Come si spiega la riduzione di mortalità associata agli inibitori di SGLT2?

Antonio C. Bossi
UOC Malattie Endocrine
Centro Regionale per il Diabete
ASST Bergamo Ovest - Treviglio

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DISCLOSURES

Hereby, I declare that, during the latest three years, I received research grants, contributions and fees by the following pharmaceutical companies:

- ***Lilly Italia Spa***
- ***Novo Nordisk Italia SpA***
- ***Johnson & Johnson SpA***
- ***Boehringer Ingelheim SpA***
- ***Artsana SpA***
- ***Takeda SpA***
- ***Bayer SA***
- ***Sanofi SpA***
- ***Astra Zeneca SpA***
- ***MSD Italia SpA***

Thanks to SID, which provided strong impulse to my clinical, cultural, and scientific knowledge, I am actually here as a speaker.

SID
Società Italiana di Diabetologia

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Introduzione

SGLT2-i: un approccio insulino-indipendente

SGLT2-i: ripristino metabolico diurno

SGLT2-i: protezione cardio-vascolare

SGLT2-i: protezione microvascolare

SGLT2-i: molteplici aspetti renali

SGLT2-i: ematocrito

Conclusioni

Come si potrebbe spiegare la riduzione di mortalità associata agli inibitori di SGLT2?

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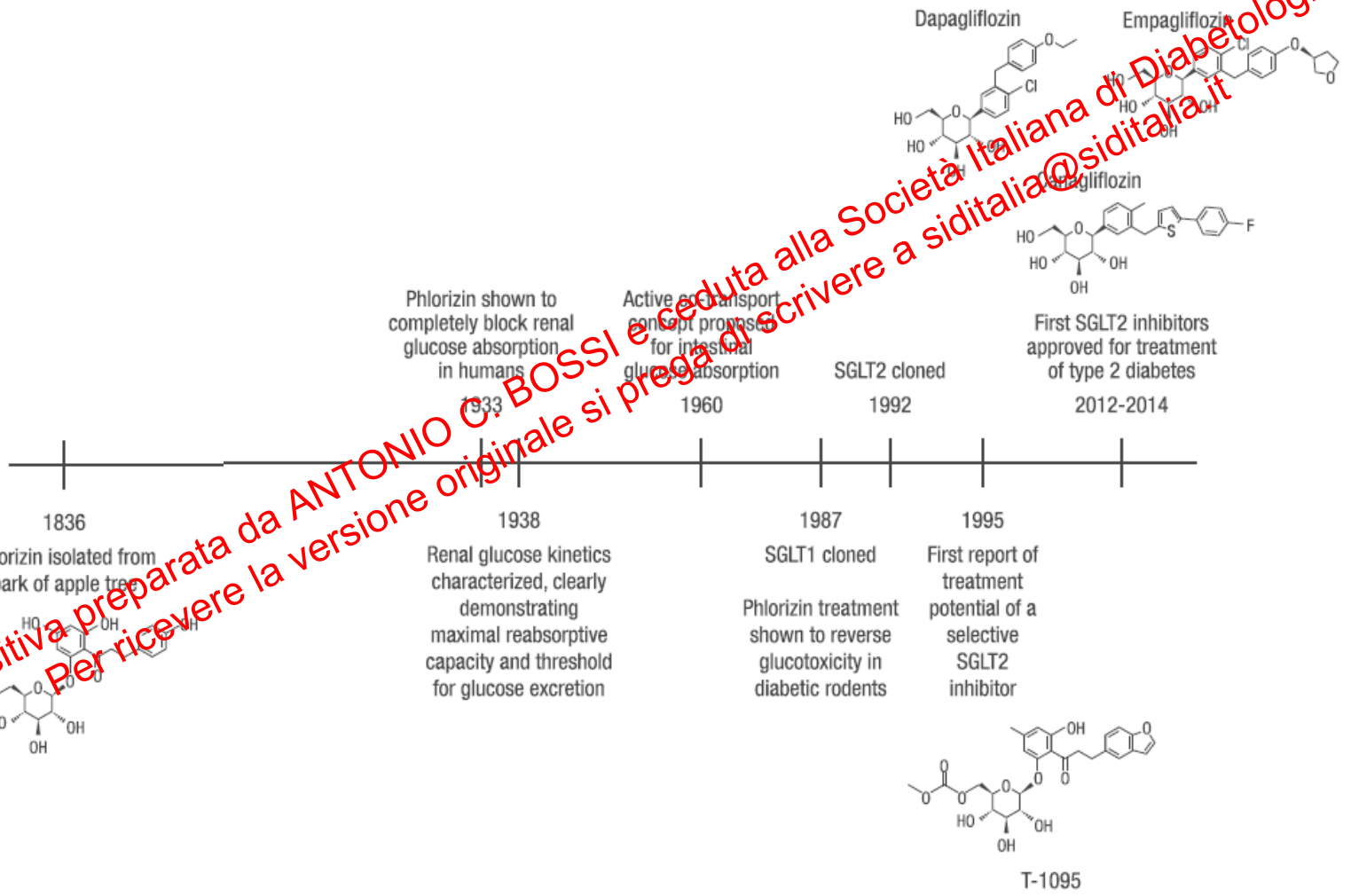
Introduzione

Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport

From Bench to Bedside

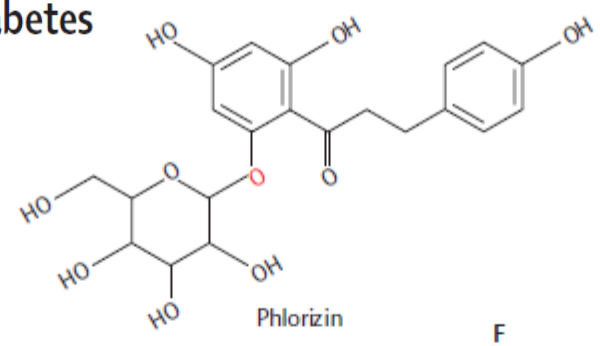
Sunder Mudaliar,[1,2] David Polidori,[3] Brian Zambrowicz,[4] and Robert R. Henry[1,2]



