I farmaci ipoglicemizzanti nefroprotettivi

Il punto di vista del nefrologo

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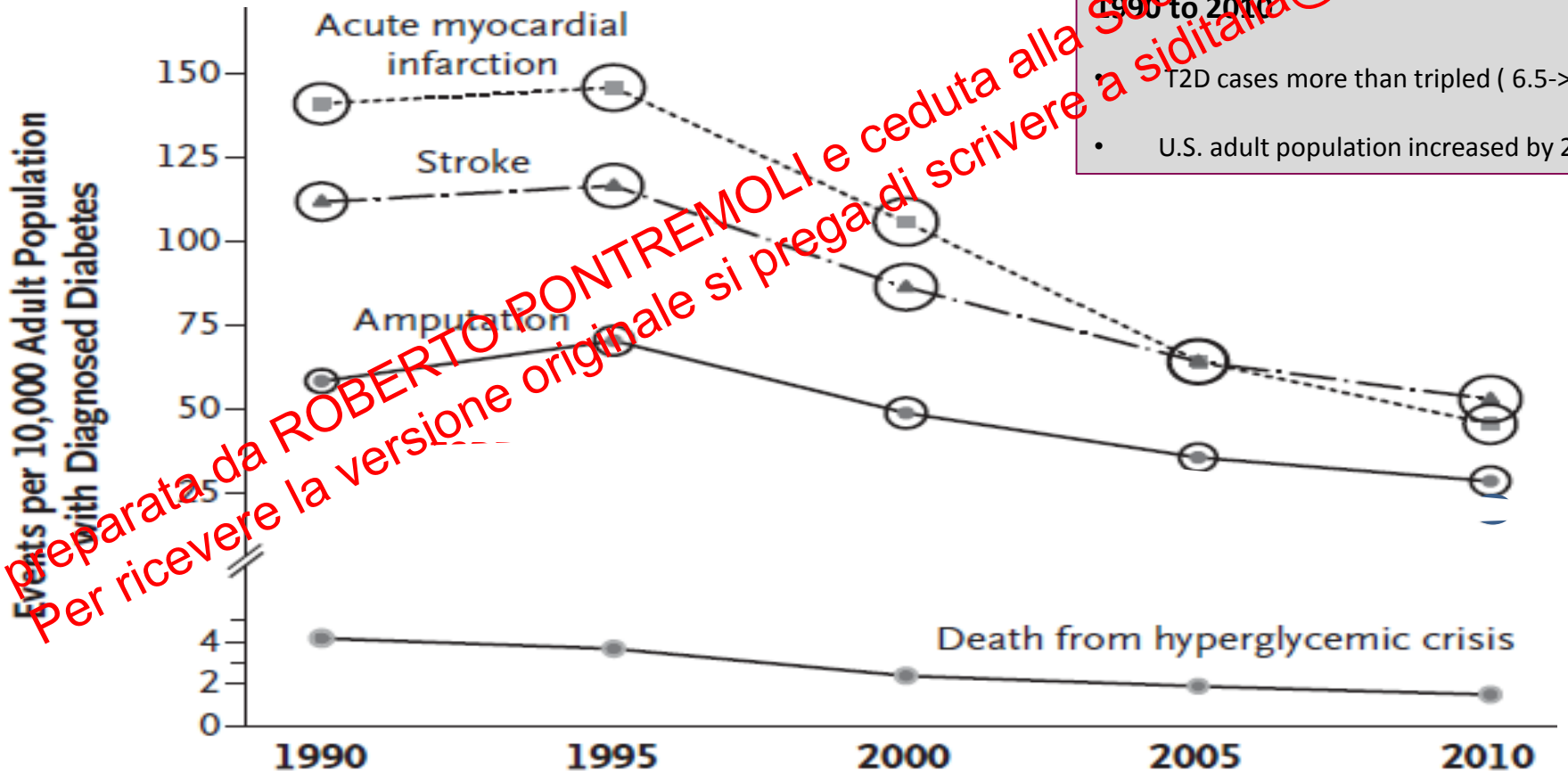
CONFLITTO DI INTERESSE

- ASTRAZENECA
- BOEHRNGER-INGELHEIM
- MENARINI
- LILLY
- MSD
- NOVARTIS
- ALFA-SIGMA
- ASTELLAS
- TEIJIN PHARMA
- ALGORYTM SAS

Changes in Diabetes-Related Complications in the United States, 1990–2010

Data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System



1990 to 2010

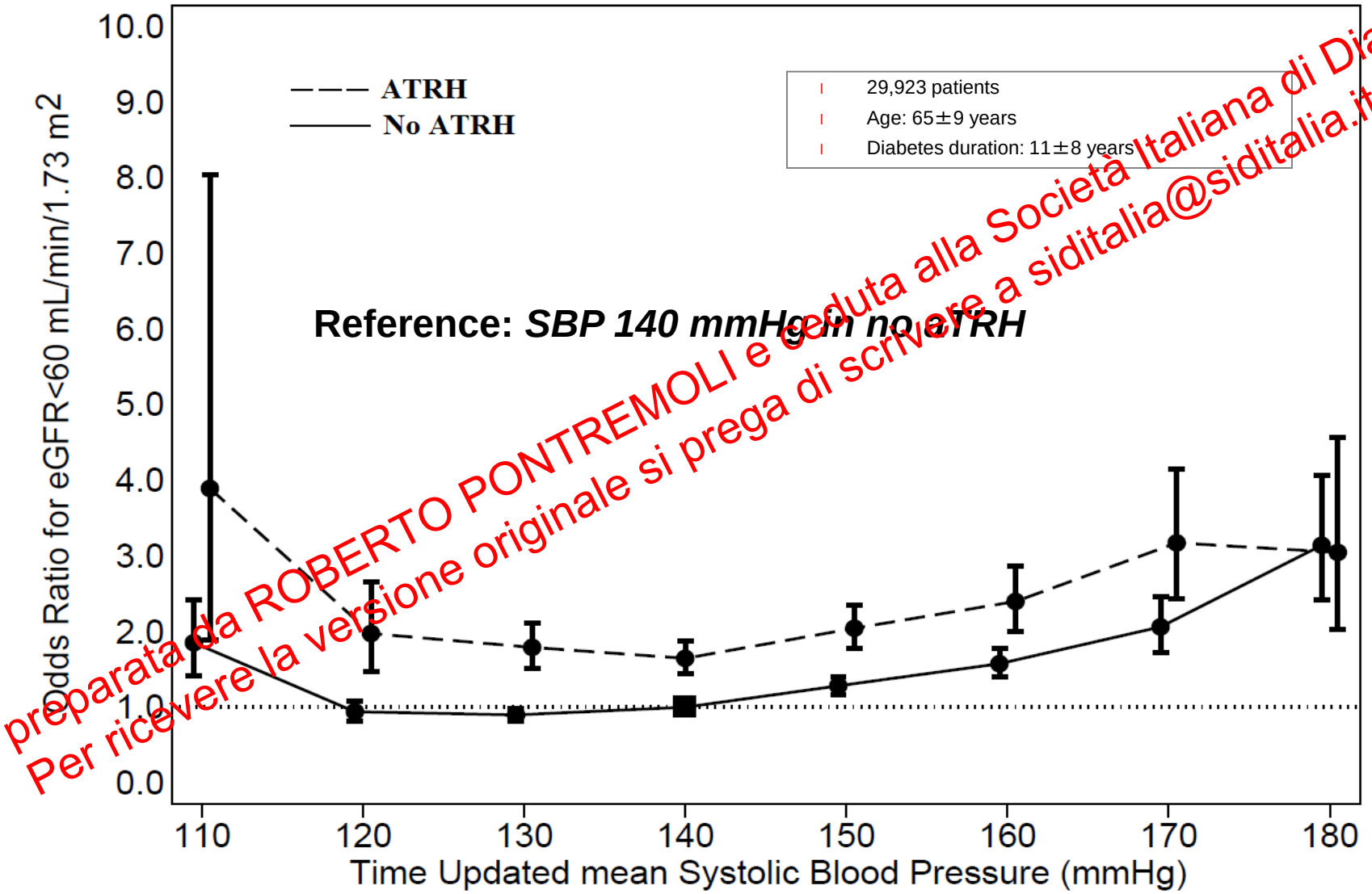
- T2D cases more than tripled (6.5->20.7 m)
- U.S. adult population increased by 27% (178->226 m)

