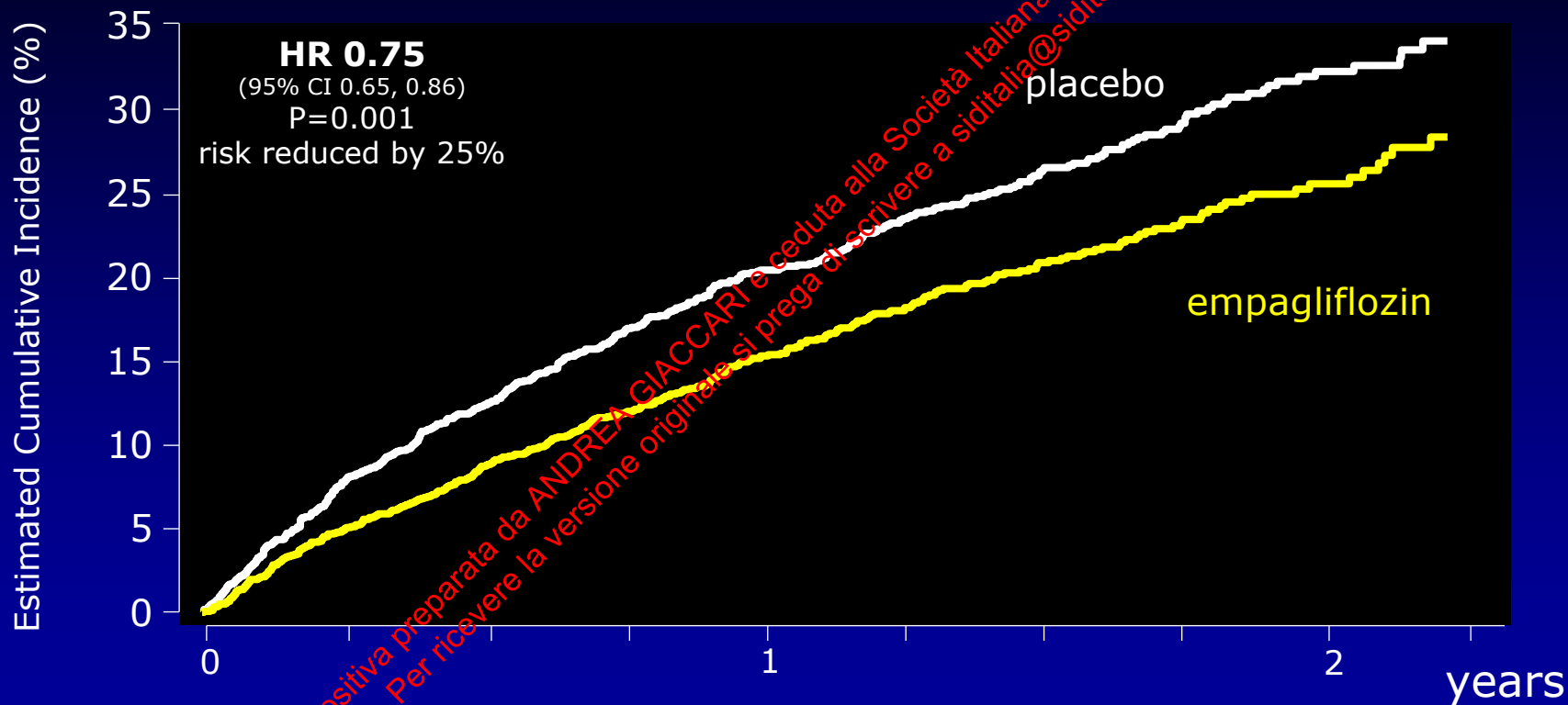


*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR $<15\text{mL/min/1.73m}^2$ for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld

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

EMPEROR-Reduced: primary outcome (hHF and CV death)

Patients with Heart Failure and Reduced Ejection Fraction



ADA/EASD Consensus 2022

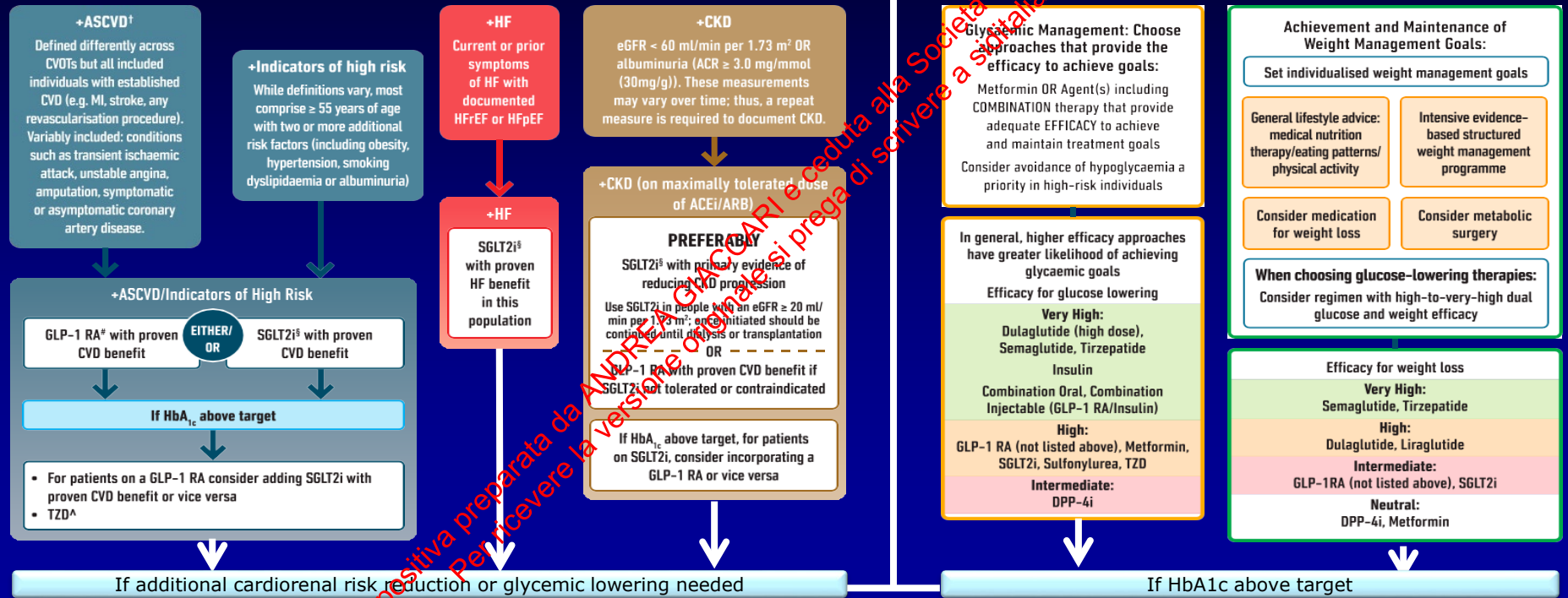
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