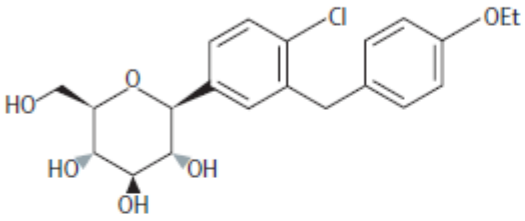
Diabetes Care 2015;38:2344–2353 | DOI: 10.2337/dc15-0642

SGLT inhibitors in management of diabetes

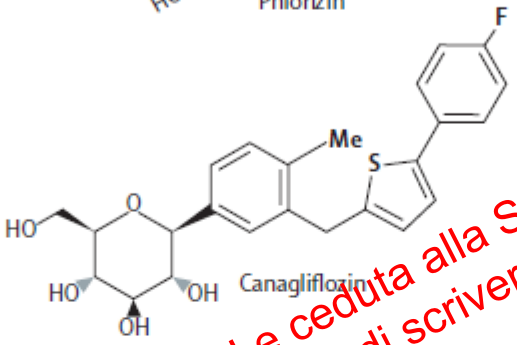
Abd A Tahrani, Anthony H Barnett, Clifford J Bailey



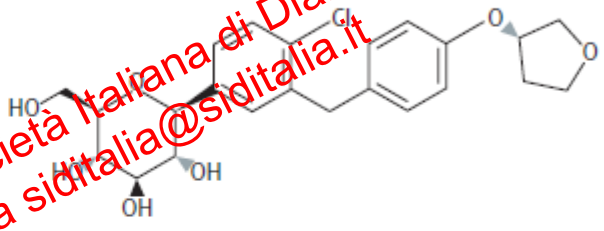
Phlorizin



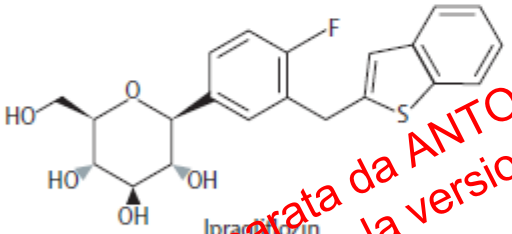
Dapagliflozin



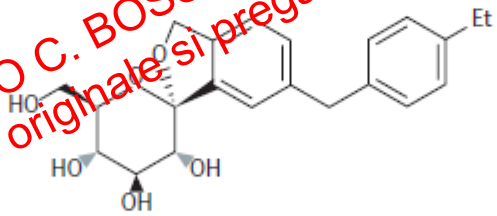
Canagliflozin



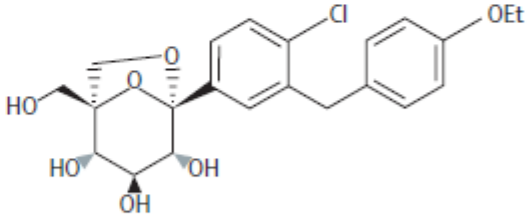
Empagliflozin



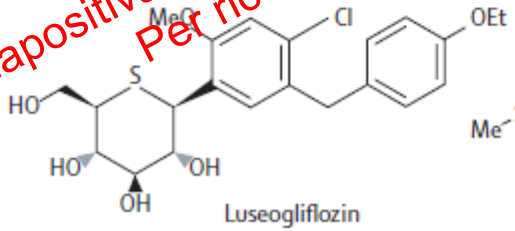
Ipragliflozin



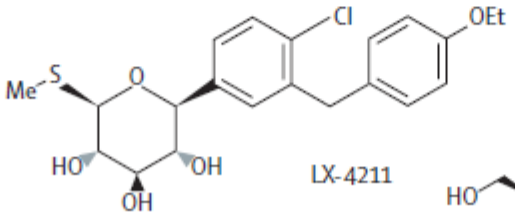
Tofogliflozin



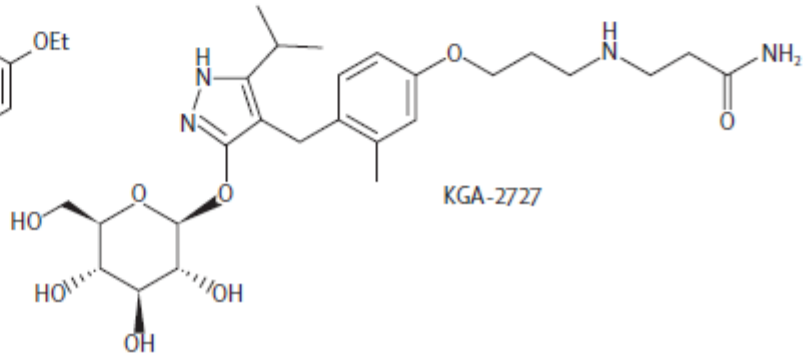
Ertugliflozin



Luseogliflozin



LX-4211



KGA-2727

Lancet Diabetes Endocrinol 2013; 1: 140–51

Come si potrebbe spiegare la riduzione di mortalità associata agli inibitori di SGLT2?