Gregg, NEJM 2014

Despite experimental evidence supporting *super-normalization* of risk multiple factors, a J-curve phenomenon has traditionally curbed renal protection in clinical practice.

Resistant hypertension and renal outcome in T2DM

The J curve relationship between BP and renal function



Viazzi F, Pontremoli R et al. J Am Heart Assoc 2017

SGLT2-i and GLP-1ras:
the dawn of a new era in renal protection?

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	1359	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**

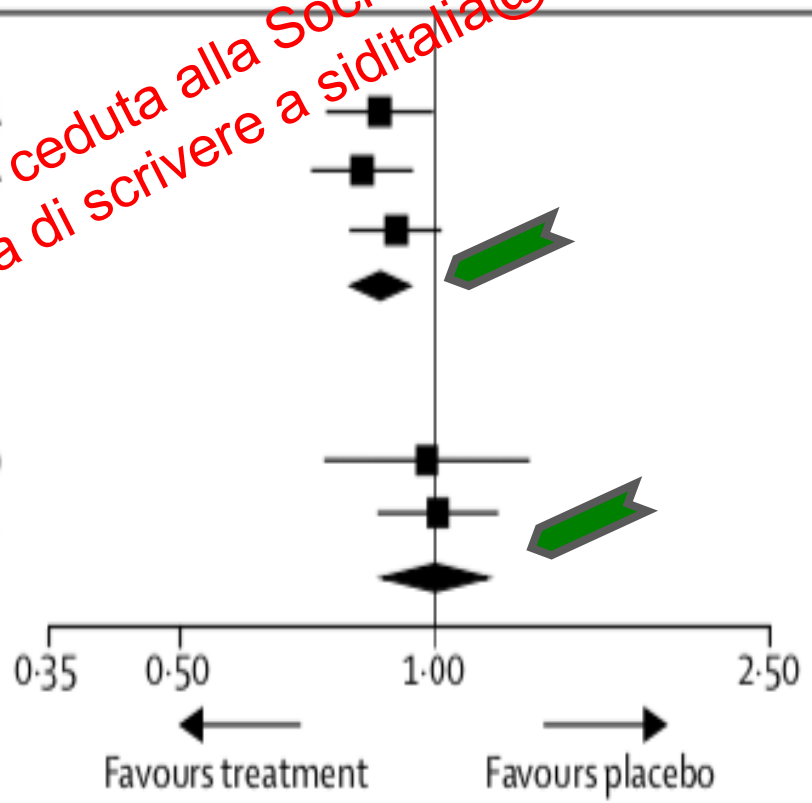
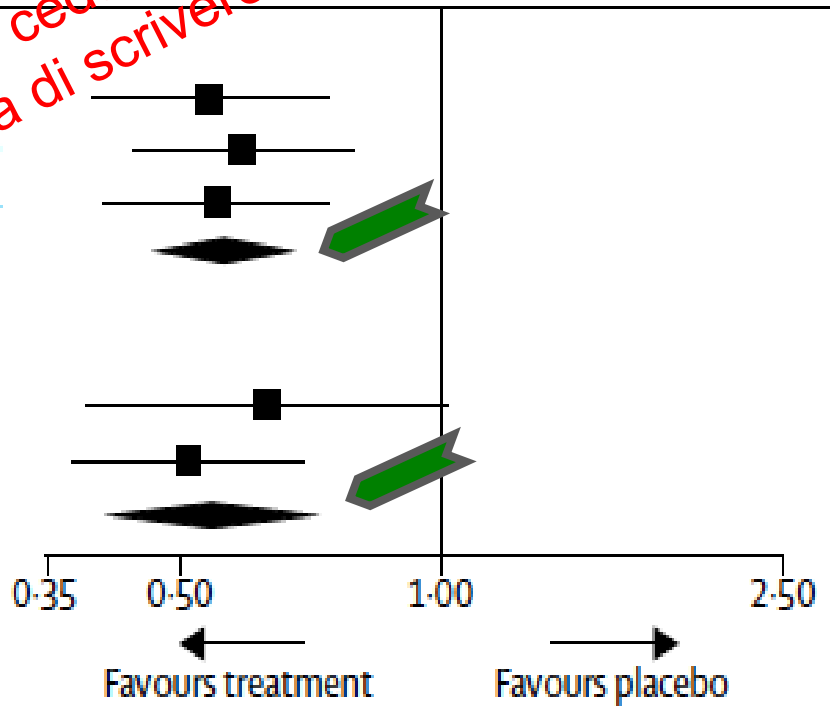


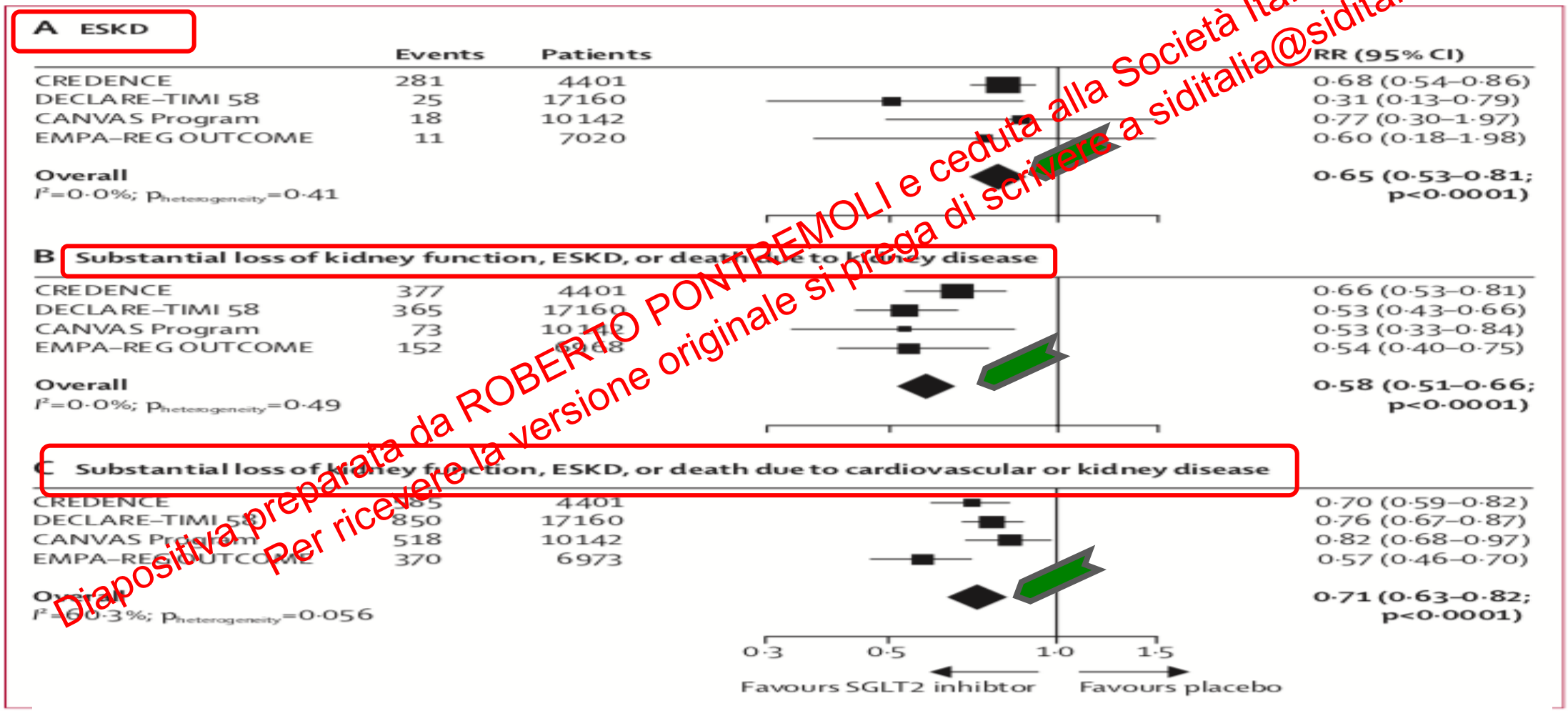
Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	2144/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**



SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine



www.thelancet.com/diabetes-endocrinology Published online September 5, 2019 http://dx.doi.org/10.1016/S2213-8587(19)30256-6

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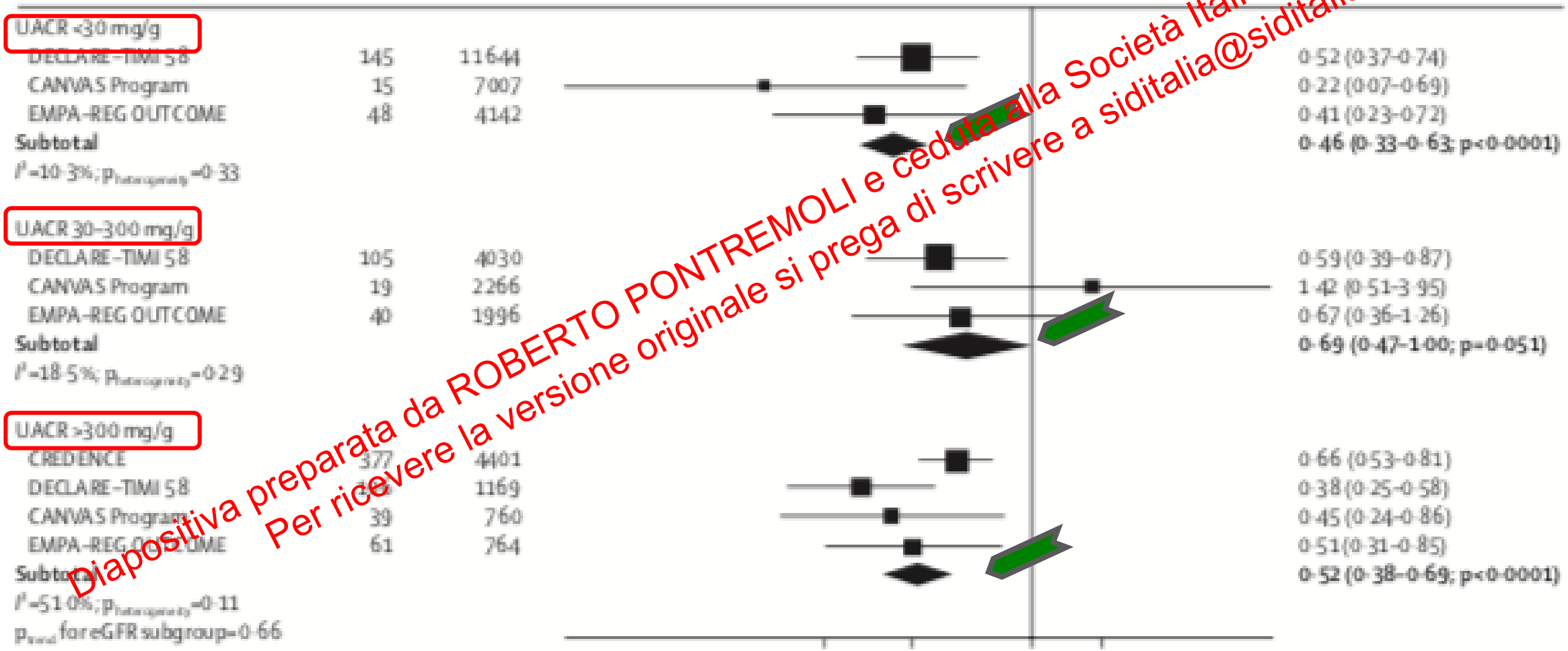

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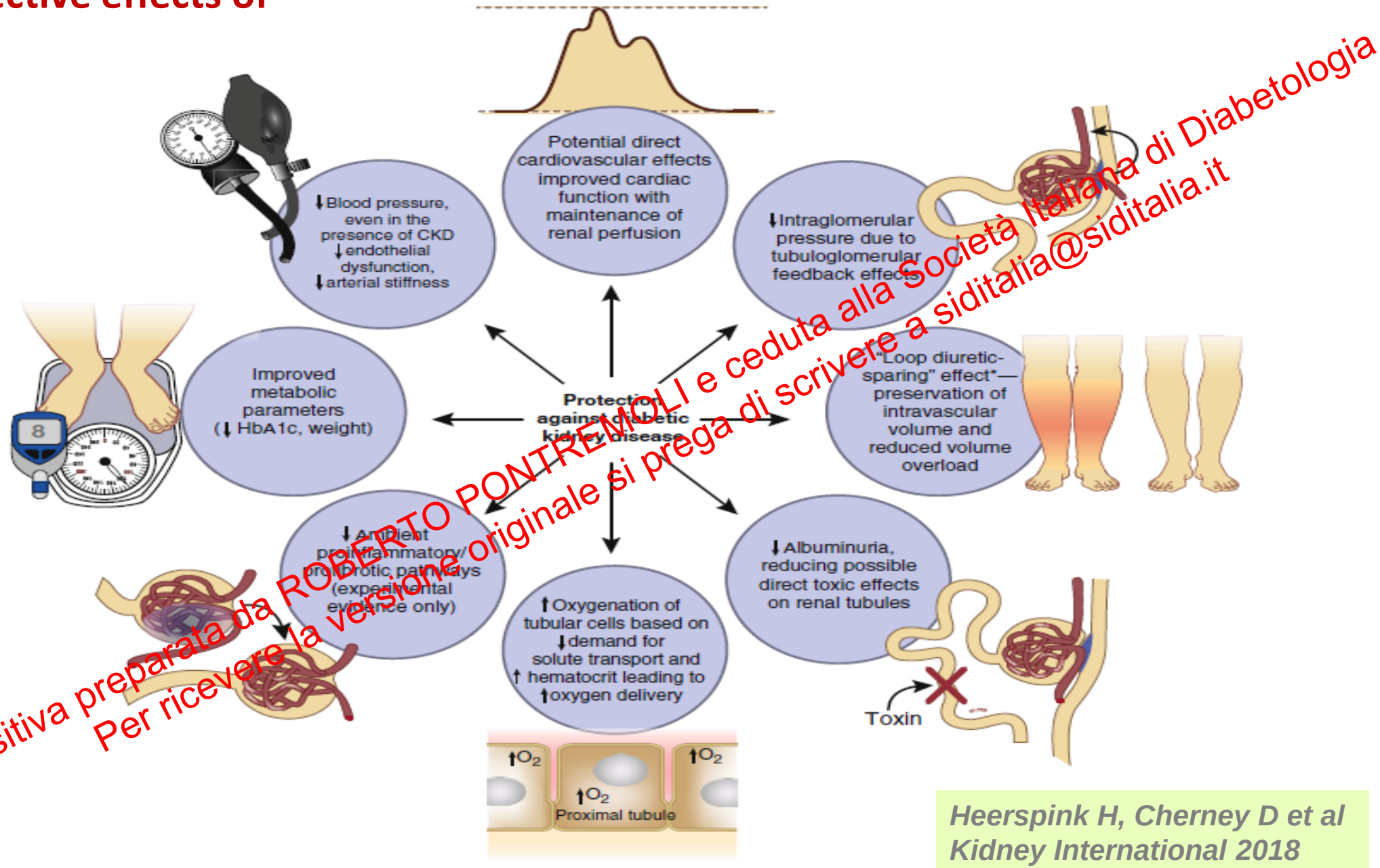
Renoprotective effects of SGLT2-i