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

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)*

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals



outcome trials with SGLT-2i or GLP-1 RA in patients w/o diabetes

outcome trial

DAPA-HF

EMPEROR-Reduced

EMPEROR-Preserved

DELIVER

DAPA-CKD

EMPA-Kidney

SELECT

HR (95% CI)

0.73 (0.60 – 0.88)

0.78 (0.64 – 0.97)

0.78 (0.64 – 0.94)

0.81 (0.68 – 0.96)

0.50 (0.35 – 0.72)

0.82 (0.68 – 0.99)

0.80 (0.72 – 0.90)

0.25 1.0 2.0
favors drug favors placebo

1 Packer M et al.: NEJM 383:1413, 2020 doi: 10.1056/NEJMoa2022190

2 McMurray JJV et al.: NEJM 381:1995, 2019 doi: 10.1056/NEJMoa1911303

3 Filippatos G et al.: Circulation 146:676, 2022 doi: 10.1056/NEJMoa1911303

4 Solomon SD et al.: NEJM 387:1089, 2022 doi: 10.1056/NEJMoa2206286

5 Heerspink HJL et al.: NEJM 383:1436, 2020 doi: 10.1056/NEJMoa2024816

6 Herrington WG et al.: NEJM 288:117, 2023 doi: 10.1056/NEJMoa2204233

7 Lincoff AM et al.: NEJM 389:2221, 2023 doi: 10.1056/NEJMoa2307563

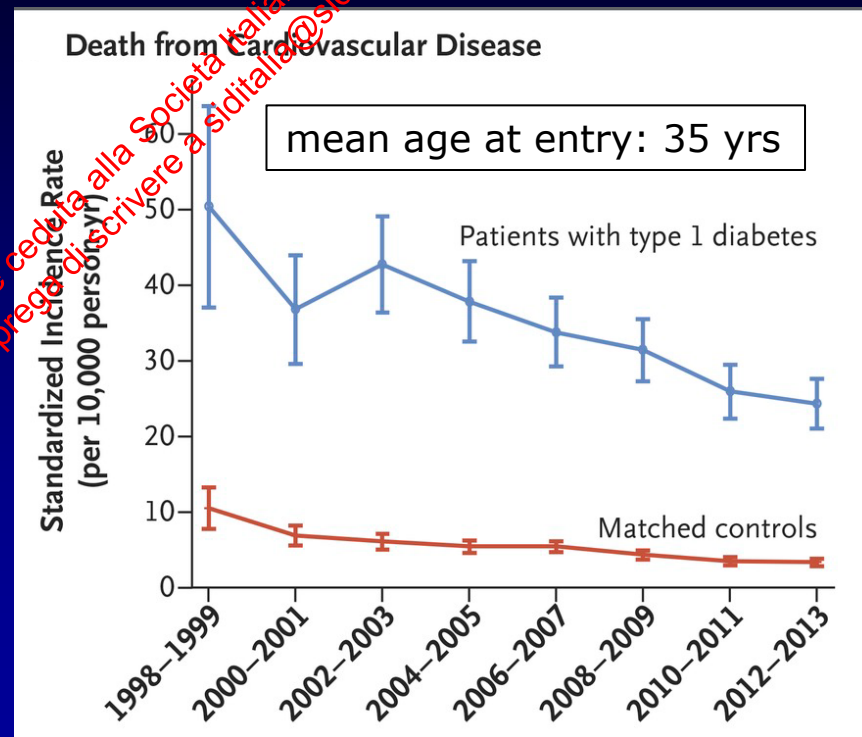
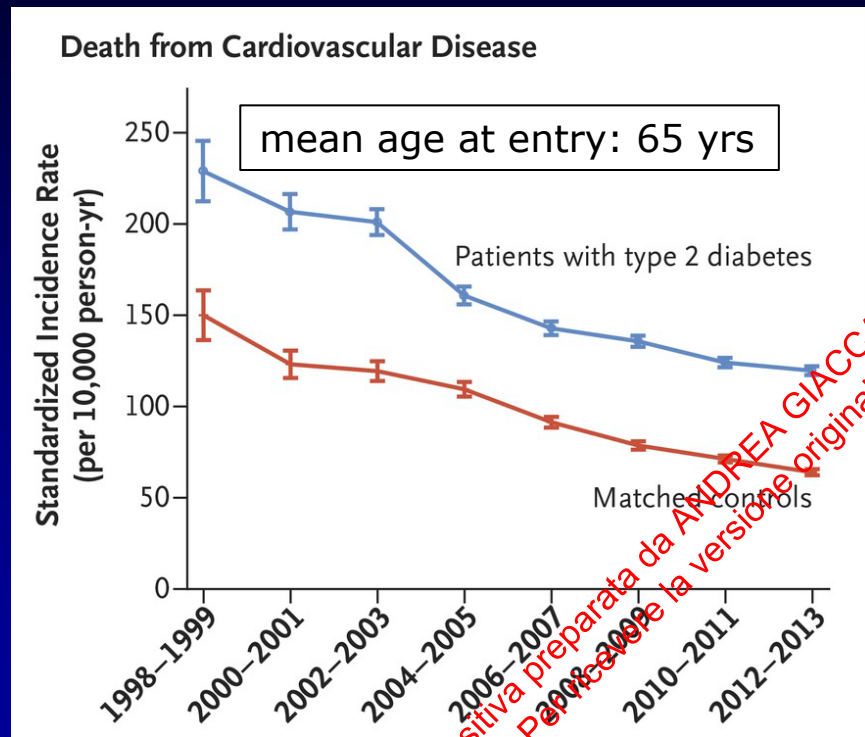
alcune considerazioni

esistono numerose evidenze di efficacia di SGLT-2i e GLP-1 RA in pazienti con diabete NON di tipo 2

