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- SANOFI
- LILLY
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- ASTRA ZENECA
- MEDTRONIC
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Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e la 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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e progressione della **malattia renale**
nel **diabete tipo 2**

Meccanismi nefroprotettivi degli SGLT2 inibitori

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ASST Papa Giovanni XXIII, Bergamo*

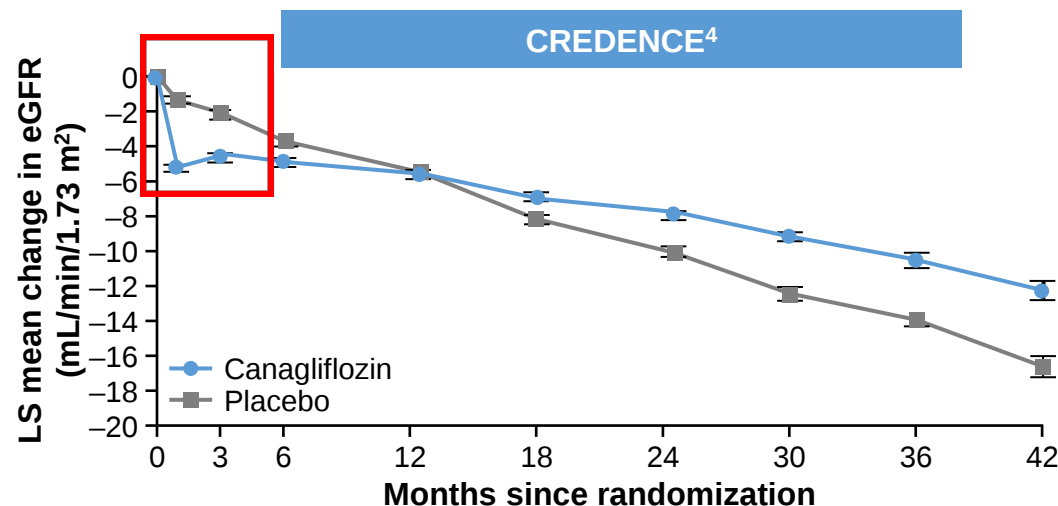
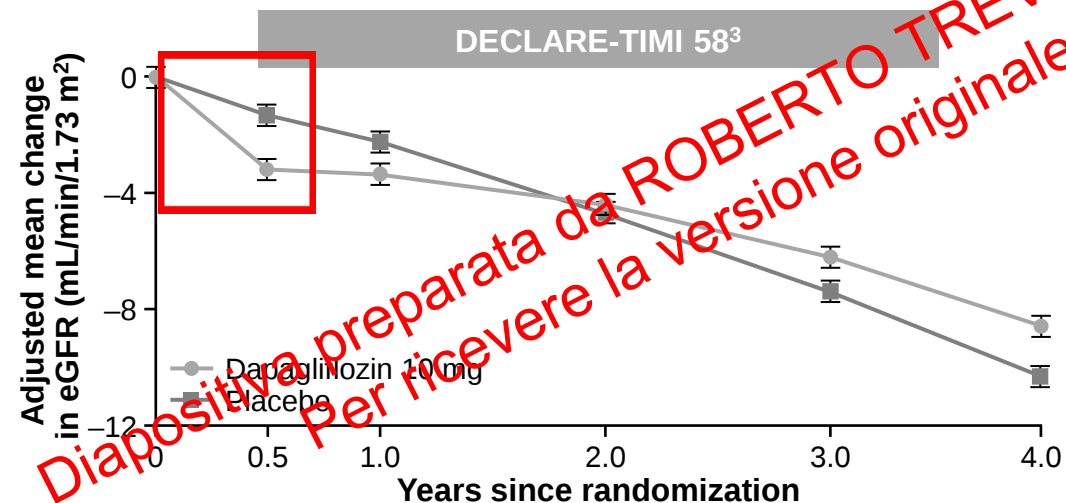
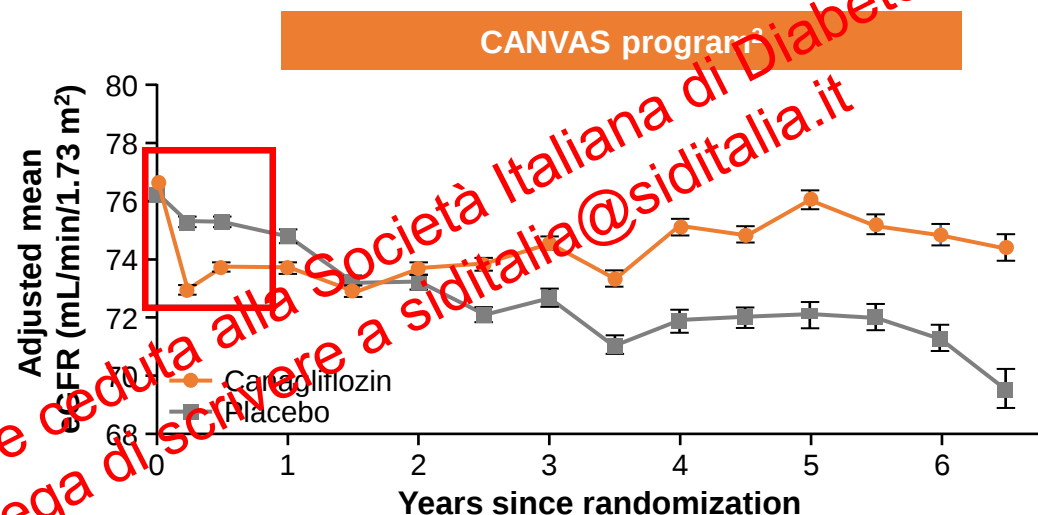
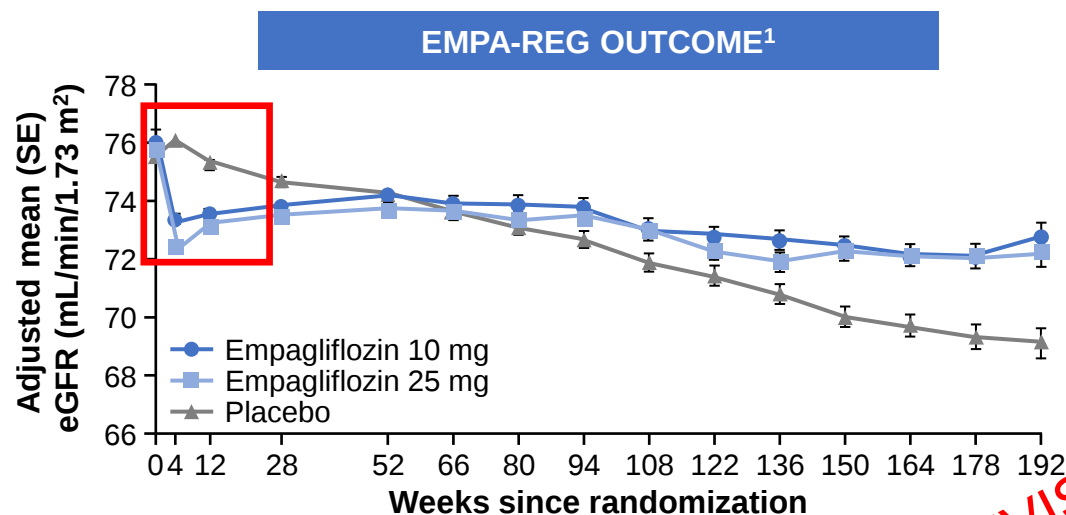
Sistema Socio Sanitario