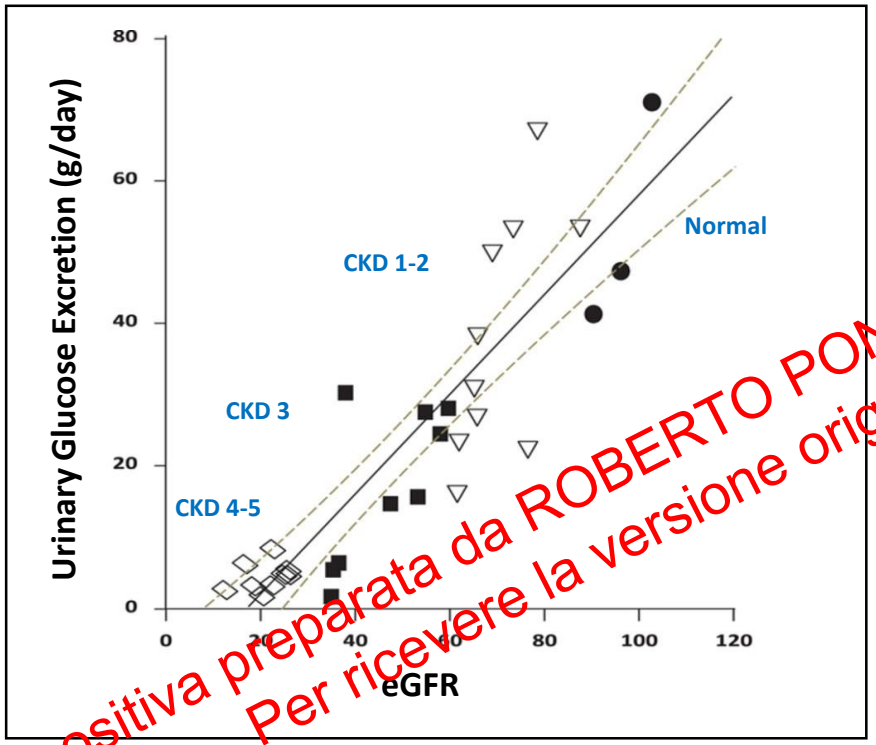
Heerspink H, Cherney D et al
Kidney International 2018

Figure 3 | Summary of potential mechanisms leading to renal protection with sodium glucose cotransport 2 inhibition. *Loop diuretic sparing as defined by a longer time until requiring institution of a loop diuretic in the EMPA-REG OUTCOME trial.[108]

SGLT2i and renal protection in CKD: does glucose lowering matters?