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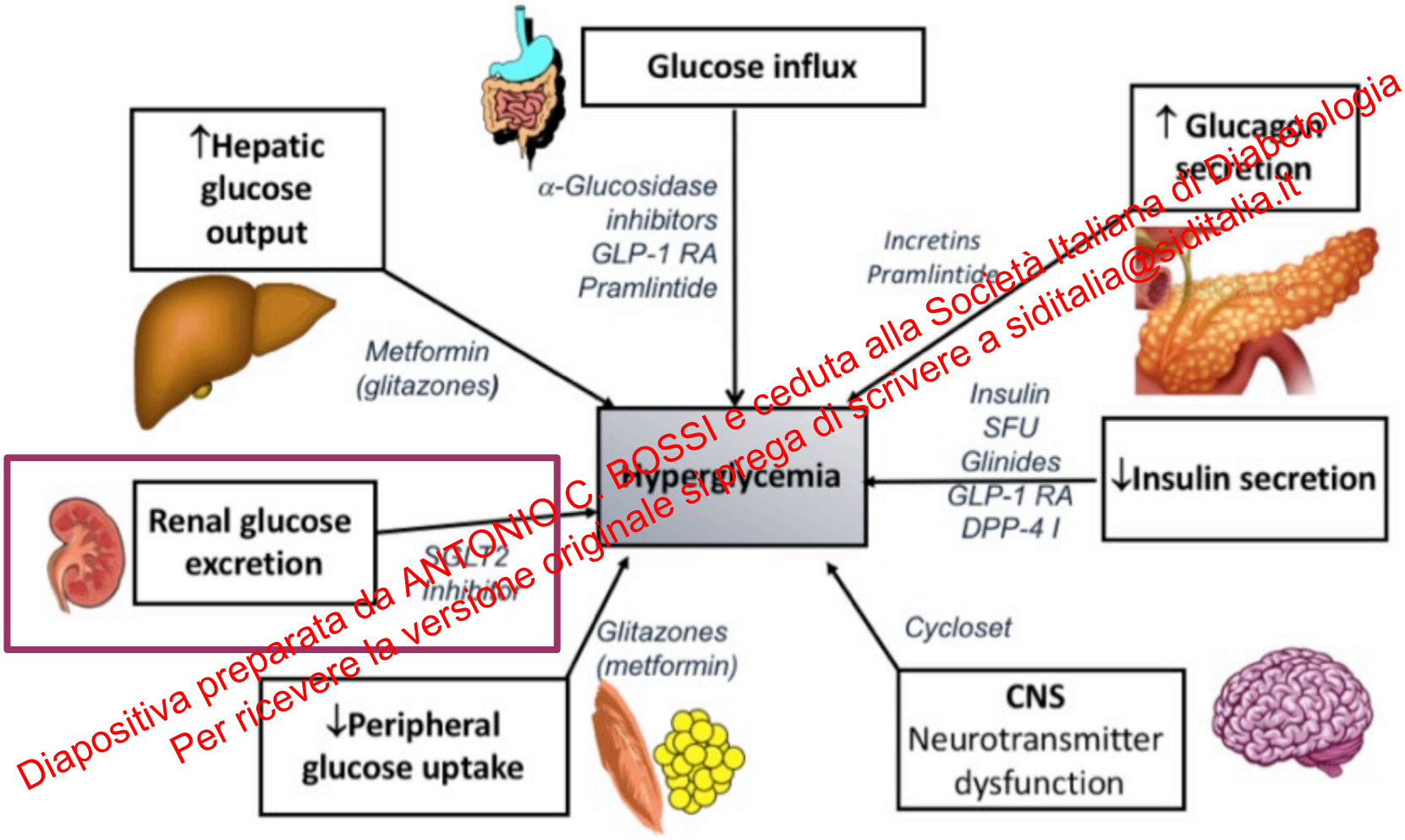
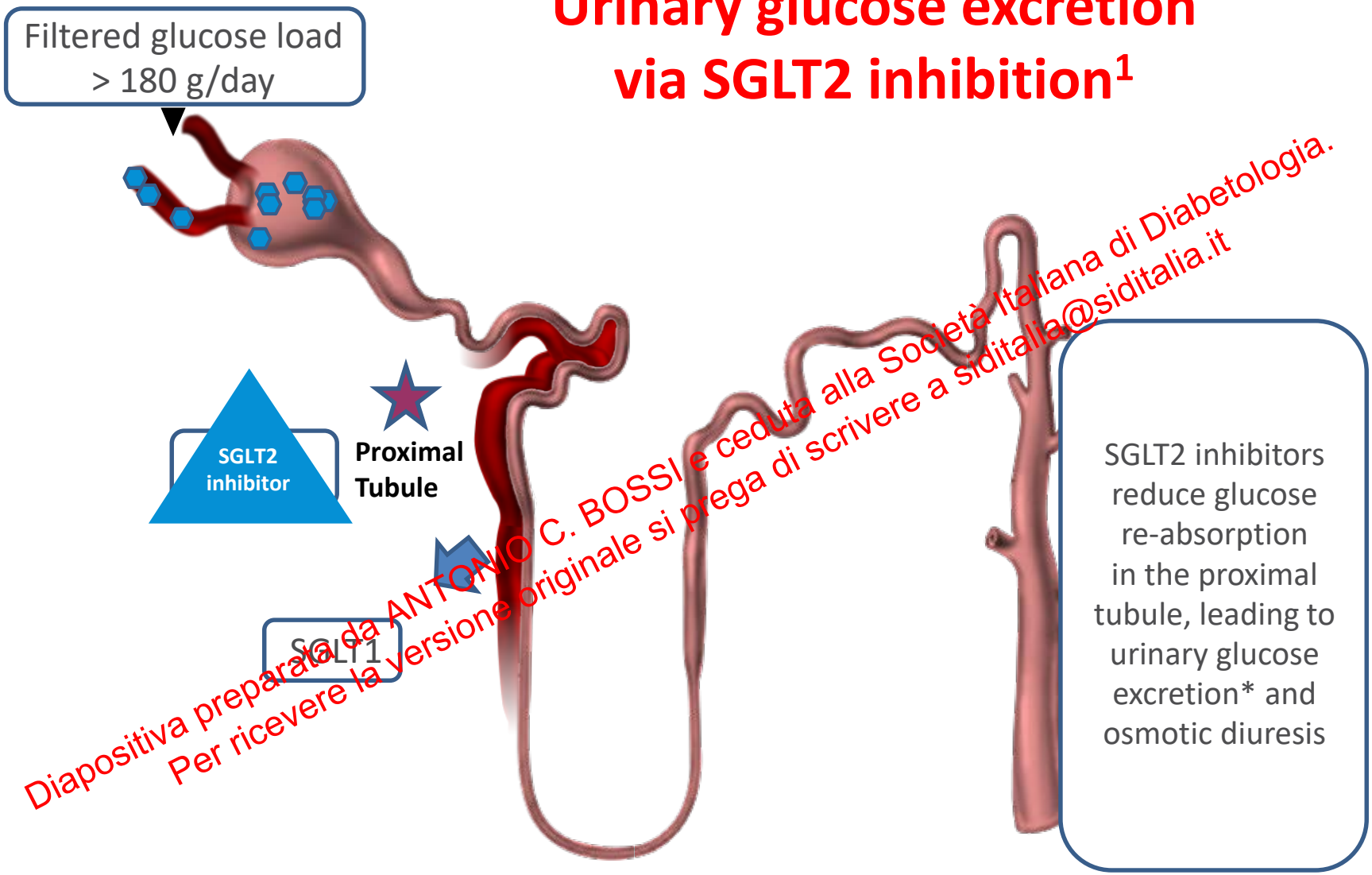
SGLT2-i: un approccio insulino-indipendente

The Ominous Octet Pathways
(and Agents That Target Them)



Mod. from DeFronzo RA.
Diabetes. 2009;58:773-795;
Tahrani AA et al. *Lancet* 2011;378:182–197.