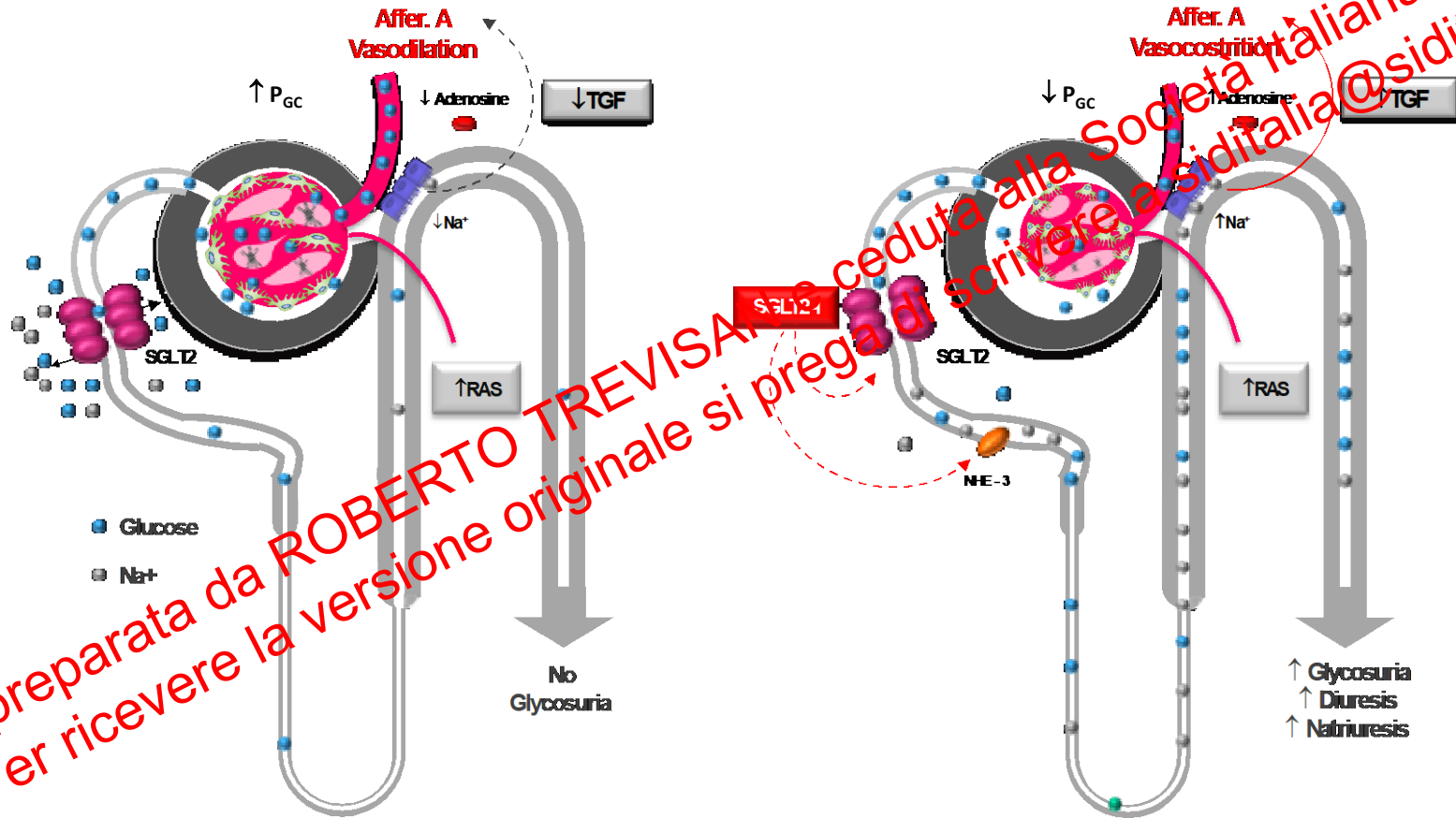
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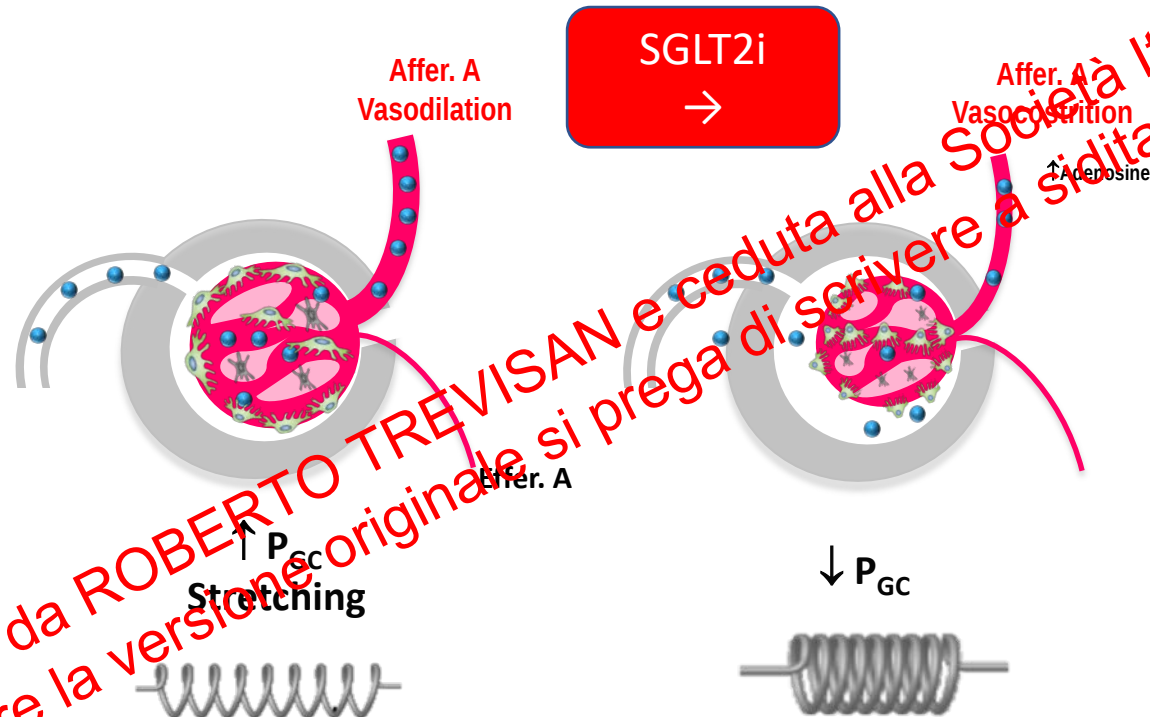
The effects of SGLT2i: an initial decline in eGFR, which subsequently stabilizes