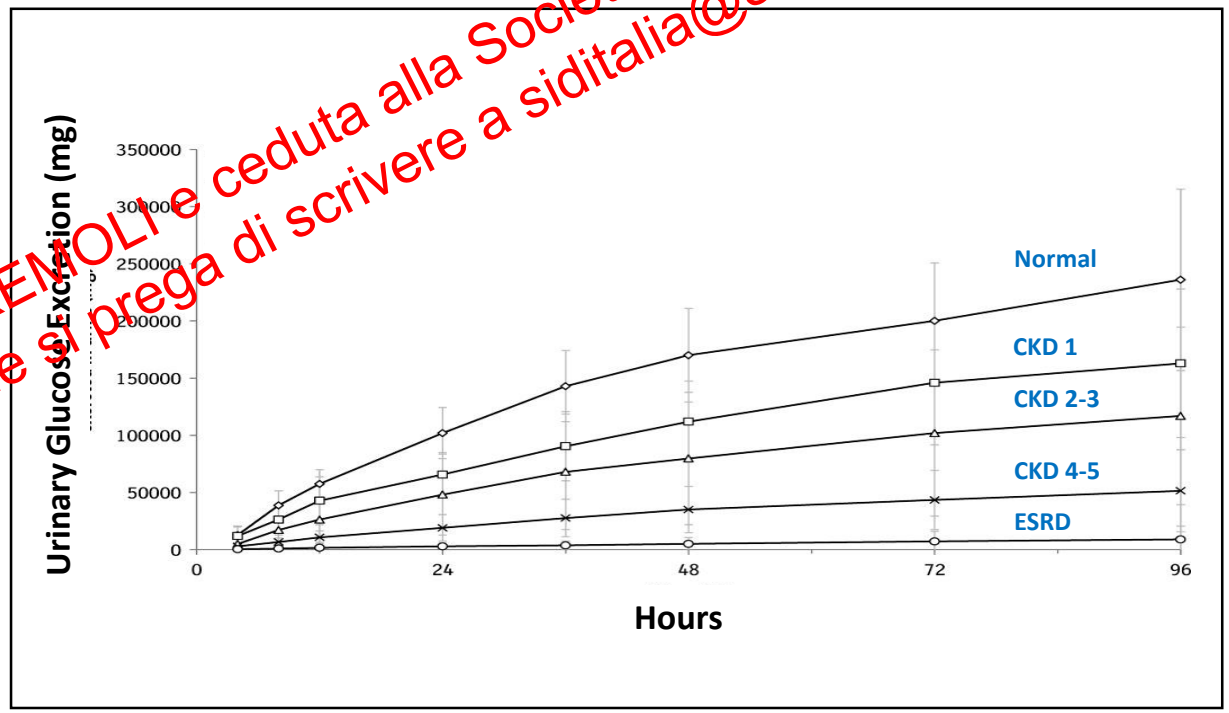
SGLT2i and Glycosuria: eGFR Dependence

Canagliflozin



Heerspink et al, Circulation 2016

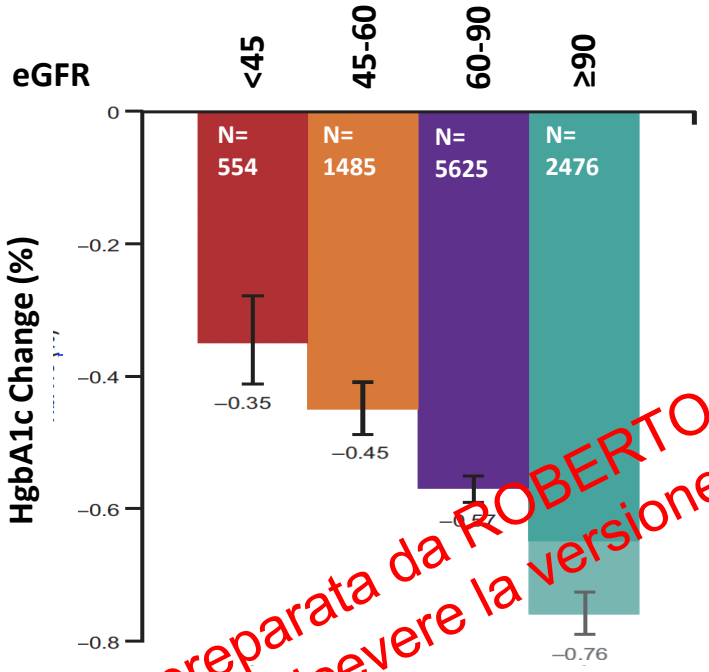
Empagliflozin



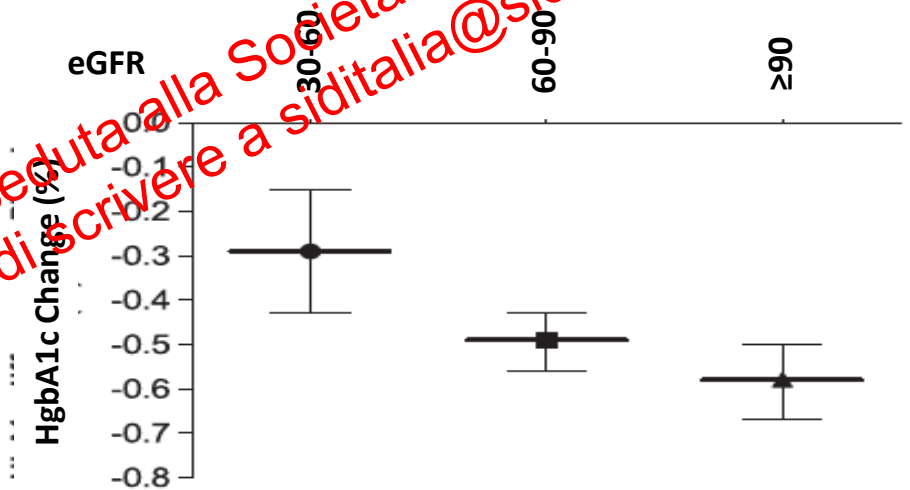
Macha et al, Diabetes Obes Metab, 2014

SGLT2i and HgbA1c: eGFR Dependence

Canagliflozin



Dapagliflozin



Neuen et al, Circulation 2018; Van Bommel et al, CJASN 2017

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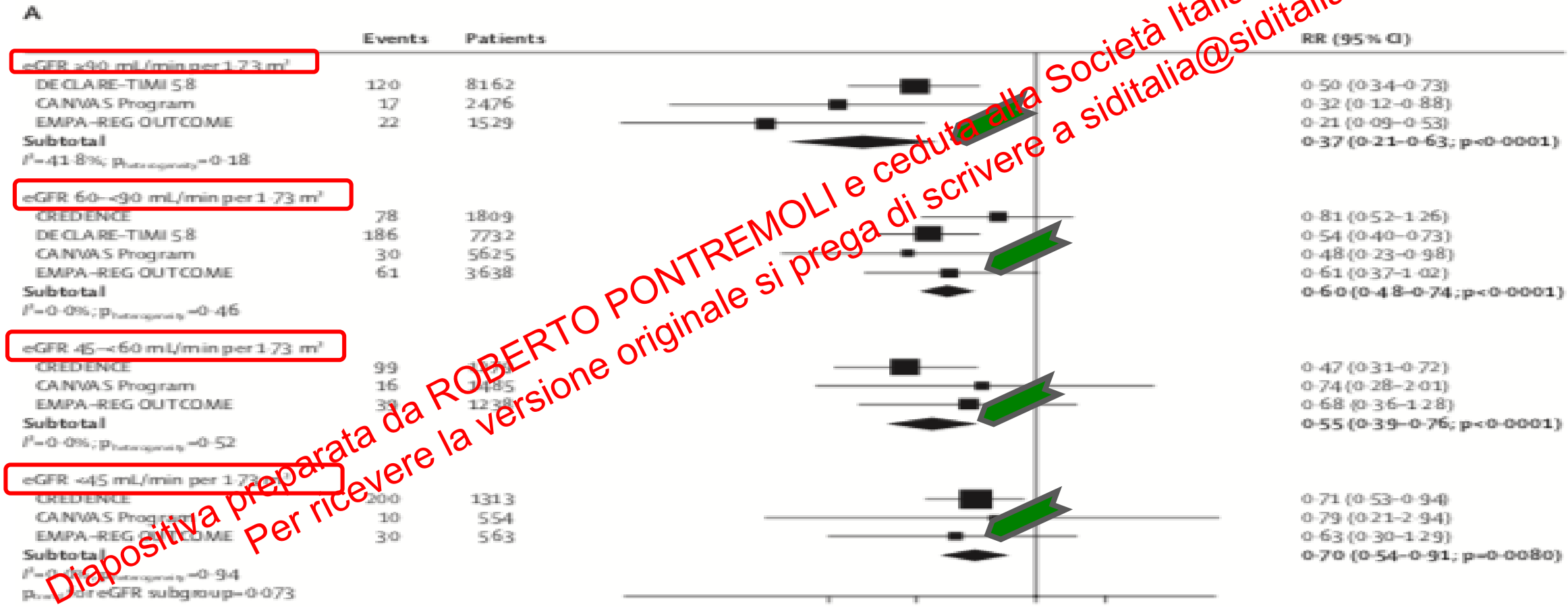