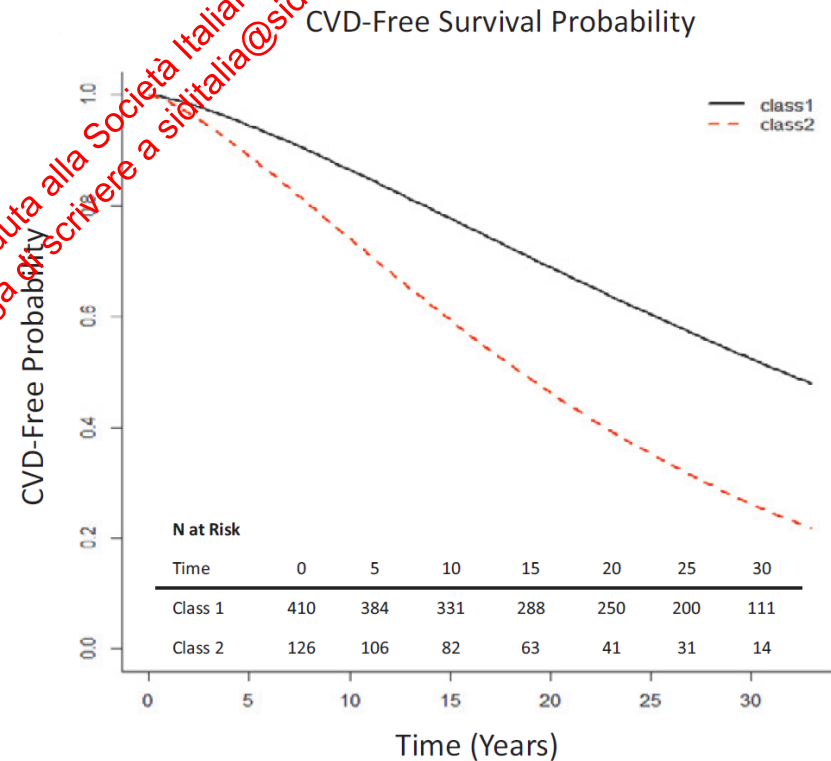
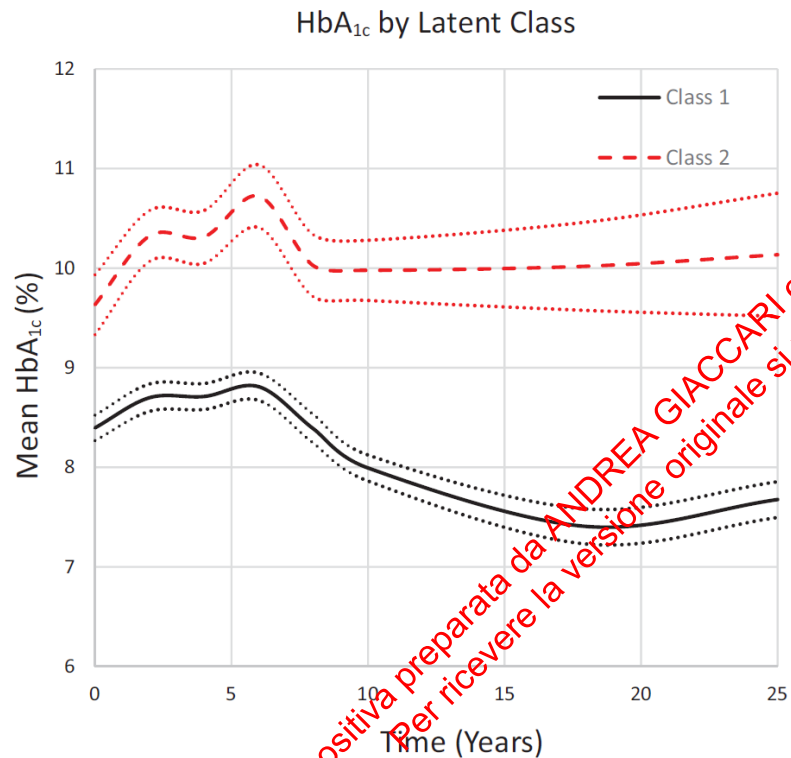
SGLT-2i e GLP-1 RA hanno efficacia di prevenzione (e indicazione) cardiovascolare e renale anche in pazienti NON diabetici

ma i pazienti con diabete NON di tipo 2 hanno bisogno di prevenzione cardiovascolare e renale?