IPIERFILTRAZIONE e SGLT2i



STRETCHING

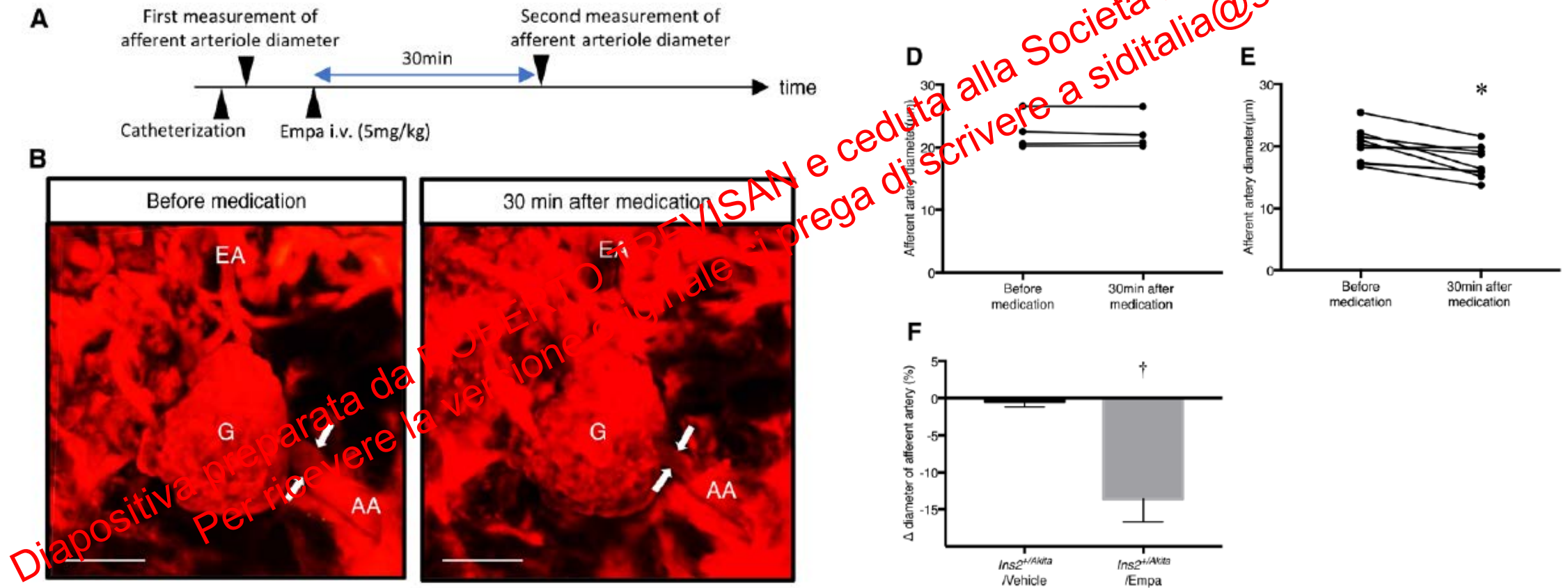


Albuminuria
Rapid GFR decline

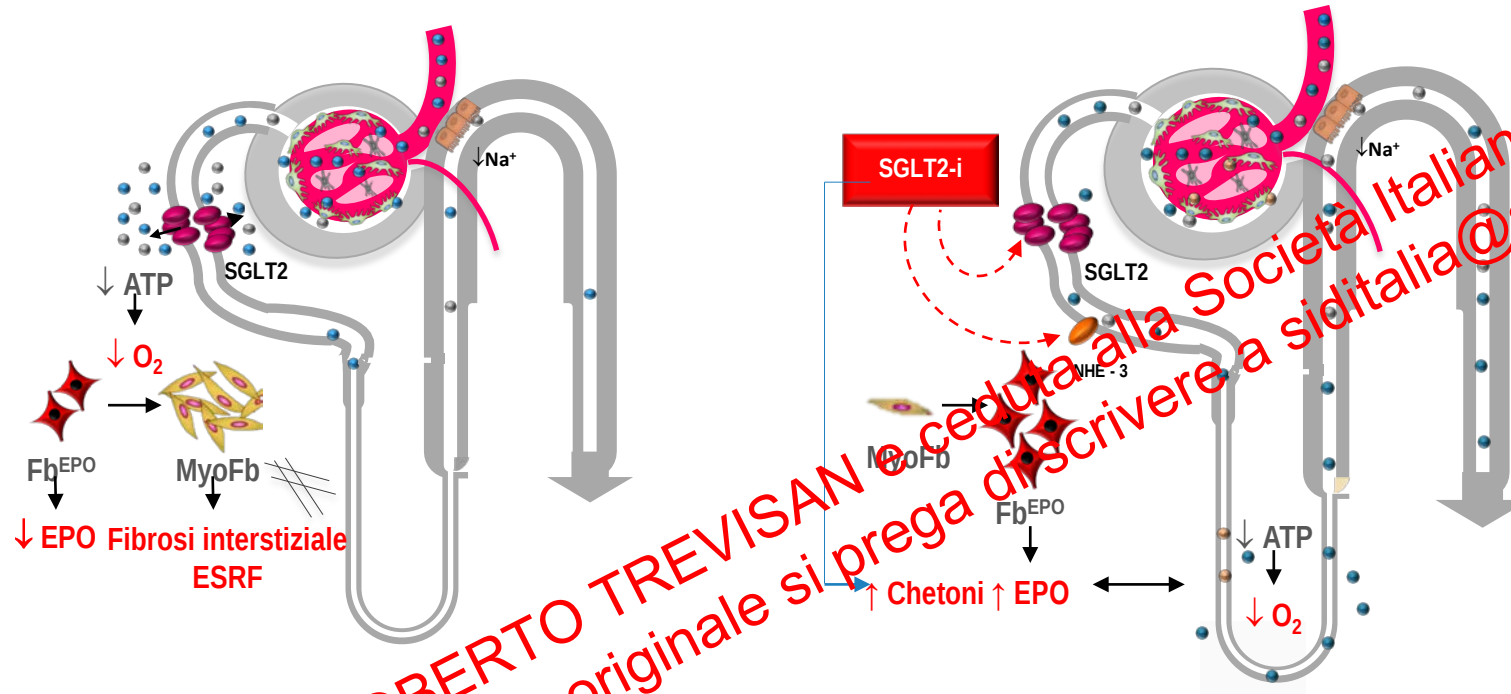
Gruden g et al: J Am Soc Nephrol. 2005;16:688-96.

Cherney D et al. Circulation 2014;129:587-597

The acute effect in alterations of afferent arteriole of the same nephrons by empagliflozin