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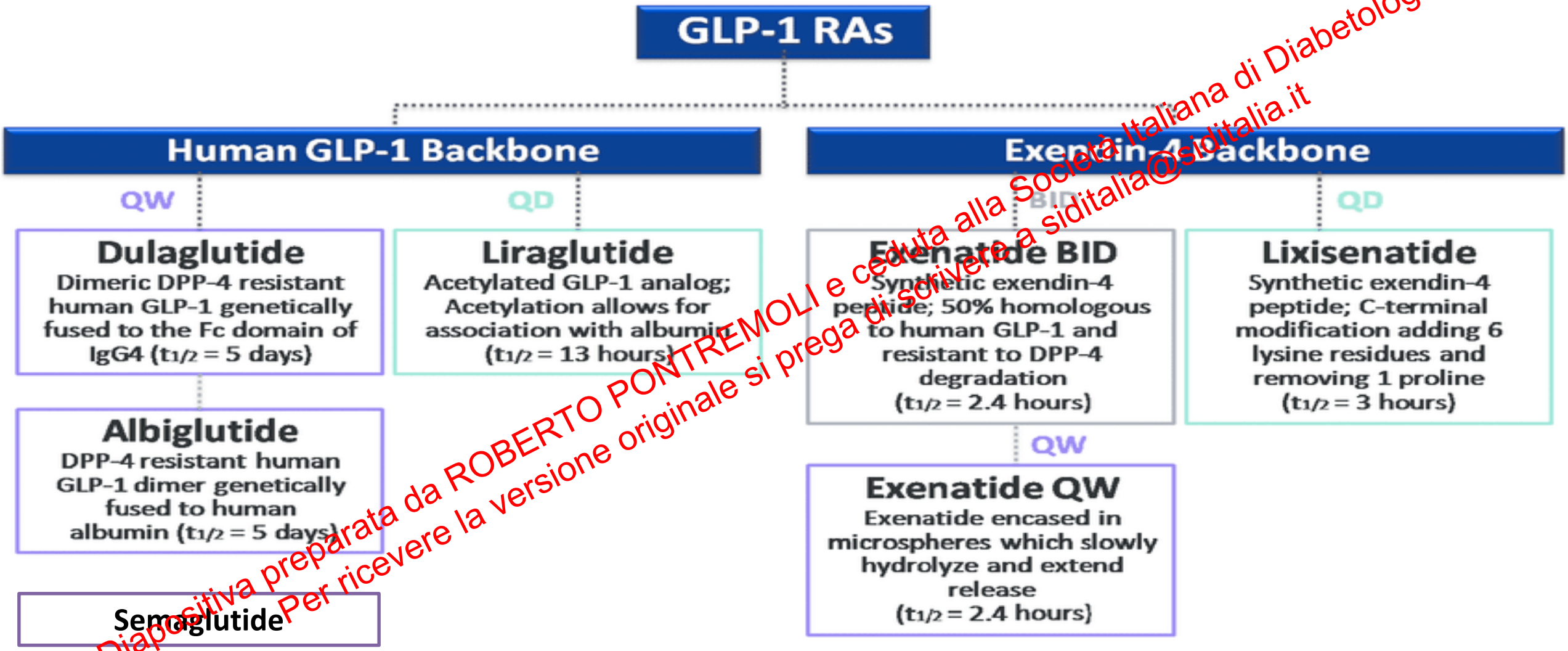
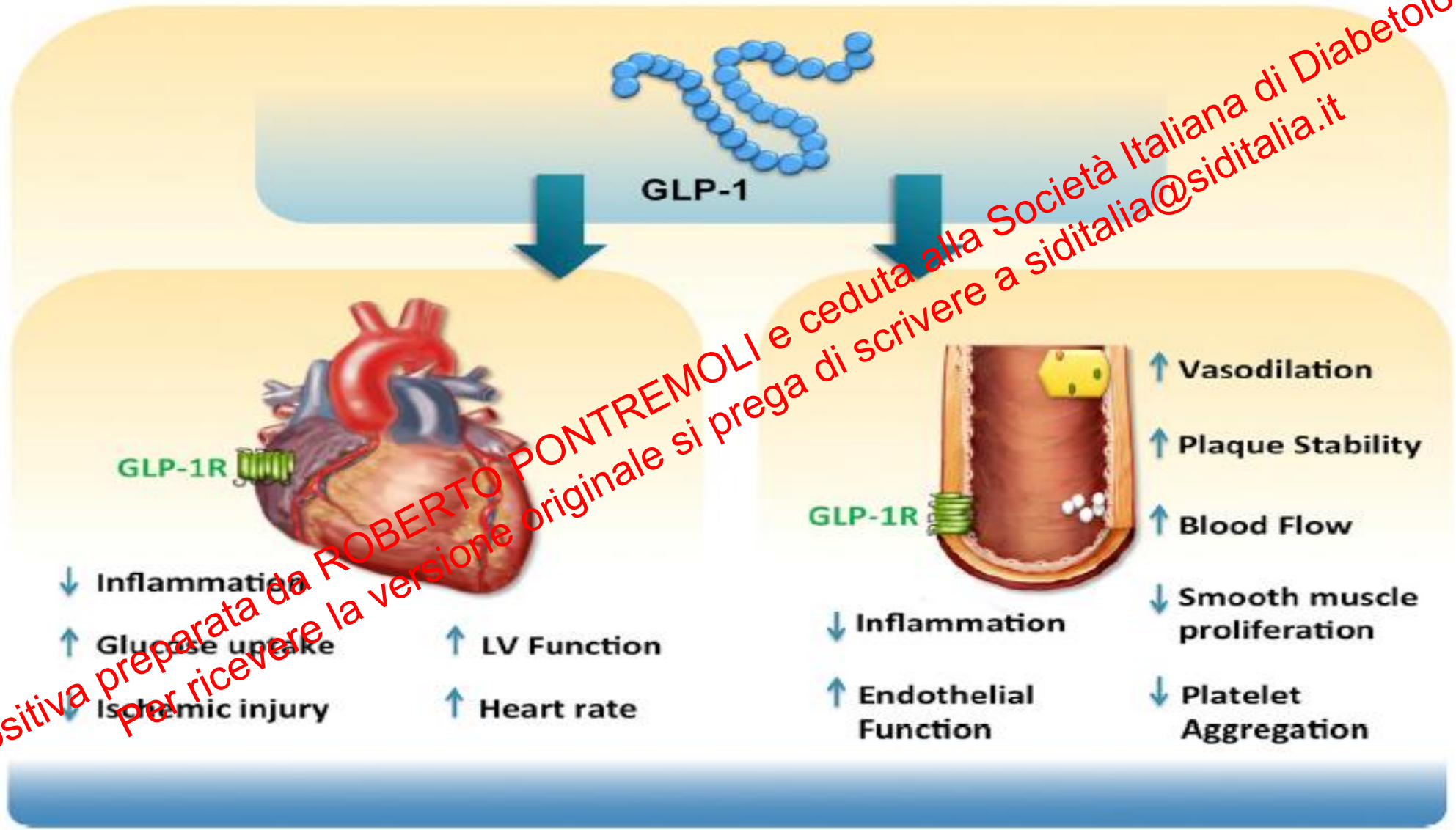
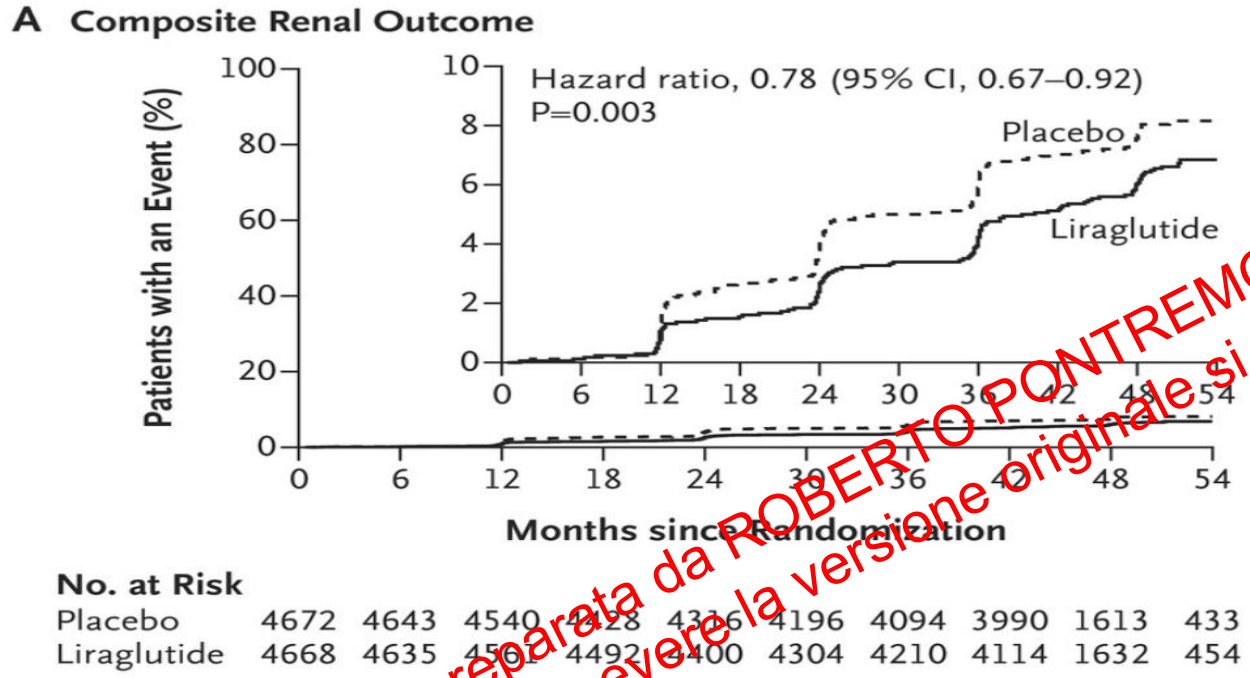