death from cardiovascular disease in diabetes

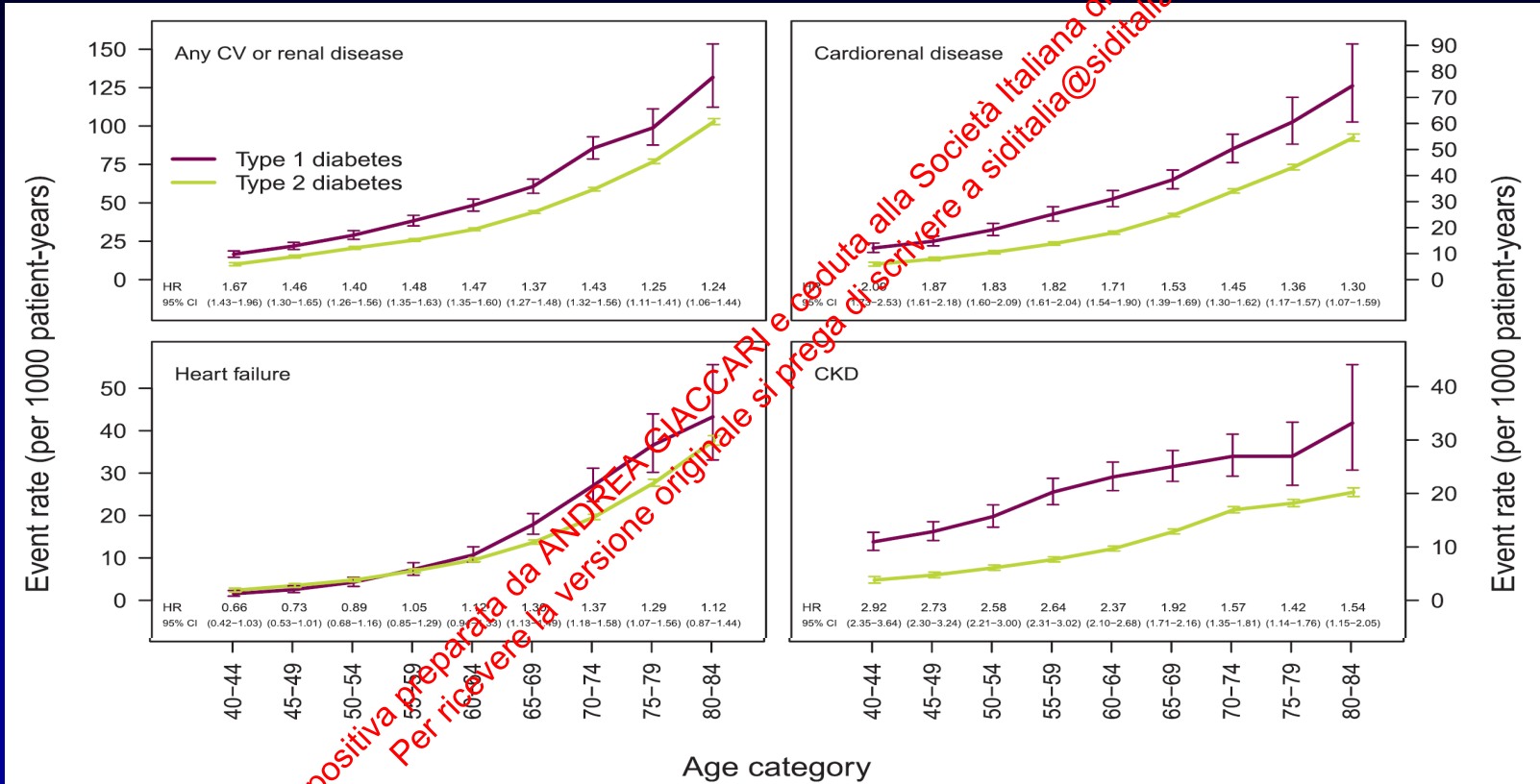


HbA_{1c} trajectories and cardiovascular risk in type 1 diabetes

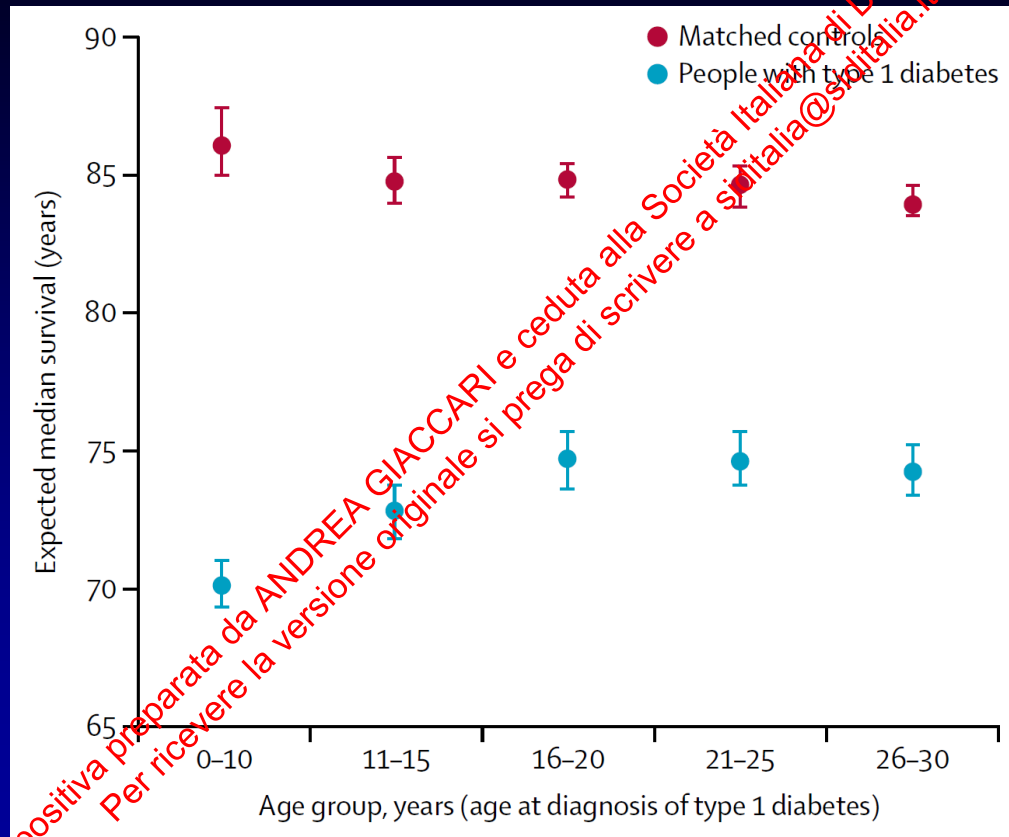


cardio-renal burden in type 1 diabetes

as compared with age-matched type 2 diabetes

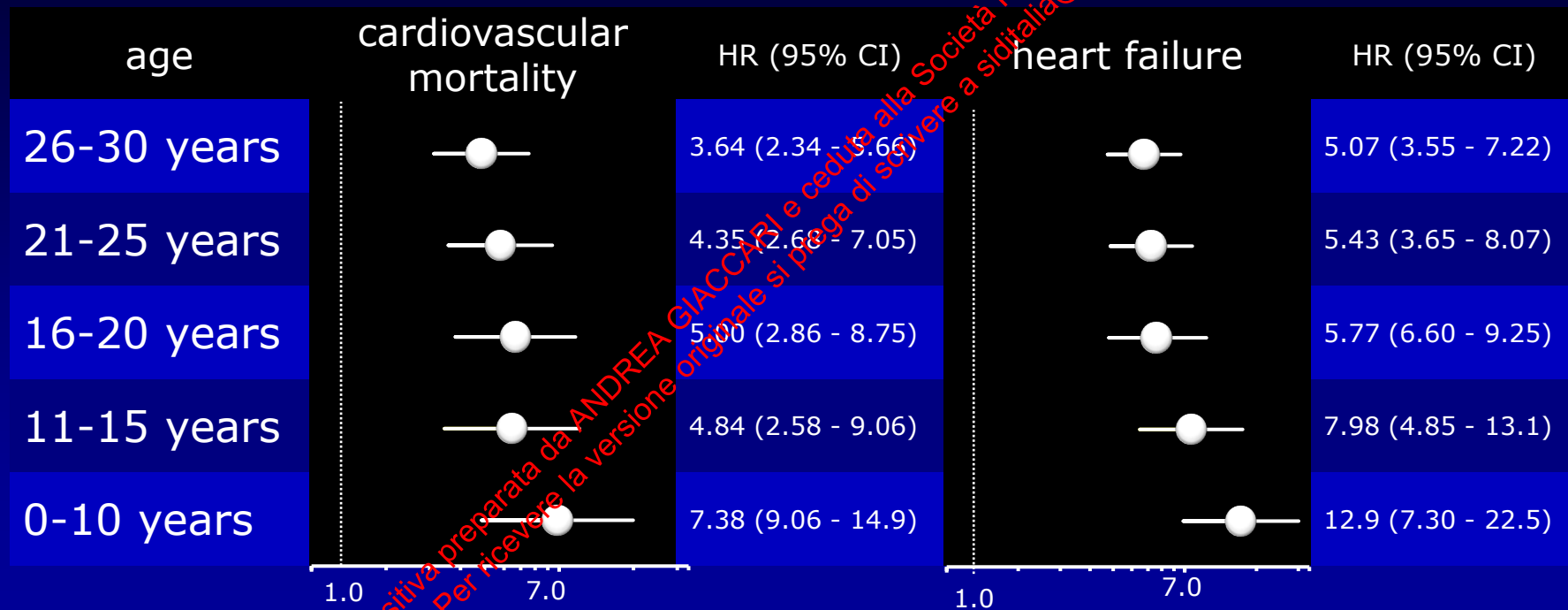


Life-years lost in type 1 diabetes



excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset

a real-world study in UK



alcune considerazioni

esistono numerose evidenze di efficacia di SGLT-2i e GLP-1 RA in pazienti con diabete NON di tipo 2