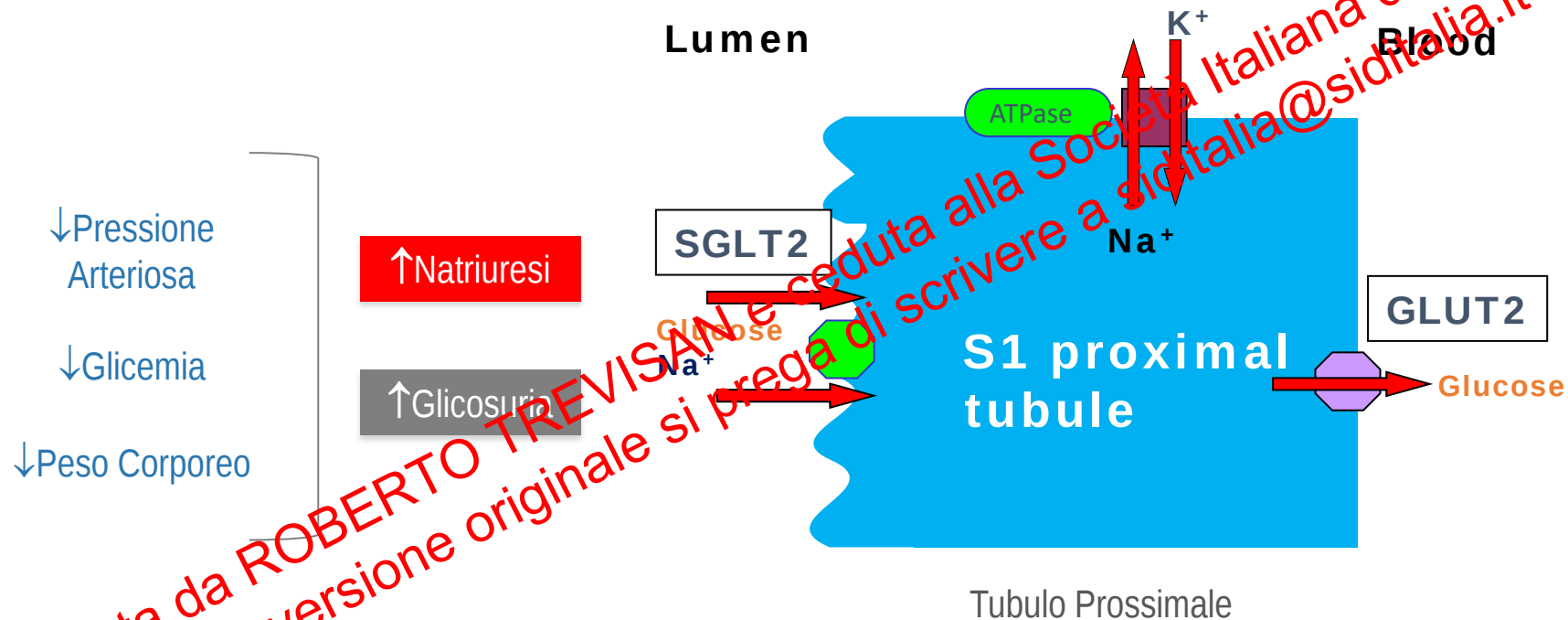
IPOTESI DELL'IPOSSIA



Diabete

- Riassorbimento Na-Glucosio TP
- Elevato consumo O₂
- Ipossia tubulo-interstiziale
- Fibroblasti^{FbEPO} → miofibroblasti

SGLT2 INIBITORI

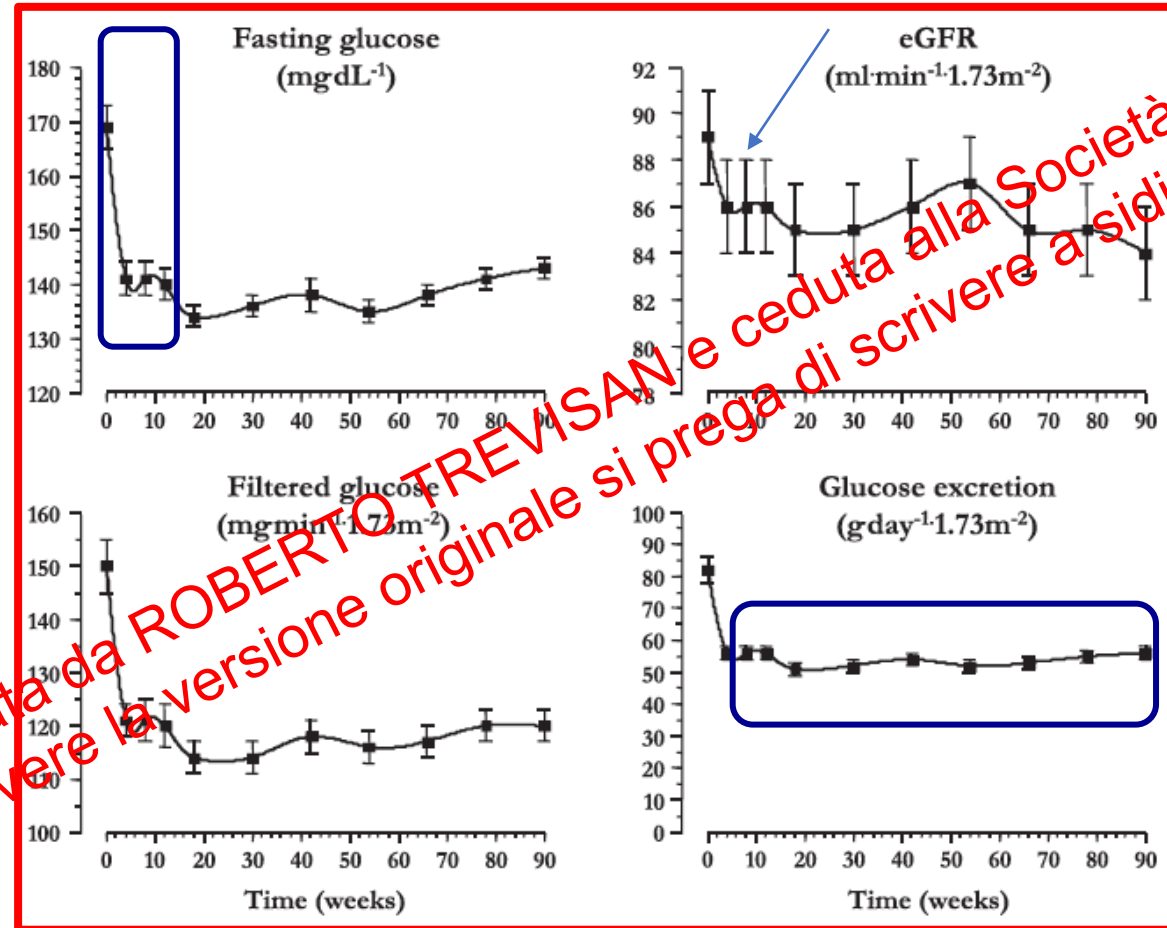


¹Hediger MA, Rhoads DB. *Physiol Rev* 1994;74:993-1026;

²Magen D, et al. *Kidney Int.* 2005;67:34-41;