Cell Metabolism 2016

LEADER: Time to first renal event

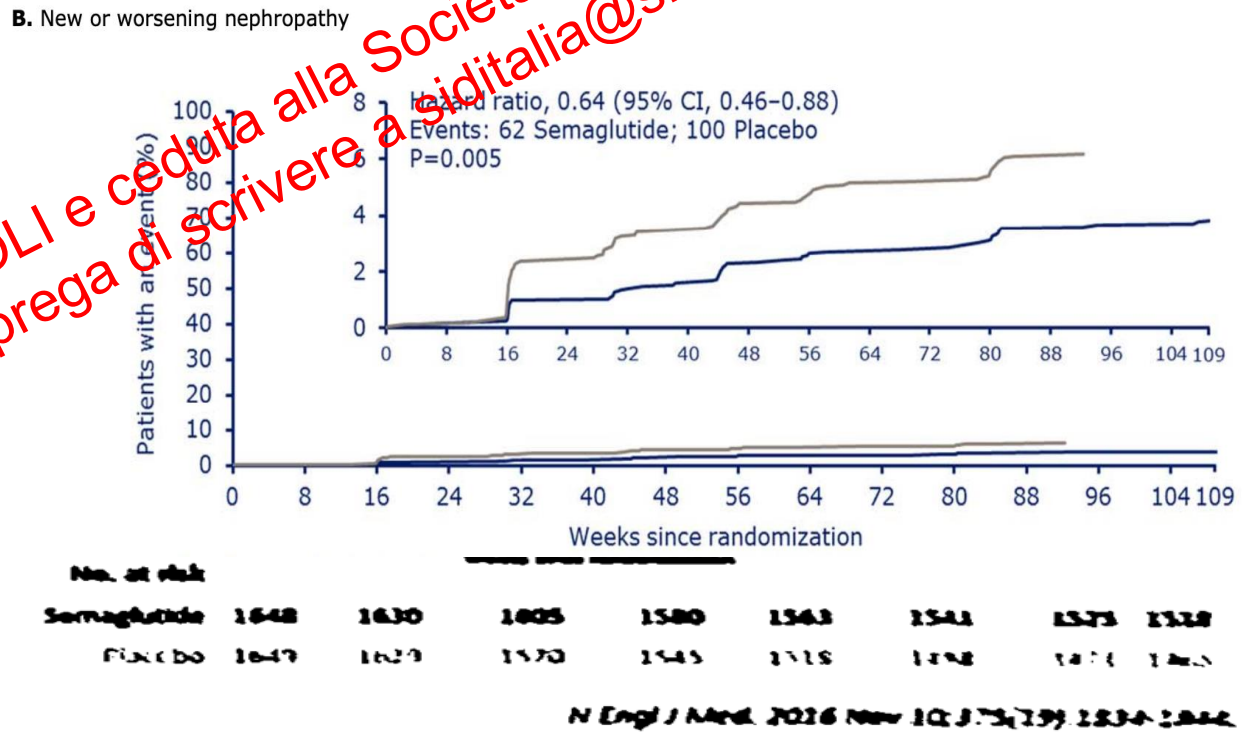
Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



N Engl J Med 2016; 375:311-22.

SUSTAIN 6: Time to first renal event

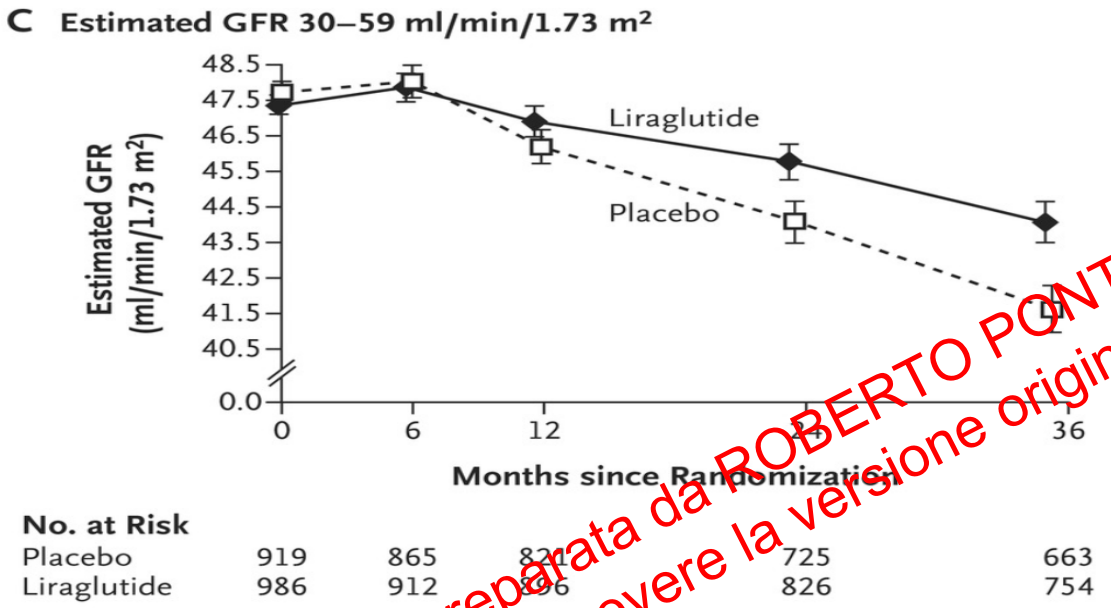
Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



N Engl J Med 2016

Leader study

Mean Estimated GFR during the Trial in Subgroup with Estimated GFR at Baseline between 30-59 ml/min/1.73m²