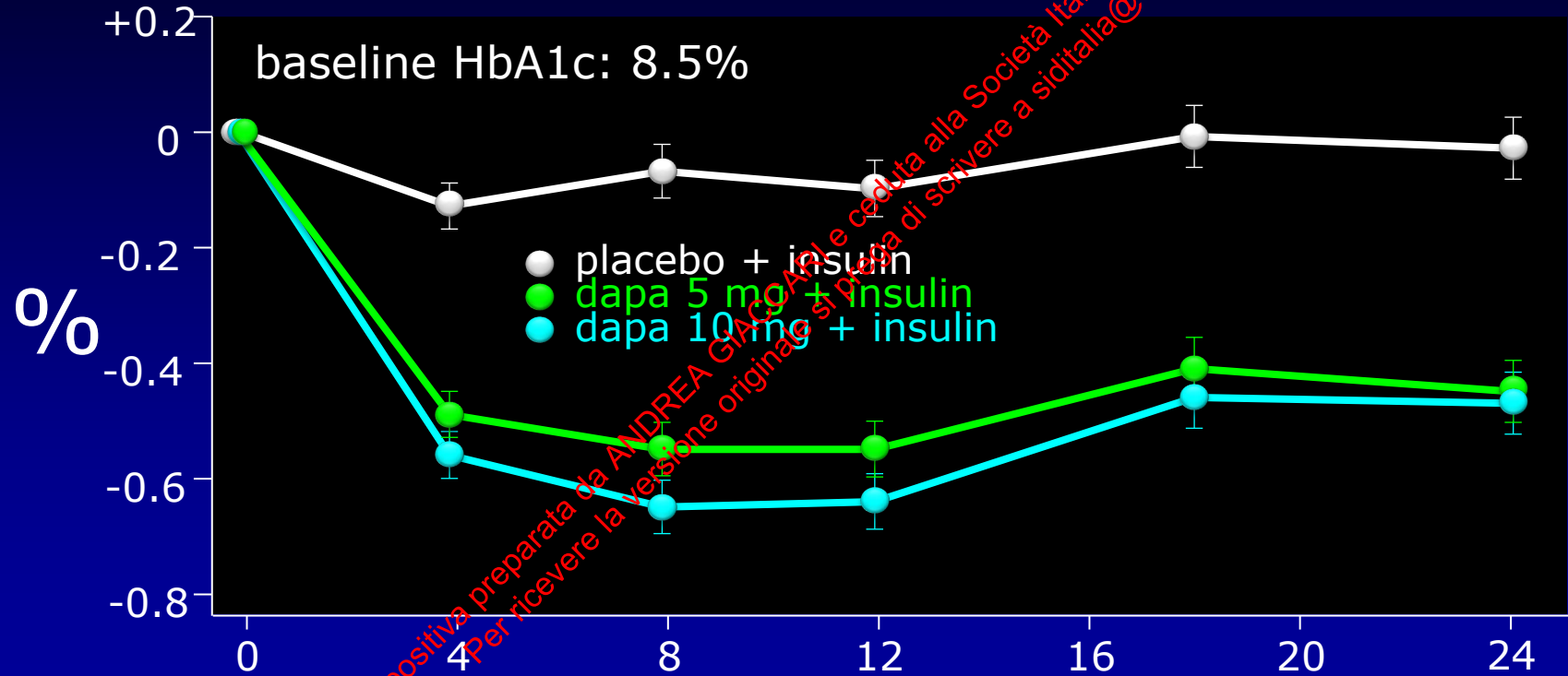
SGLT-2i e GLP-1 RA hanno efficacia di prevenzione (e indicazione) cardiovascolare e renale anche in pazienti NON diabetici

i pazienti con diabete NON di tipo 2 hanno bisogno di prevenzione cardiovascolare e renale

quali sono i rischi nell'uso di SGLT-2i e GLP-1 RA?

SGLT2i in type 1 diabetes: DEPICT-1

primary outcome: change in HbA1c over 24 weeks



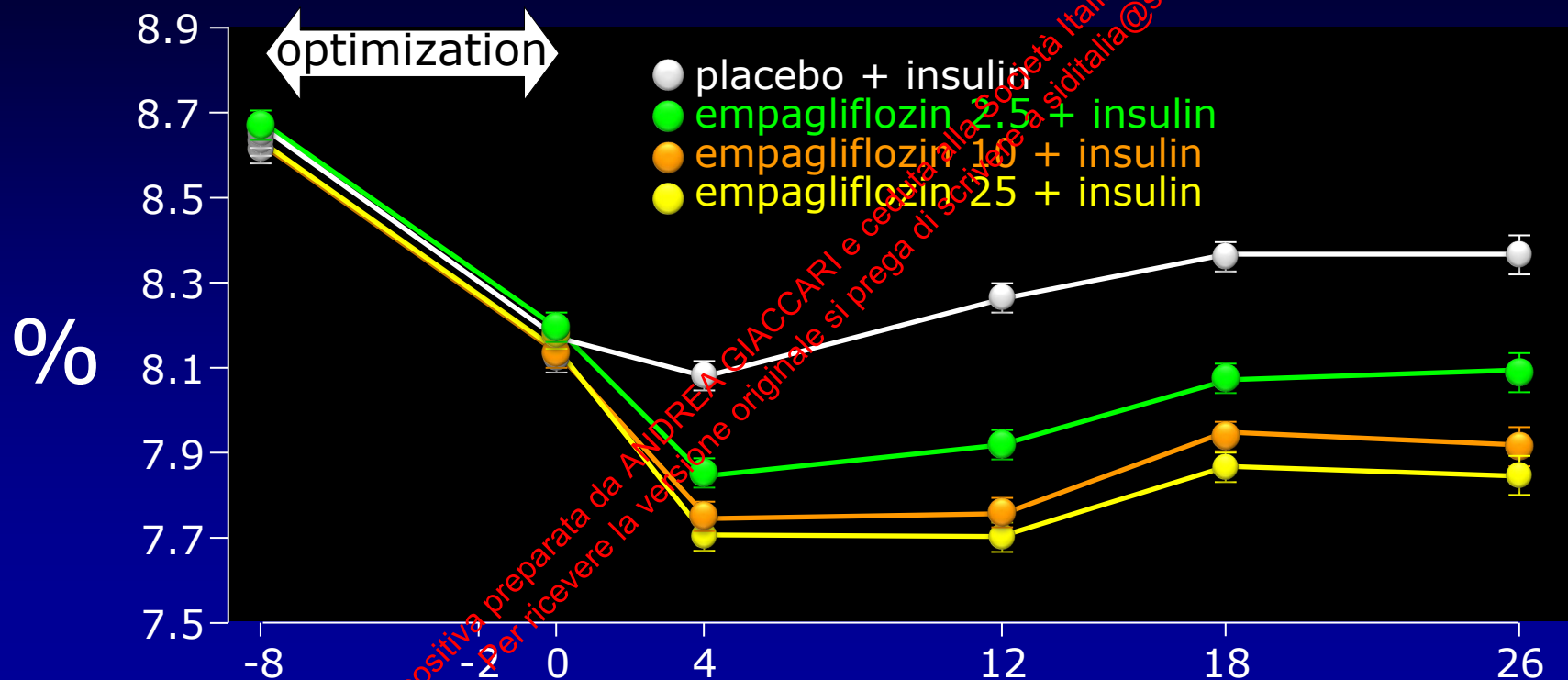
Dandona P, et al. Lancet DE 5:864, 2017

SGLT2i in type 1 diabetes: DEFICT-2

serious adverse events

	dapa 5 + insulin (n=271)	dapa 10 + insulin (n=270)	placebo + insulin (n=272)
Serious adverse event leading to study discontinuation	17 (6.3%)	12 (4.4%)	11 (4.0%)
Hypoglycaemia			
At least one serious adverse event of hypoglycaemia	5 (1.8%)	0	1 (0.4%)
Hypoglycaemia leading to study discontinuation	2 (0.7%)	0	0
Ketone-related events			
One or more ketone-related serious adverse events	9 (3.3%)	3 (1.1%)	0
DKA leading to study discontinuation	8 (3.0%)	3 (0.7%)	0
Death	0	0	0

EASE 3: change in HbA1c after insulin optimization efficacy with low dose empagliflozin



EASE 1-3: risk of DKA

low risk with low dose empagliflozin?