³Kanai Y, et al. *J Clin Invest* 1994;93:397-404

Effect of SGLT2 Inhibition on FBG, GFR, filtered glucose and glucose excretion

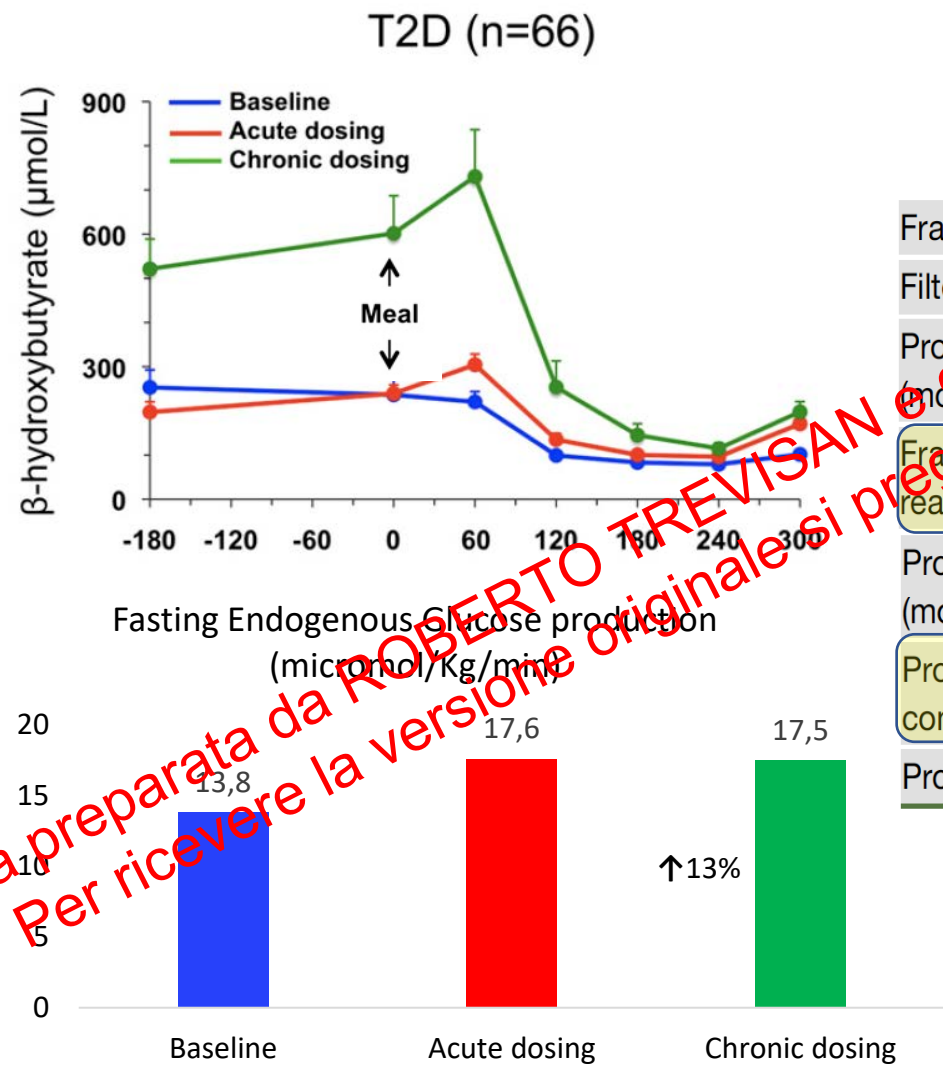


Glucagone



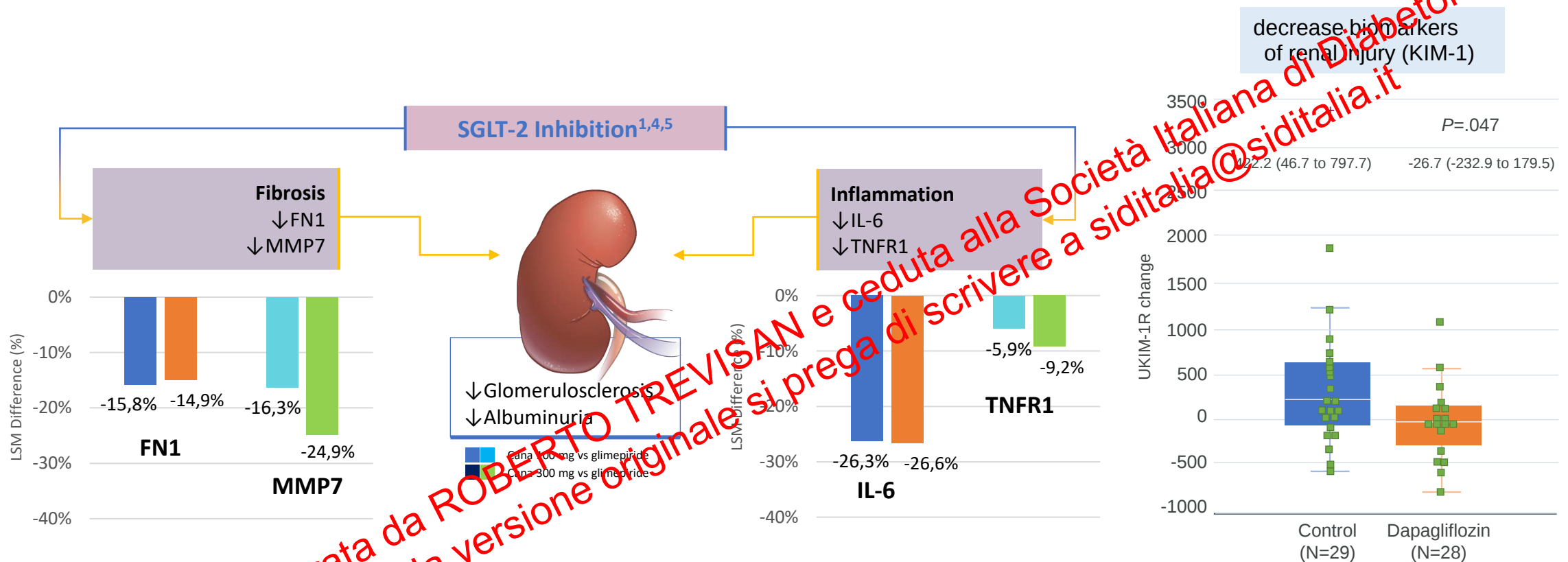
FFA

SGLT2i (Empaglifozin): Effetto su chetoni, EPG e energetica



	T2DM	SGLT2i Tx	
Fractional glucose absorption (%)	98	57	↓ 41.9%
Filtered Na ⁺ (mol/day) ^d	24.2	20.4	↓ 15.7%
Proximal Na ⁺ reabsorption (mol/day) ^e	1.70	0.73	↓ 57.1%
Fractional proximal Na ⁺ reabsorption (%)	7.1	3.6	↓ 49.3%
Proximal ATP consumption (mol/day) ^h	0.58	0.24	↓ 58.7%
Proximal/kidney ATP consumption (%)	18	8	↓ 55.6%
Proximal ATP saving (mol/day)	–	0.34	