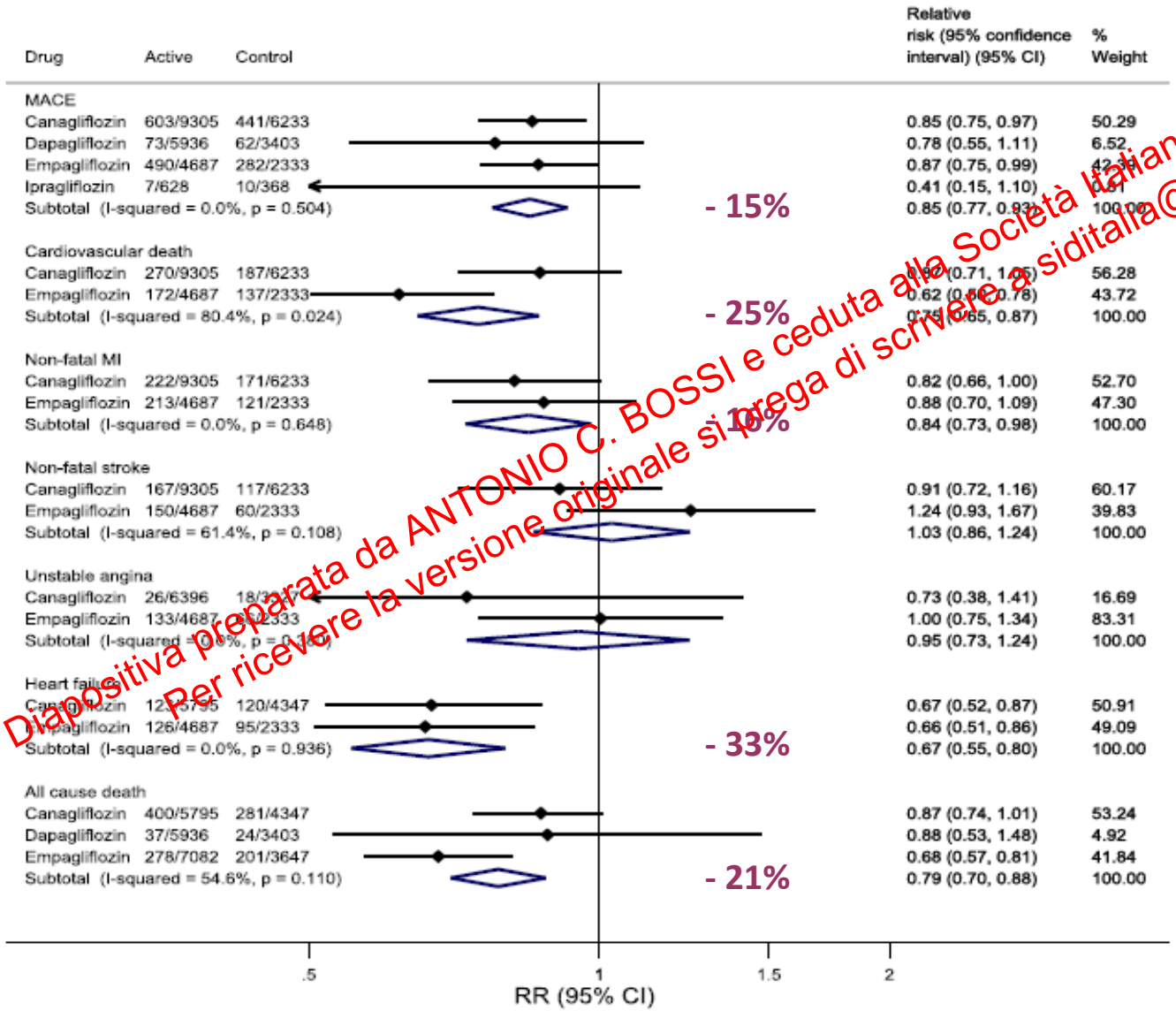
Urinary glucose excretion via SGLT2 inhibition[1]

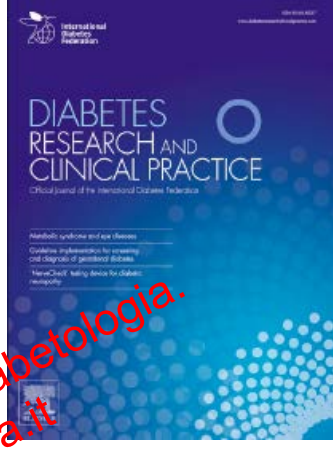


SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.

1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular disease, death and safety outcomes in type 2 diabetes – a systematic review