	EASE 2 and 3 pooled			EASE 3	
	empa 10mg (N = 491)	empa 25mg (N = 489)	Placebo (N = 484)	empa 2.5 mg (N = 241)	Placebo (N = 241)
Patients with certain DKA	21 (4.3)	16 (3.3)	6 (1.2)	2 (0.8)	3 (1.2)
Patients with >1 event	0	1	0	0	0
Number of events	21	18	6	2	3
Rate per 100 PY	5.94	5.05	1.77	1.65	2.52
Severe events	2	6	1	0	1
Moderate events	13	8	4	0	1
Mild events	6	4	1	2	1
Patients with potential DKA	15 (3.1)	13 (2.7)	6 (1.2)	3 (1.2)	1 (0.4)
Patients with ketosis	155 (31.6)	178 (36.4)	76 (15.7)	41 (17.0)	32 (13.3)
Patients with BHB >3.8 mmol	21 (13.5)	17 (9.6)	4 (5.3)	7 (17.1)	2 (6.3)

SGLT-2i company renounces to type 1 diabetes

NEWS



The BMJ

Cite this as: *BMJ* 2022;376:o373
<http://dx.doi.org/10.1136/bmj.o373>
Published: 14 February 2022

Type 1 diabetes drug was withdrawn because of a “commercial conflict of interest,” charity argues

Elisabeth Mahase

Pharmaceutical company AstraZeneca has withdrawn the type 1 diabetes indication for its drug dapagliflozin because of fears that required changes to the product label would cause confusion among doctors when prescribing it for other conditions.

The company voluntarily removed the type 1 diabetes indication for 5 mg dapagliflozin in October 2021 after UK and EU medicines regulators advised that—despite there being no new safety or efficacy concerns—an inverted black triangle would need to be added to the label to signify that additional monitoring is required when this drug is prescribed.

Black triangle awareness

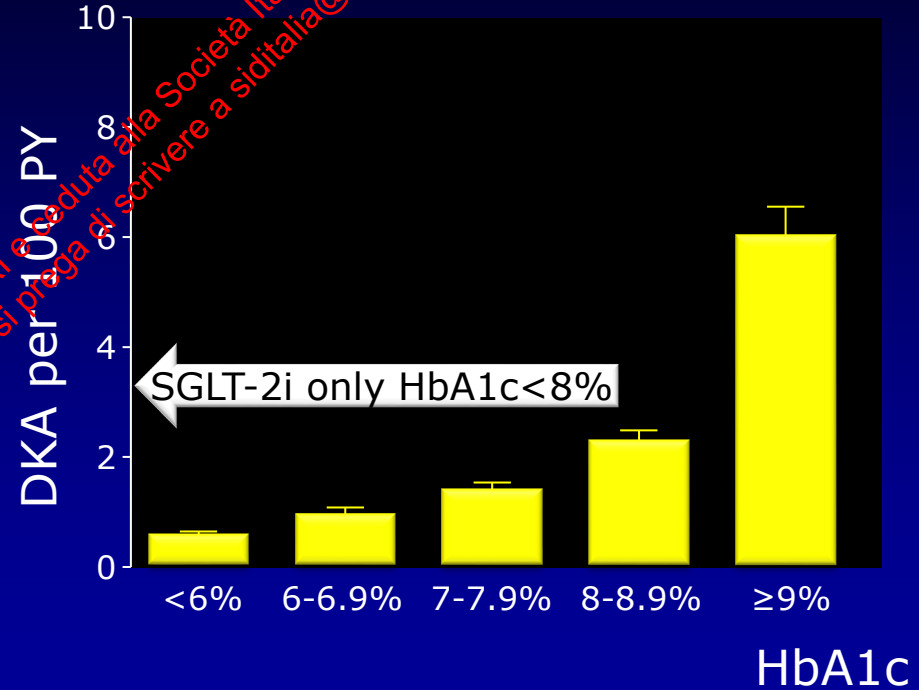
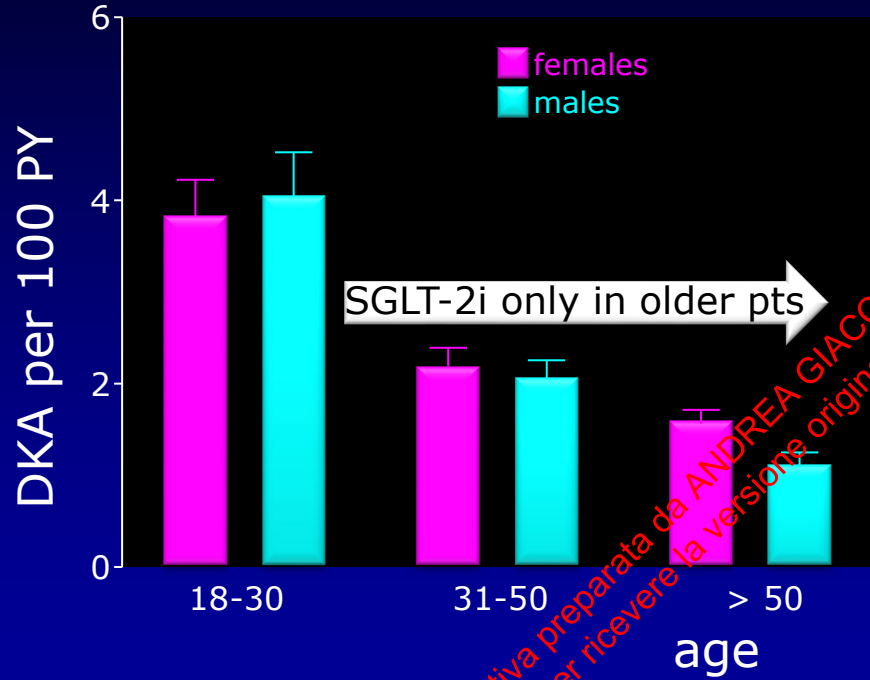
While the use of the inverted black triangle is a relatively common practice with drugs new to the European market or those that have a new indication added,¹ research by the European Medicines Agency found that only 51% of the 2918 people asked said they had seen the black triangle and the accompanying statement before.