SGLT-2 Inhibitors May Protect Against Inflammatory and Fibrotic Responses



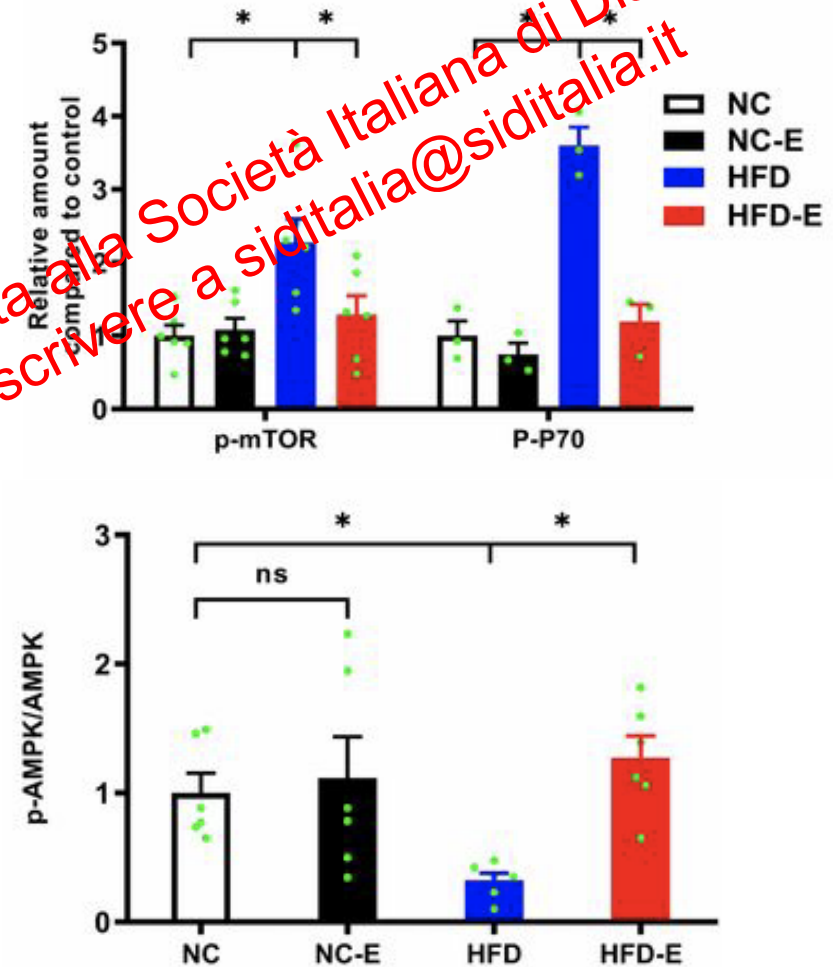
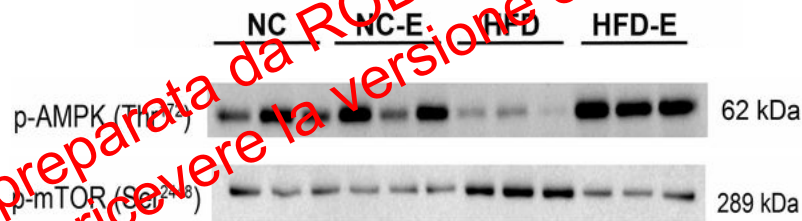
Dekkers CCJ, et al. *Diabetes Obes Metab.* 2018;20(8):1988-1993.

CKD=chronic kidney disease; FN1=fibronectin-1; IL-6=interleukin-6; LSM=least square mean; MMP7=matrix metalloproteinase-7; TNFR1=tumor necrosis factor receptor-1.

1. Heerspink HJL, et al. *Diabetologia.* 2019;62:1154-1166.
 2. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39.
 3. Tamargo J. *Eur Cardiol.* 2019;14(1):23-32.
 4. Kawanami D, et al. *Int J Mol Sci.* 2017;18(5):E108.
 5. Ke B, et al. *Front Physiol.* 2017;8:21. doi: 10.3389/fphys.2017.00021.
 6. Fioretto P, et al. *Diabetes Care.* 2016;39(suppl. 2):S165-S171.
 7. Liu Y. *J Am Soc Nephrol.* 2010;21:212-222.
 8. Terami N, et al. *PLoS One.* 2014;9:e100777.
9. Dekkers CCJ, et al. *Diabetes Obes Metab.* 2018;20(8):1988-1993.

Effects of EMPA treatment on the Sesn2-AMPK-mTOR and PI3K-Akt-eNOS signaling pathways

- AMPK is a major cellular sensor of energy availability.
- In diabetes and obesity, AMPK phosphorylation in the heart is often downregulated due to overnutrition.
- Acting as a renoprotective molecule, AMPK balances oxidative stress and inhibits mTOR signaling.
- This AMPK-mediated mTOR regulation has been shown to have pleiotropic protective effects, including improving the energy supply and regulating other physiological processes.

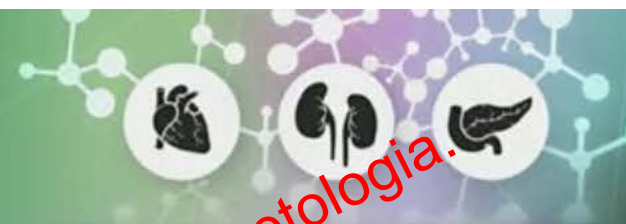


Many of the effects of SGLT2 resemble those present in the dormant state



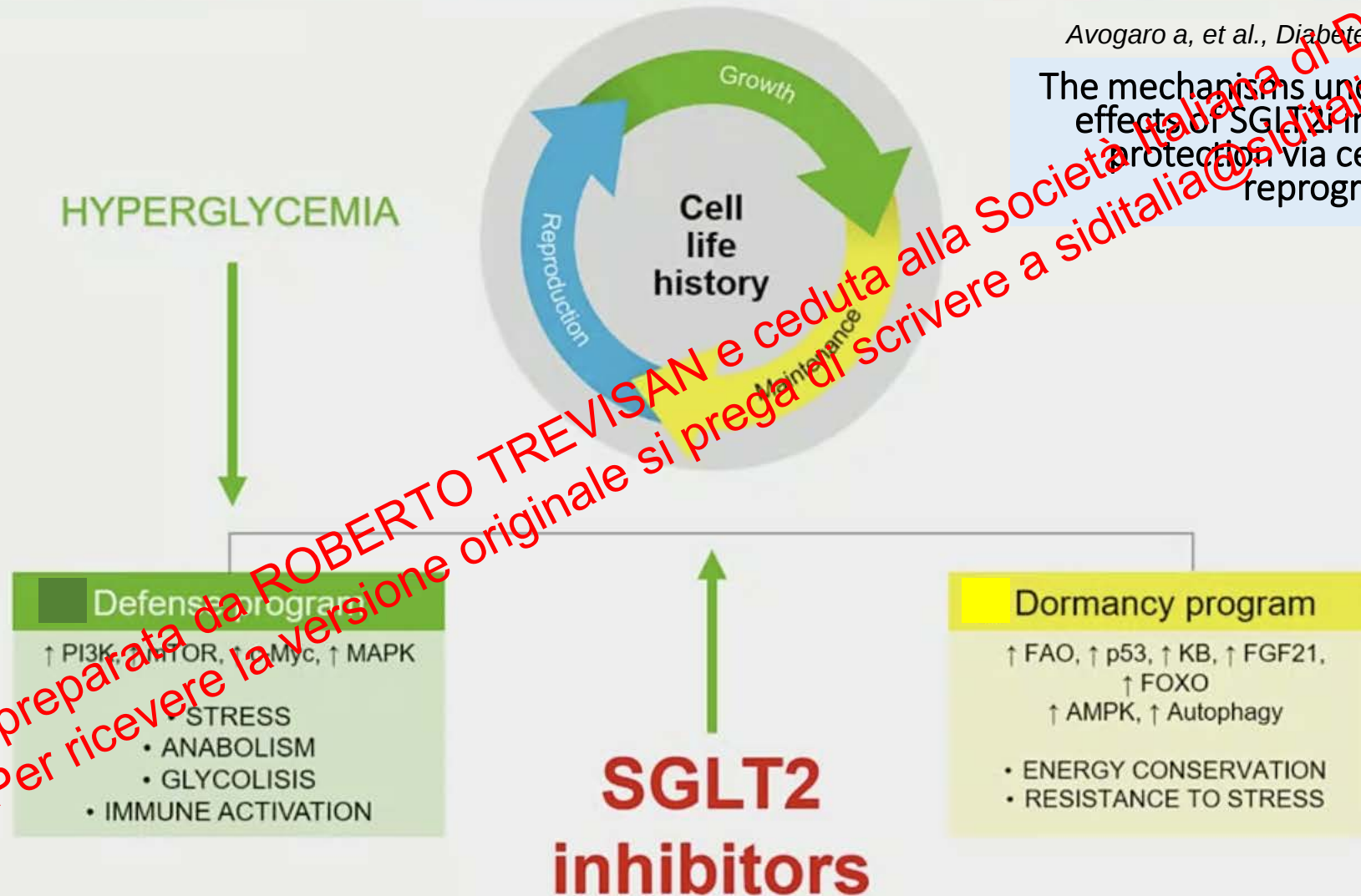
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SGLT2 inhibitors favor a dormancy cell program



Avogaro a, et al., *Diabetes Care* 2020;43:501–507

The mechanisms underlying the potential effects of SGLT2i in determining their protection via cellular life history reprogramming



What Evidence Supports Enhanced Nutrient Deprivation Signaling During SGLT2 Inhibitors?