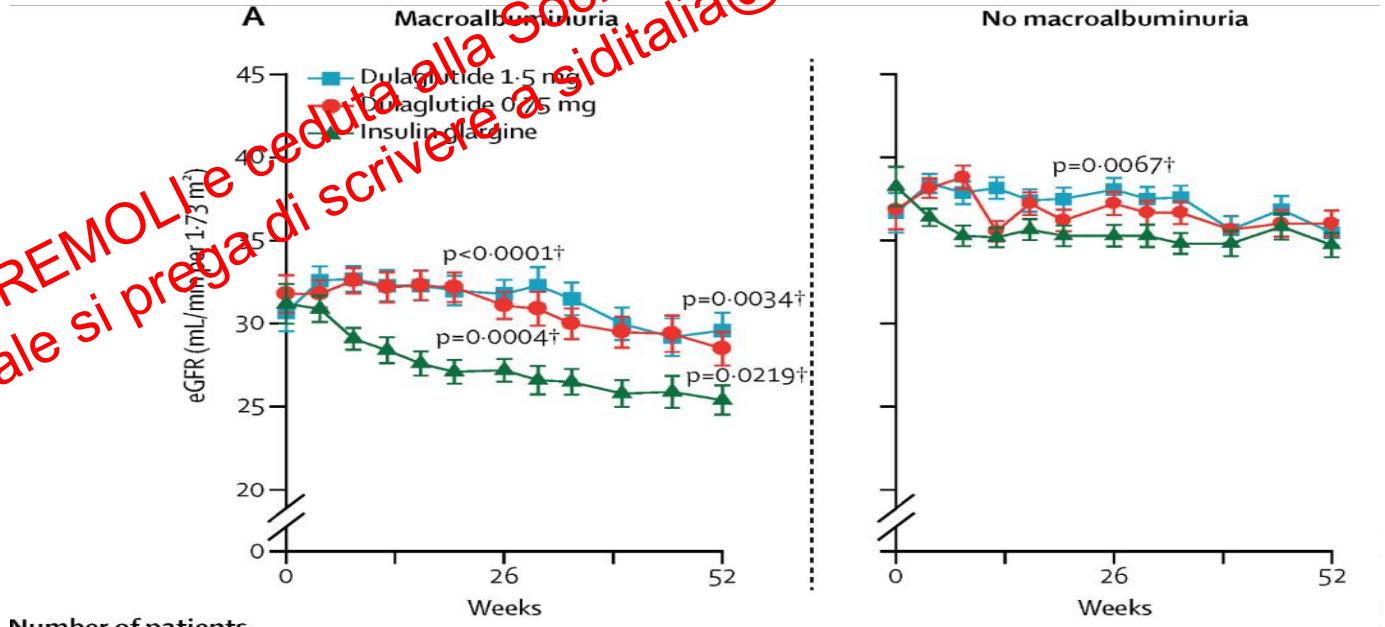


No. at Risk					
Placebo	919	865	821	725	663
Liraglutide	986	912	896	826	754

N Engl J Med 2017;377:839-48

AWARD-7 (Dulaglutide)

Changes in estimated glomerular filtration rate by macroalbuminuria status at baseline



Number of patients						
Dulaglutide 1·5 mg	84	70	64	108	93	93
Dulaglutide 0·75mg	84	71	67	106	96	93
Insulin glargine	90	77	69	104	97	95

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use principles in Figure 1

AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

If not at HbA1c target: **ADD**

If at HbA_{1c} target:

If at HbA1c target on dual or multiple therapies: **SWITCH**

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

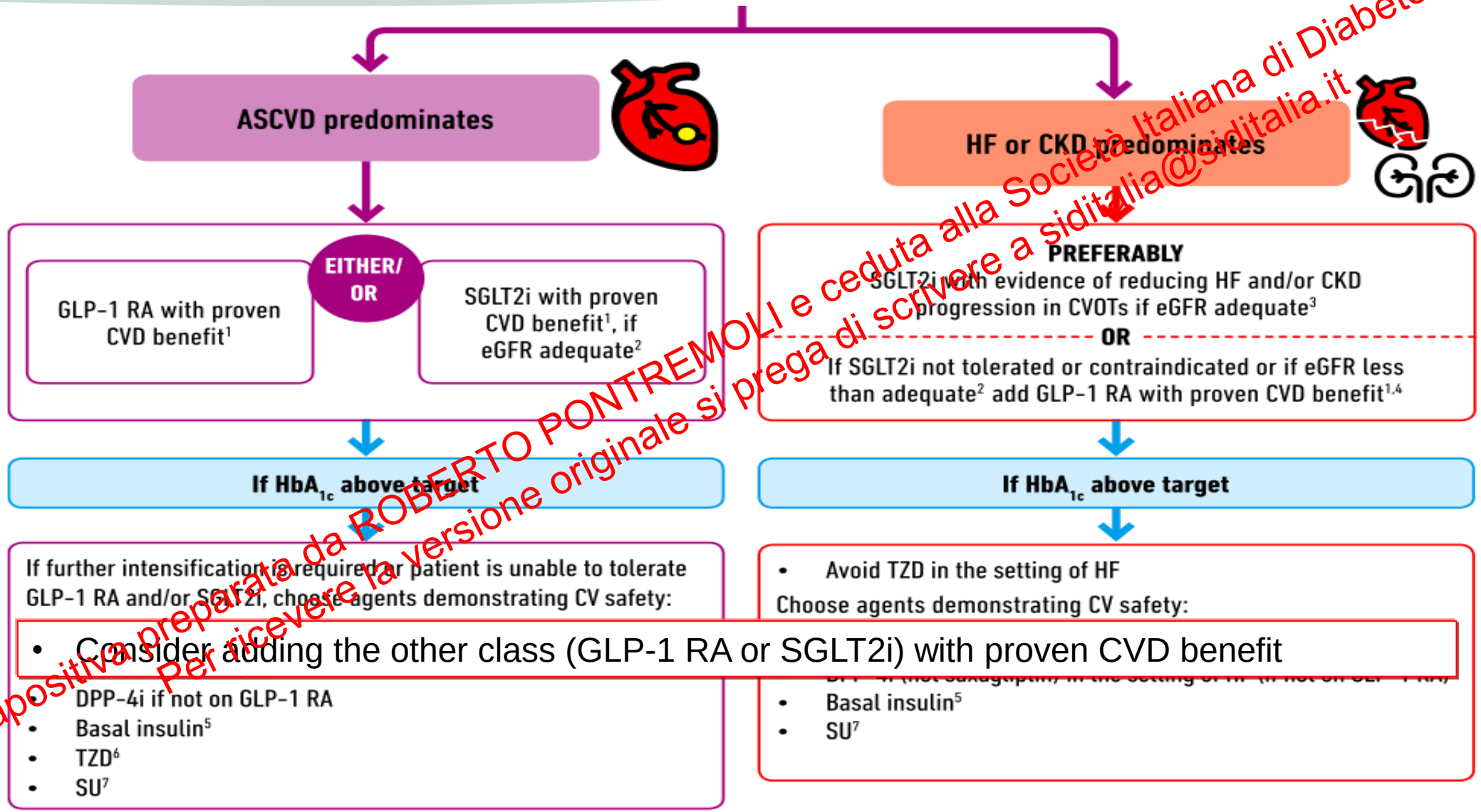
OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

HF or CKD predominates

Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

KEY Points – Conclusions 1/2

- SGLT2-is have been shown to convey cardiac (HF) and renal protection. The latter is additive to RAAS-i and independent of the underlying renal phenotype (albU/eGFR), although mechanisms are still uncompletely understood.

- Renal protection by SGLT2-is may, at least in part, be independent of their antihyperglycemic effect

- SGLT2-is seem well suited to be the treatment of choice for renal protection in all T2D patients

KEY Points – Conclusions 1/2

- GLP1-ra are potent antihyperglycemic drugs that can be safely used down to eGFR values of 30 ml/min. They also have been shown to convey cardiovascular and renal protection.

- GLP1-ra share several favorable ancillary actions with SGLT2-is (BP and weight reduction) although major renal protection mechanisms (anti inflammatory, NH3 inhibition) seem to differ from SGLT2-is

- GLP1-ra seem to combine good antihyperglycemic power and renal protection and should therefore be used more often in patients at renal risk.