Awareness of the symbol also varied between different respondents, with the lowest awareness among patients (30%) and the highest among pharmacists (83%). Additionally, only 36% (1050 of

Mahase E.: *BMJ* 2022; 376 doi: 10.1136/bmj.o373

event rates and risk factors for DKA

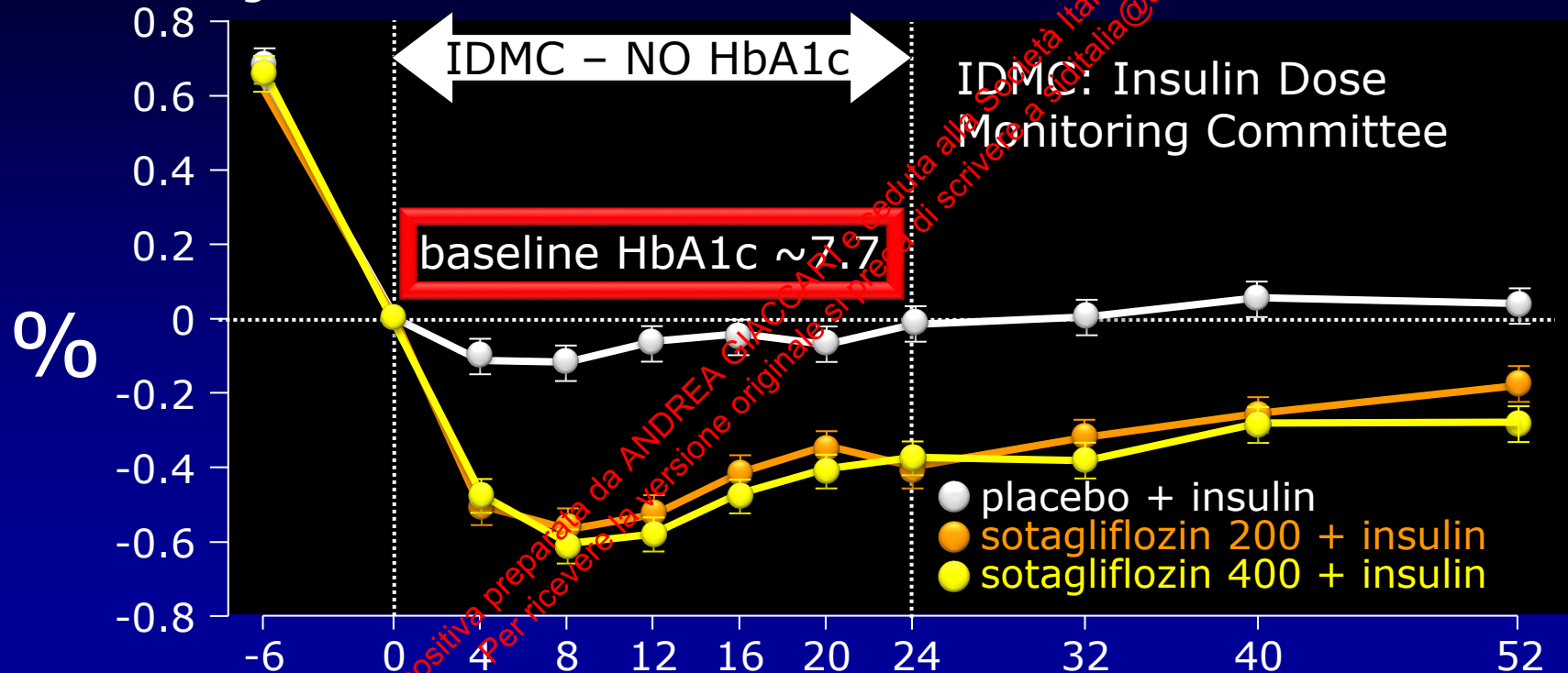
DPV Registry Based on 46,966 Patients (German)



dual SGLT*i* in type 1 diabetes: inTandem 2

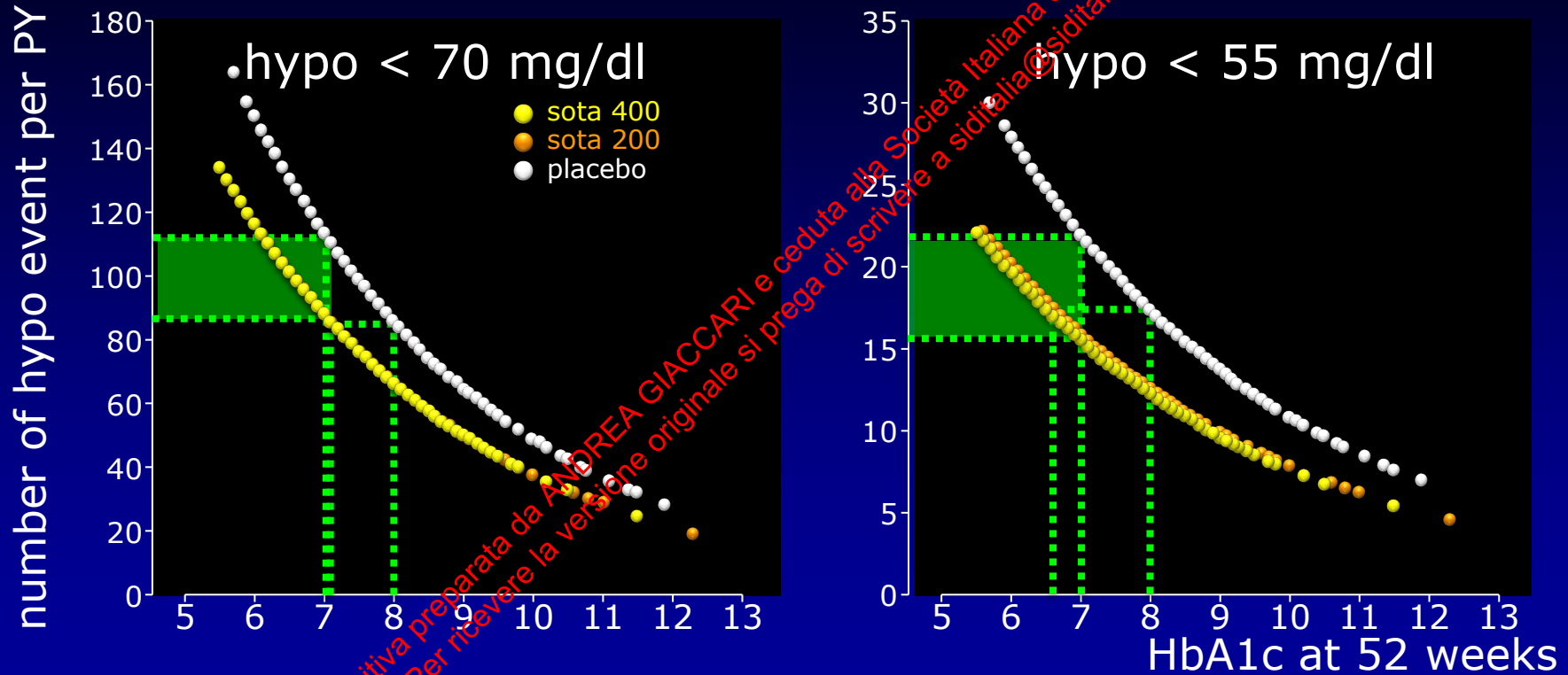
change in HbA1c after insulin optimization