- Increased activity of SIRT1, PGC-1 α and PGC21 and suppressed activity of Akt/mTORC1
- Marked reduction in oxidative stress and proinflammatory signaling in the heart and kidneys
- Increased autophagy in the heart and kidneys
- Increased mitochondrial biogenesis and reversal of mitochondrial dysfunction
- **Biomarker confirmation in clinical studies**

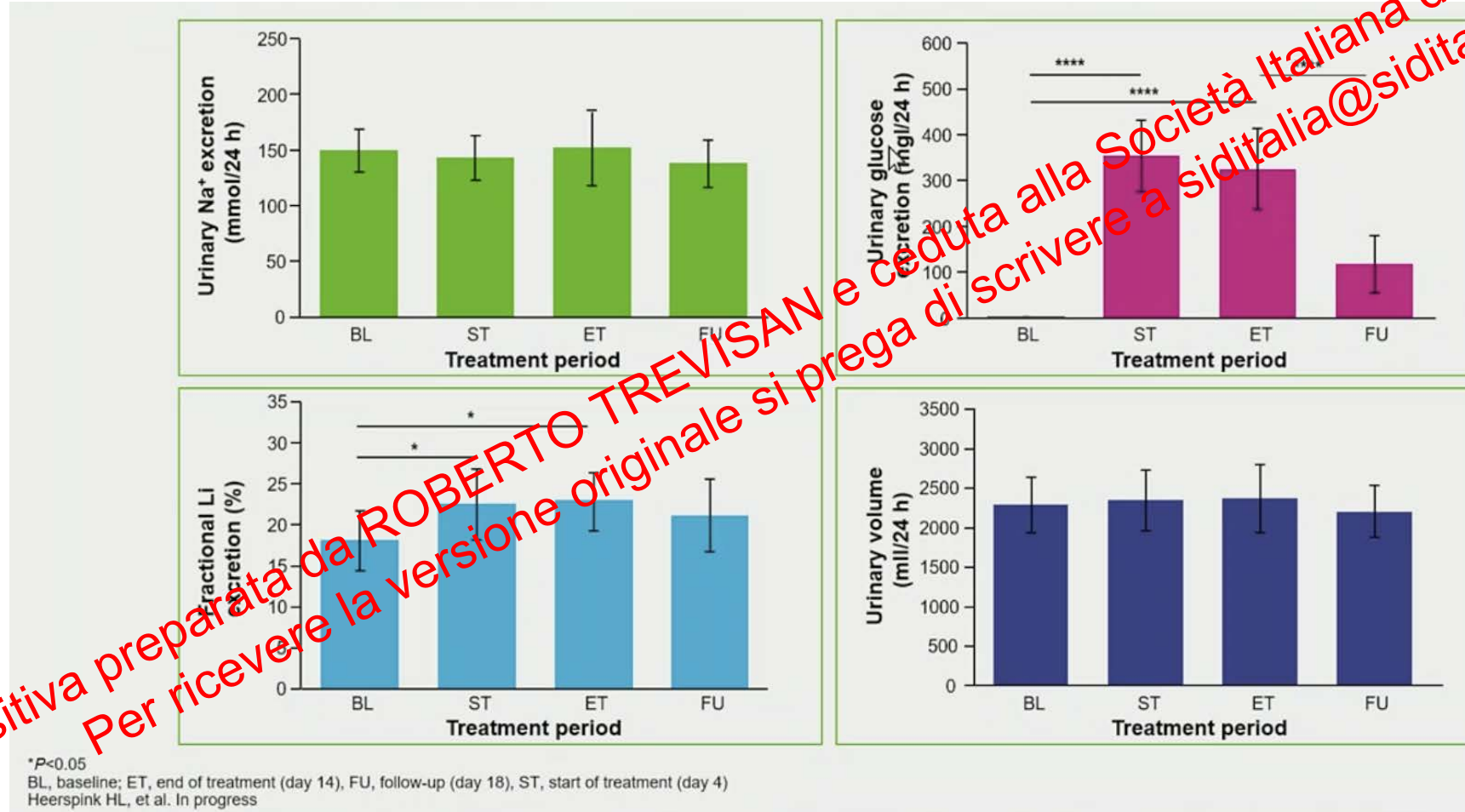
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Domanda:
gli SGLTi
aumentano
la
natriuresi?

- Sì
- No
- Solo nei primi giorni dall'inizio della terapia
- Solo nei pazienti con aumentato introito di sale

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DAPASALT: SGLT2i (Dapagliflozin) is not associated with increased natriuresis during carefully controlled conditions