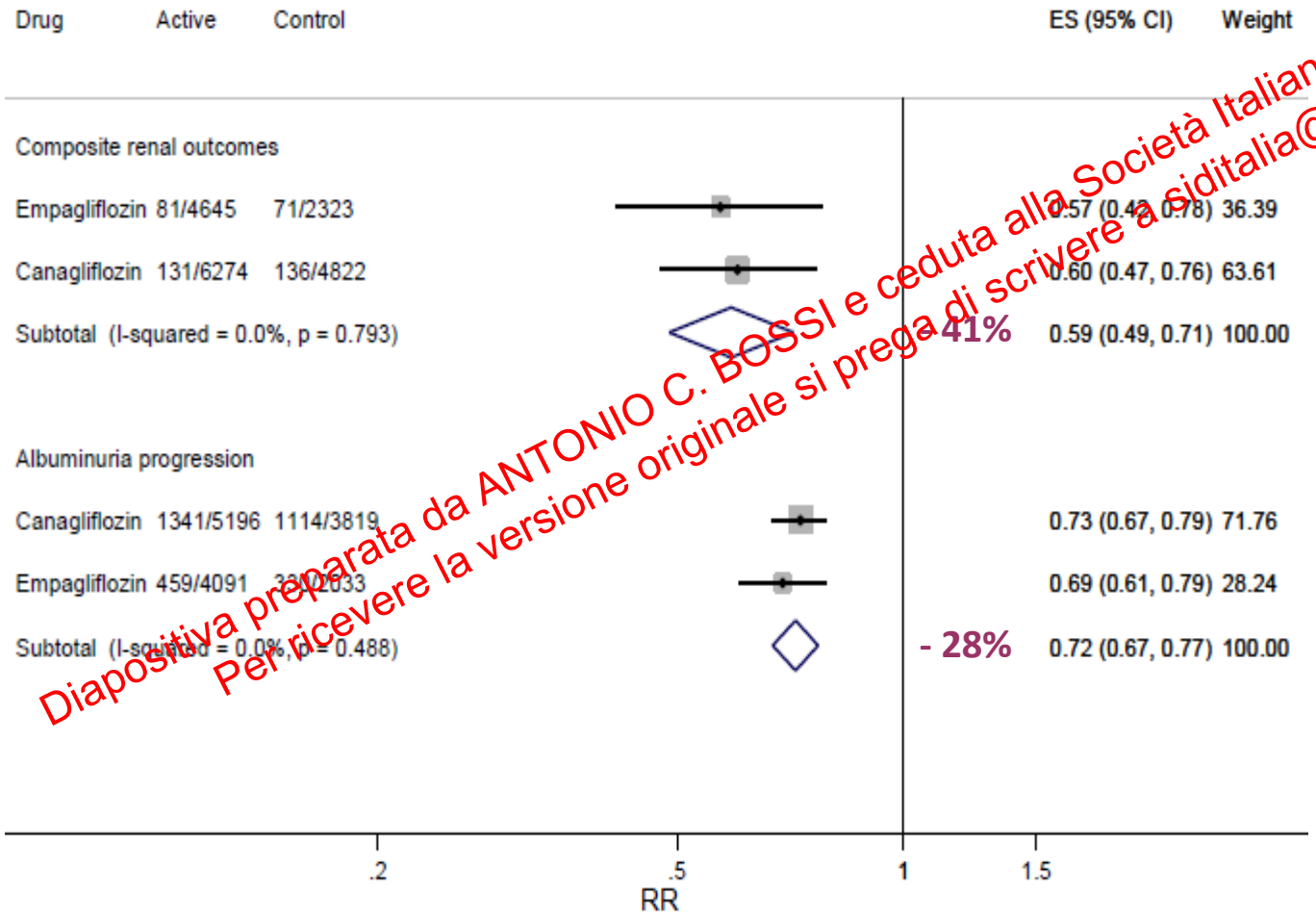




Radholm K et Al. *Diabetes Research and Clinical Practice (2018)* https://doi.org/10.1016/j.diabres.2018.03.027

Associations of SGLT2 inhibitors with cardiovascular outcomes and death, overall and for each compound

Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular disease, death and safety outcomes in type 2 diabetes – a systematic review



Associations of SGLT2 inhibitors with renal outcomes, overall and for each compound

Radholm K et Al. *Diabetes Research and Clinical Practice (2018)* https://doi.org/10.1016/j.diabres.2018.03.027

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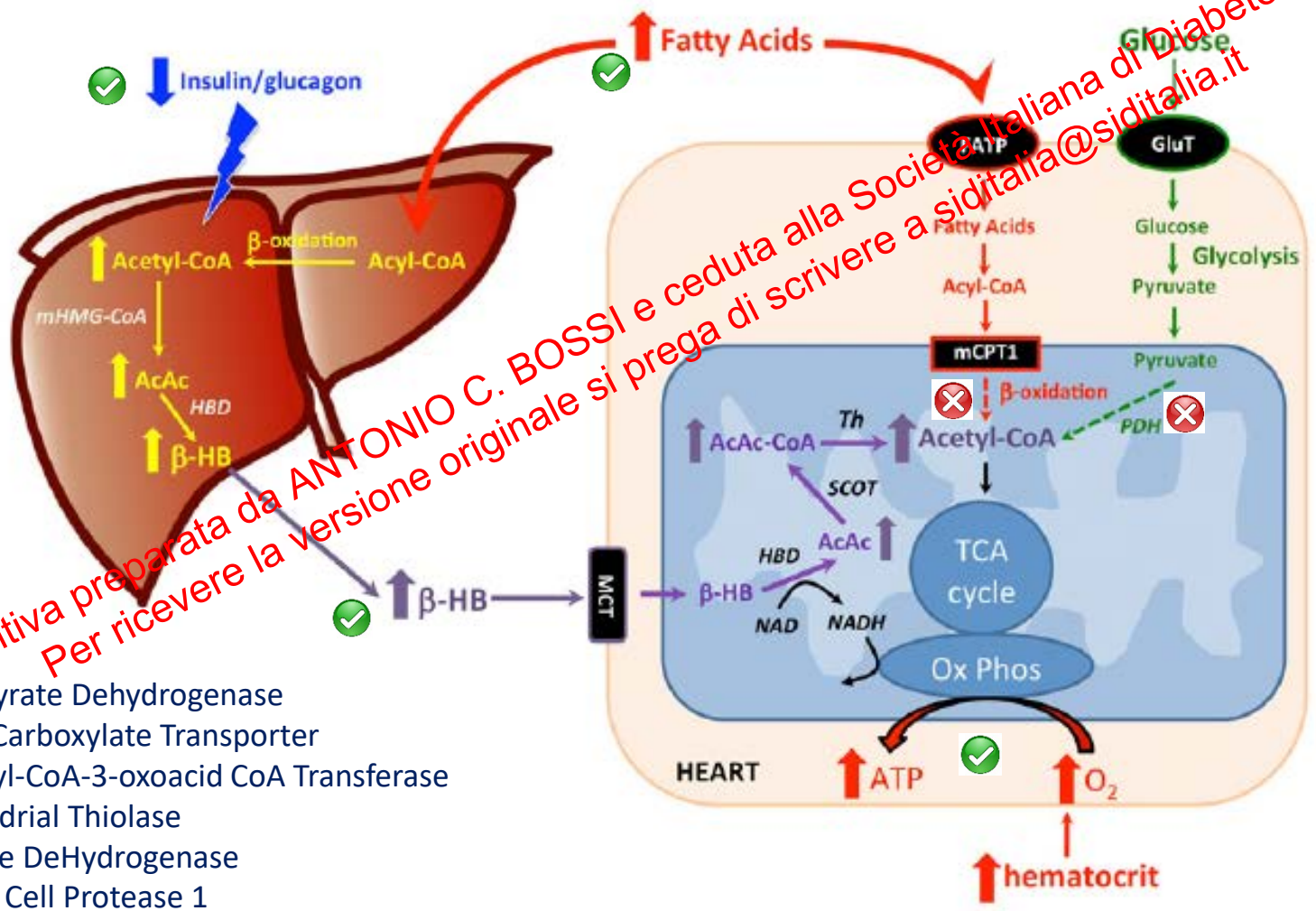
SGLT2-i: ripristino metabolico diurno