screening: HbA1c ~8.4



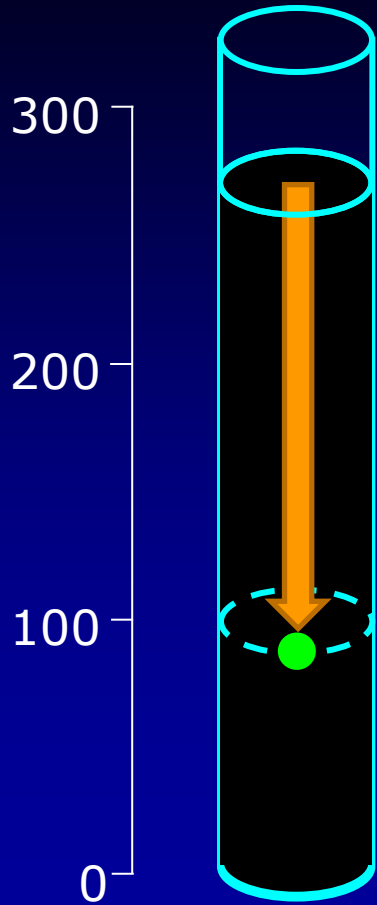
rate of hypoglycemia with sotagliflozin

inTandem 1&2 patient level meta-analysis



Danne T, Pettus J, Giaccari A. et al.: *Diabetes Technol Ther* 21:471, 2019
doi: 10.1089/dia.2019.0157.

flux in glycosuria



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

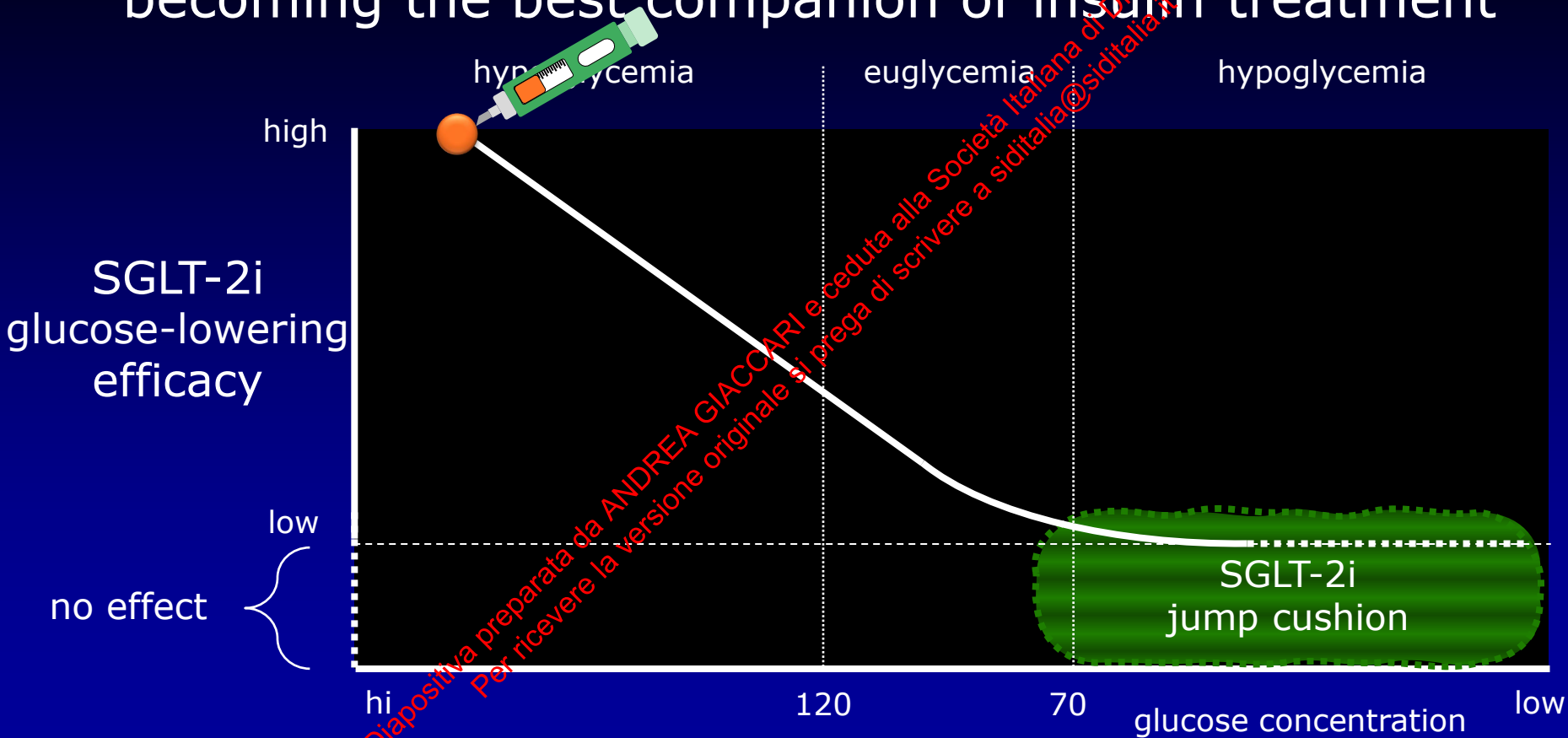
1. glycaemia
2. renal function (eGFR)

when blood glucose reaches normal values glycosuria is virtually absent

Diapositiva preparata da ANDREA GIACCARI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a andrea.giaccari@siditalia.it

SGLT-2i lose all their efficacy in hypoglycemia

becoming the best companion of insulin treatment



GLP-1 RA and SGLT-2i in patients with type 1 diabetes

a real-world study in UK

adverse event

HR (95% CI)

DKA

2.10 (1.10 - 4.10)

severe hypo

0.70 (0.51 - 1.00)

UTI/pyelonephritis

2.30 (1.12 - 4.55)

Genital candidiasis

1.00 (0.42 - 2.39)

Acute pancreatitis

1.00 (0.42 - 2.39)

Gastrointestinal upset

0.80 (2.39 - 1.20)

0.5 1.0 2.0 5.0

better SGLT-2i better GLP-1 RA

GLP-1 RA and SGLT-2i in patients with type 1 diabetes

a real-world study in UK

adverse event

HR (95% CI)

all cause mortality

0.70 (0.38 - 1.10)

Hospitalization

0.60 (0.46 - 0.76)

Heart failure

0.40 (0.23 - 0.83)

Myocardial infarction

0.80 (0.46 - 2.46)

CKD

0.50 (0.28 - 0.86)

Stroke / TIA

1.00 (0.86 - 2.30)

Neuropathy

0.60 (0.31 - 1.10)

Retinopathy

1.00 (0.56 - 1.80)

0.25 0.5 1.0 2.5
better SGLT-2i better GLP-1 RA

Final remarks

SGL
failu
with

Ho un paziente con diabete che
ha un problema (DKD, HF, CVD)

GLP
pati
in p

Ho farmaci per il diabete che
possono risolvere il problema

Oth
be a

base su che evidenze prescrivere?

Do v
how

EMA/AIFA non approvano

Diapositiva preparata da ANDREA GIACCARDI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a slutitalia@slutitalia.it

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Serena

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Umberto

Simona

Ilaria

Teresa

Michela



Gemelli



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