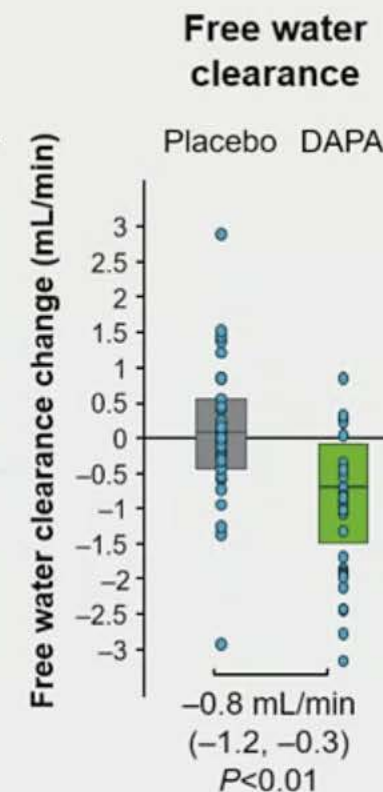
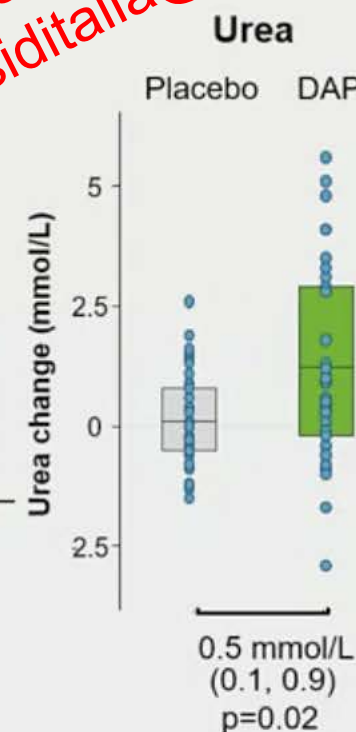
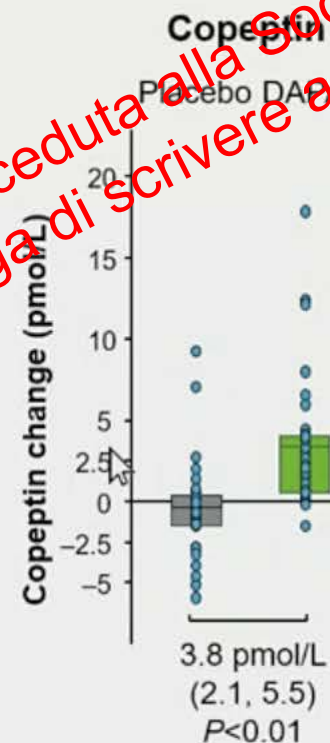
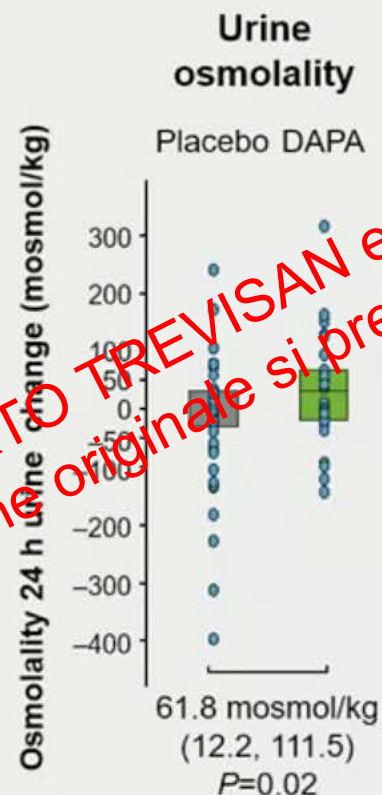
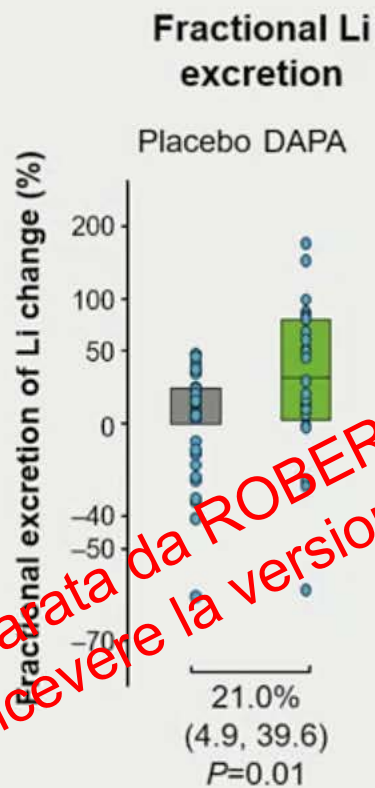
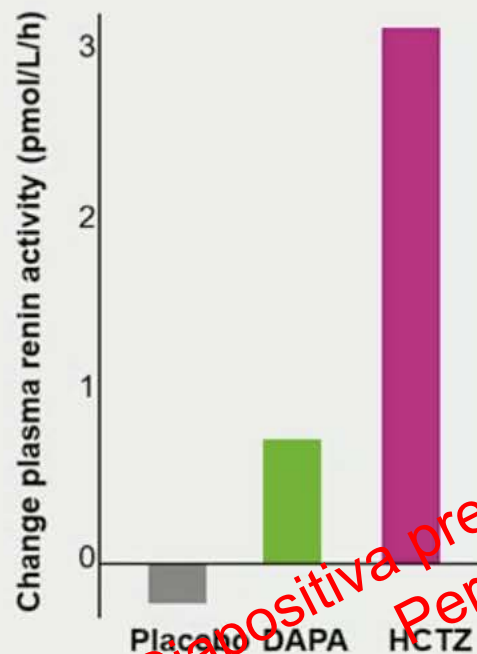


Acute and chronic effects of SGLT2 inhibition on volume status



Type 2 diabetes

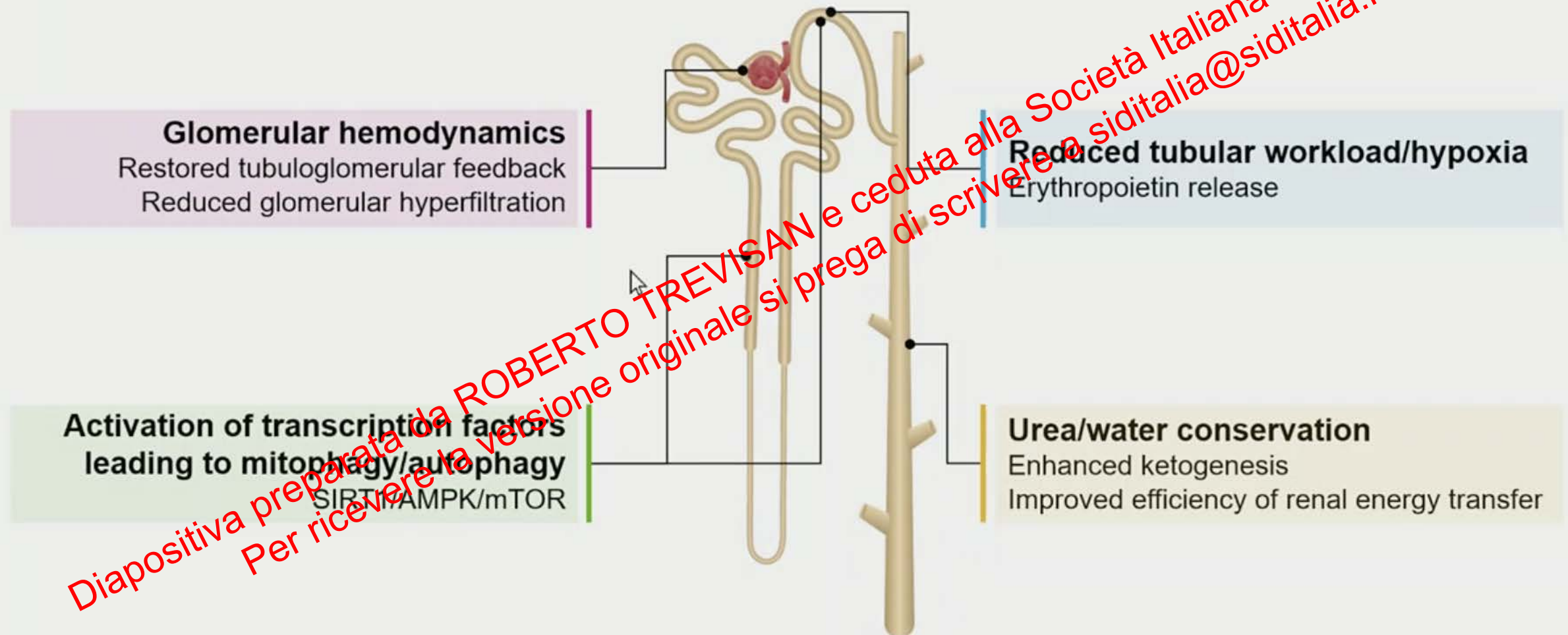
Baseline 2.84 2.13 2.37



DAPA, dapagliflozin; HCTZ, hydrochlorothiazide

1. Heerspink HL, et al. *Diabetes Obes Metab* 2013;15(9):853–862; 2. Eickhoff MK, et al. *J Clin Med* 2019;8(6):779

Possible mechanisms of renoprotection by SGLT2 inhibition





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VI RINGRAZIO PER
L'ATTENZIONE