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]

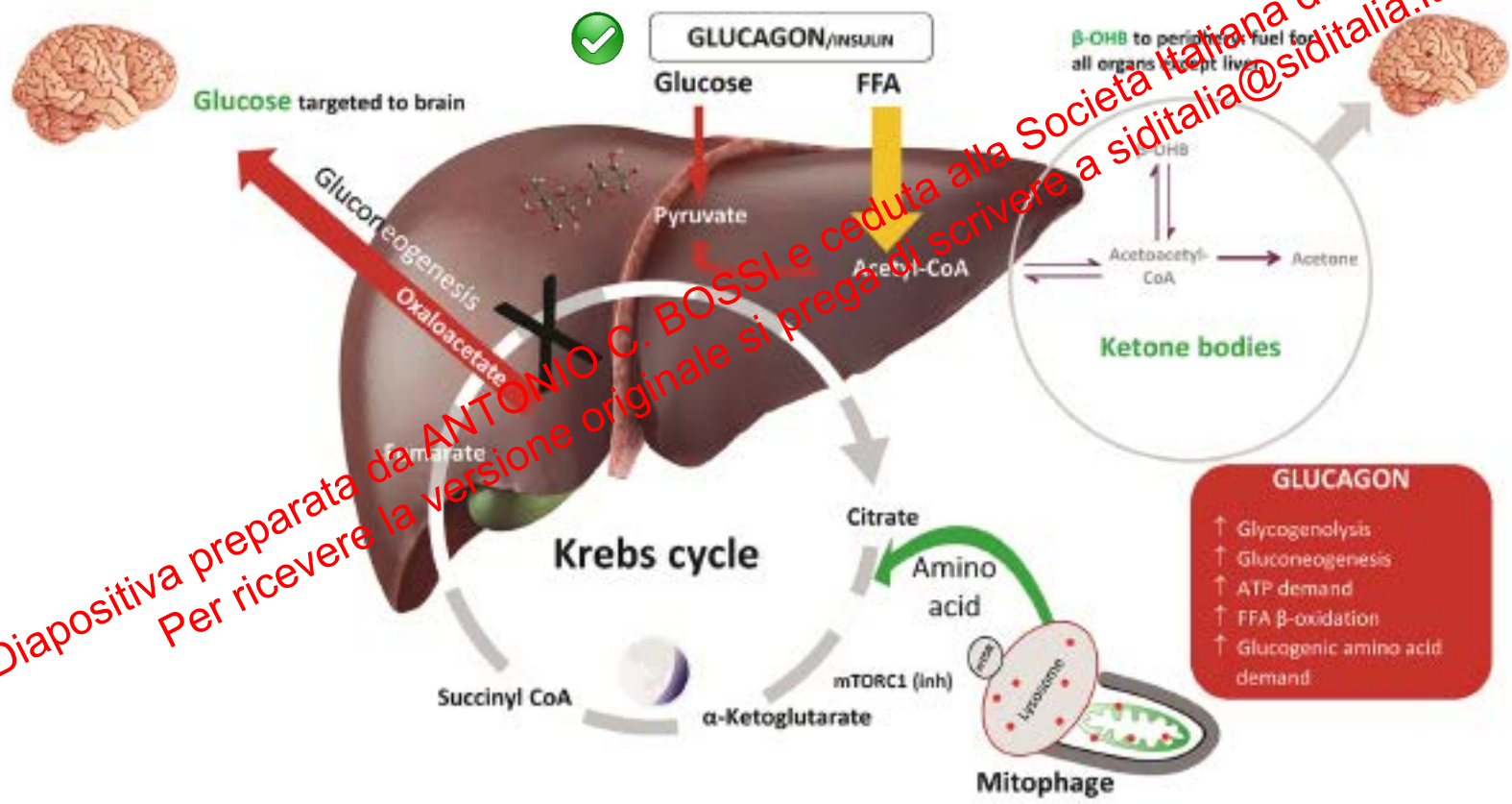
Diabetes Care 2016;39:1108–1114



HBD: OH Butyrate Dehydrogenase
MCT: Mono-Carboxylate Transporter
SCOT: Succinyl-CoA-3-oxoacid CoA Transferase
Th: mitochondrial Thiolase
PDH: Pyruvate DeHydrogenase
mCPT1: mast Cell Protease 1
FATP: Fatty Acid Transport Protein

SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

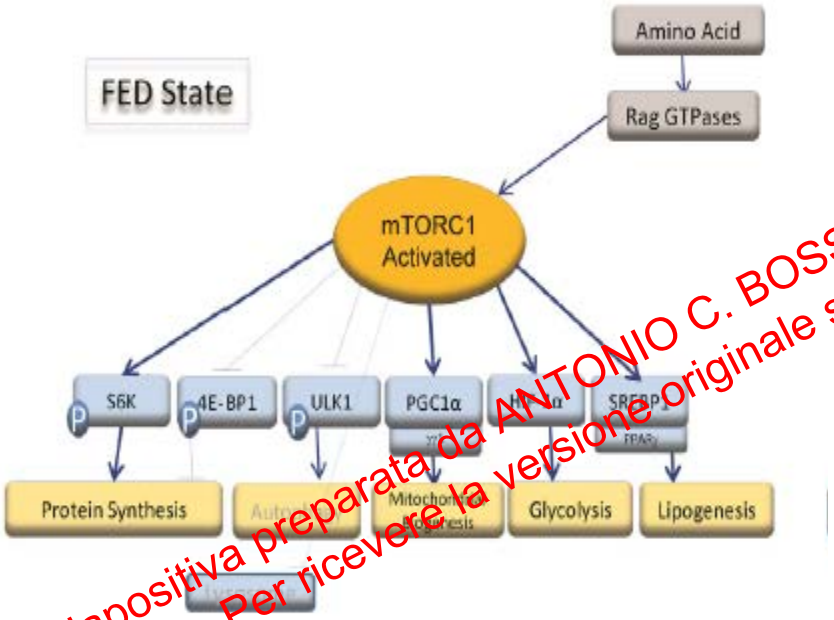
Impact of SGLT2 inhibitor-enhanced fasting on hepatic metabolism.



Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

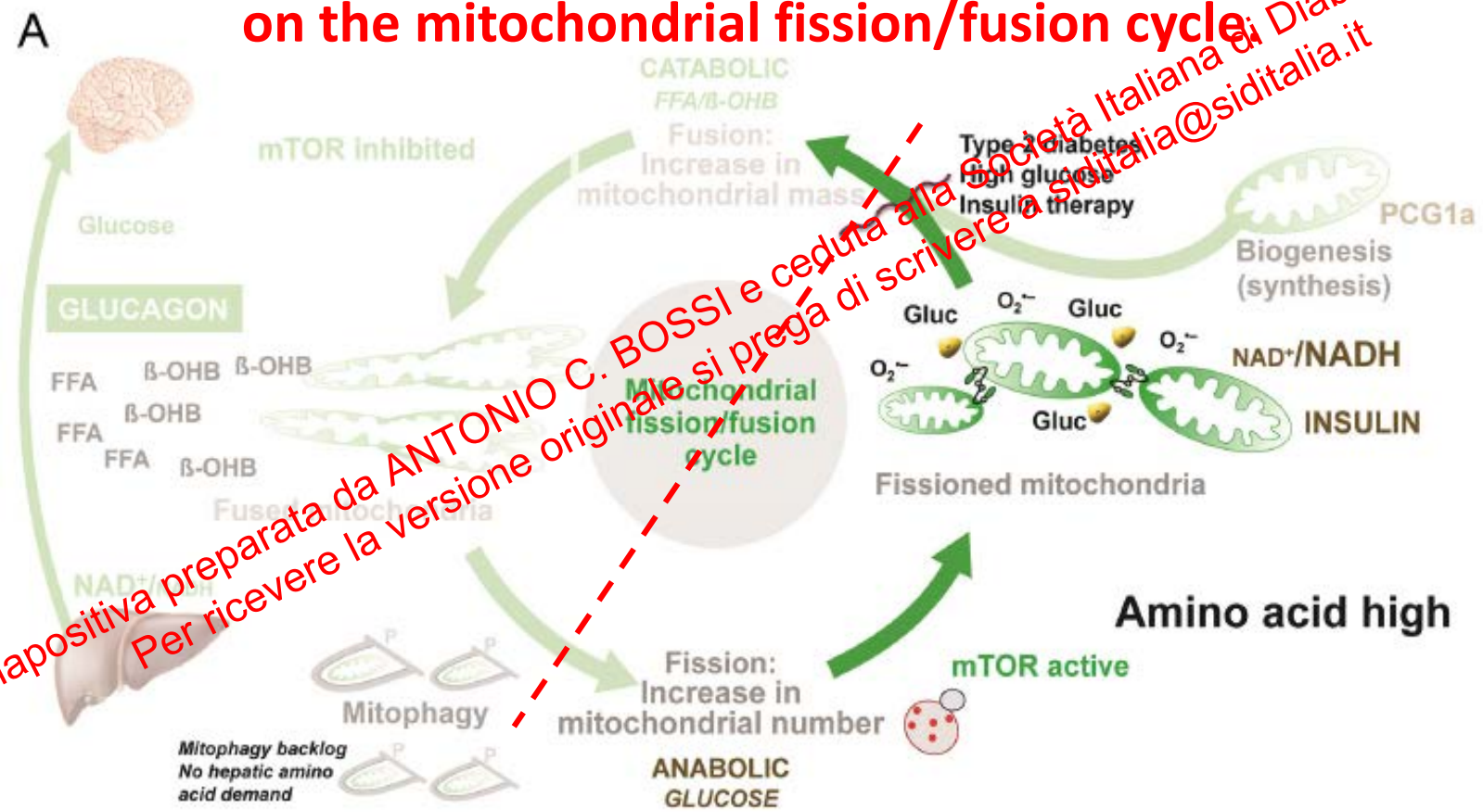
mTOR pathways in the fed and fasted states



Esterline RL et Al. *European Journal of Endocrinology, 2018, 178, R113–R125*
Adapted with permission from: Maiese K. Molecules to Medicine with mTOR, 1st Edition. Translating Critical Pathways into Novel Therapeutic Strategies. Academic Press Feb 2016.

SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

The impact of 'insulin' and SGLT2 inhibitor treatment on the mitochondrial fission/fusion cycle



Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

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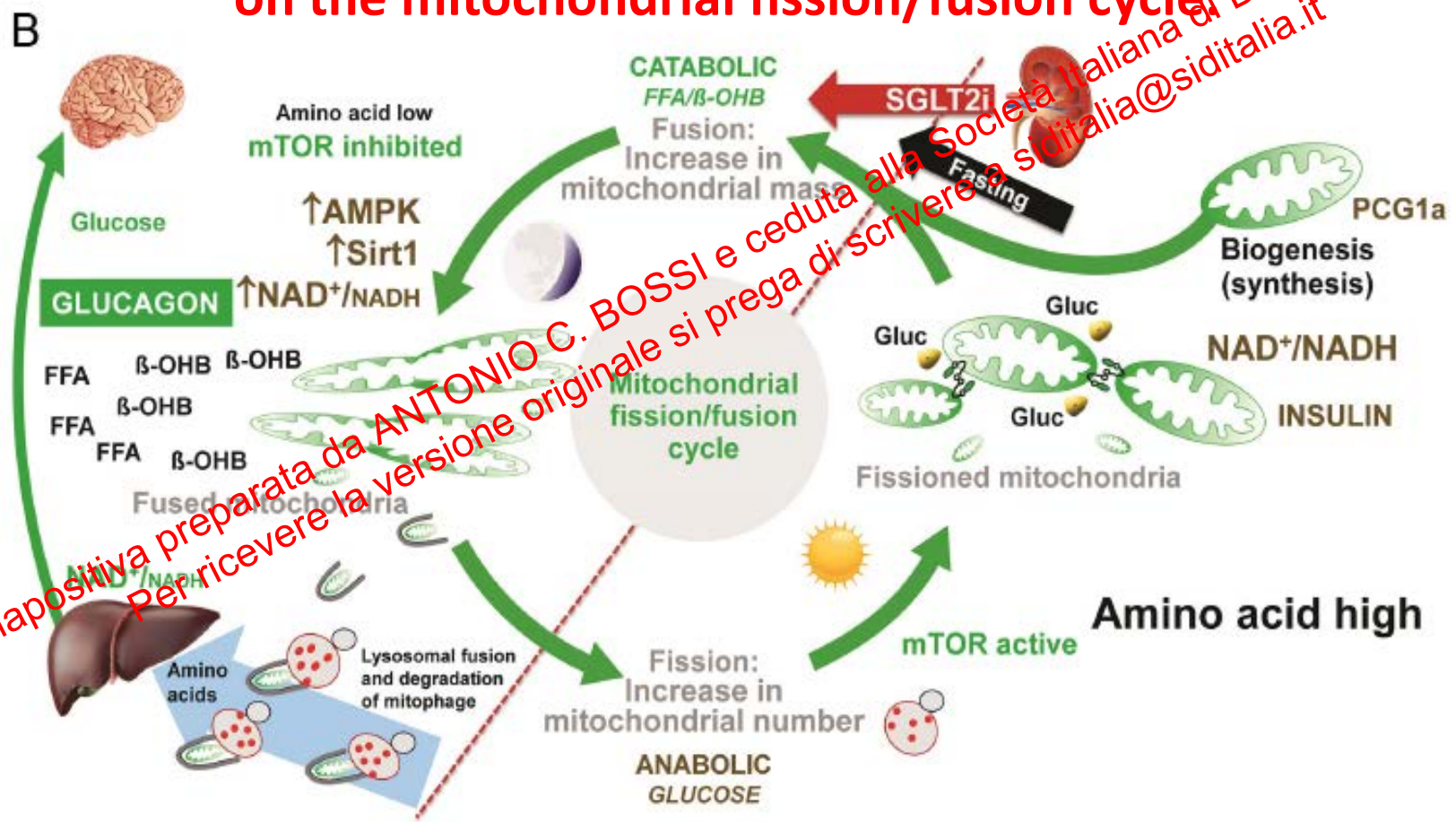
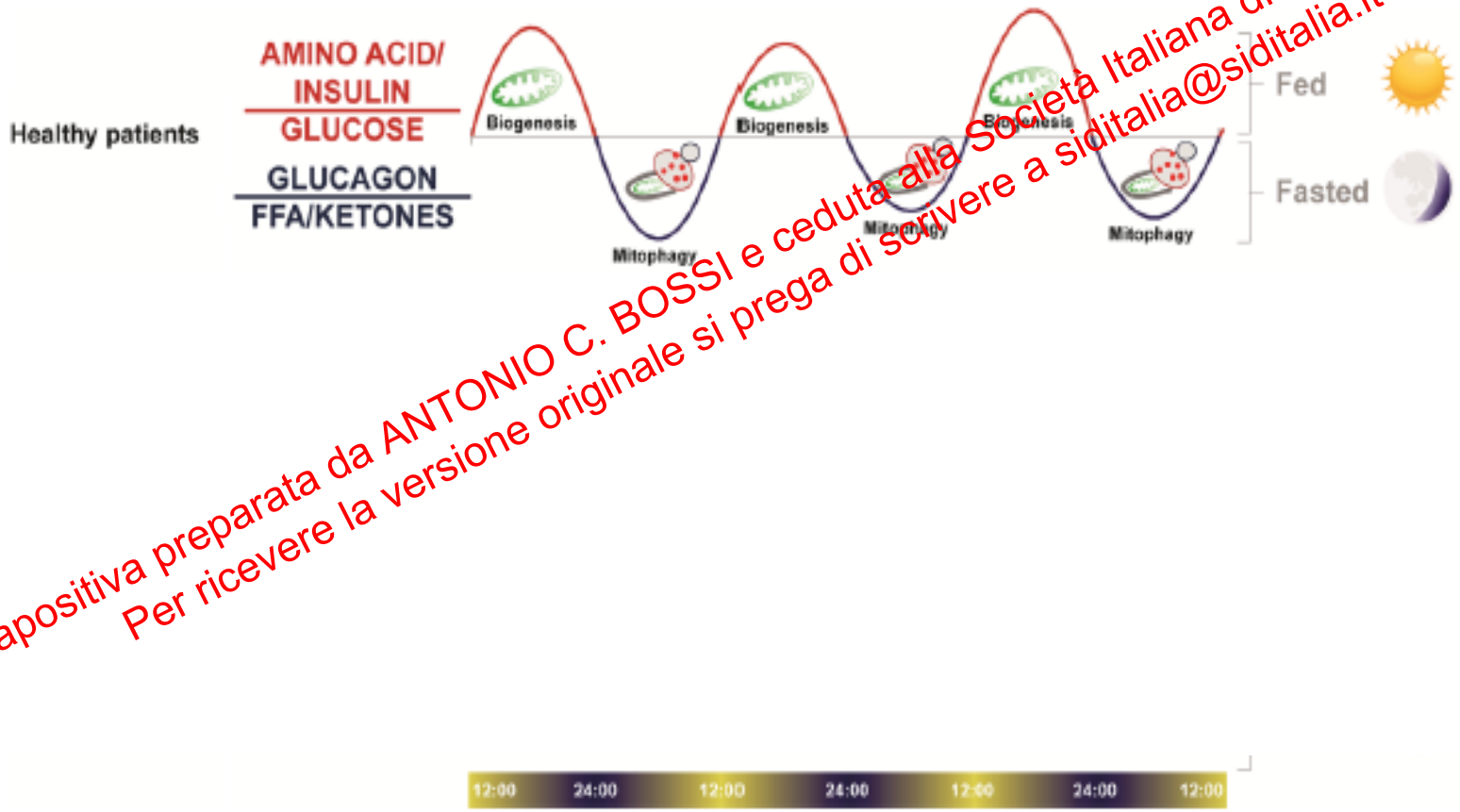


Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

MECHANISMS IN ENDOCRINOLOGY

SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

The impact of SGLT2 inhibitor treatment on mitochondrial function



Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

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SGLT2-i: ripristino metabolico diurno

SGLT2-i: protezione cardio-vascolare

Contents lists available at ScienceDirect

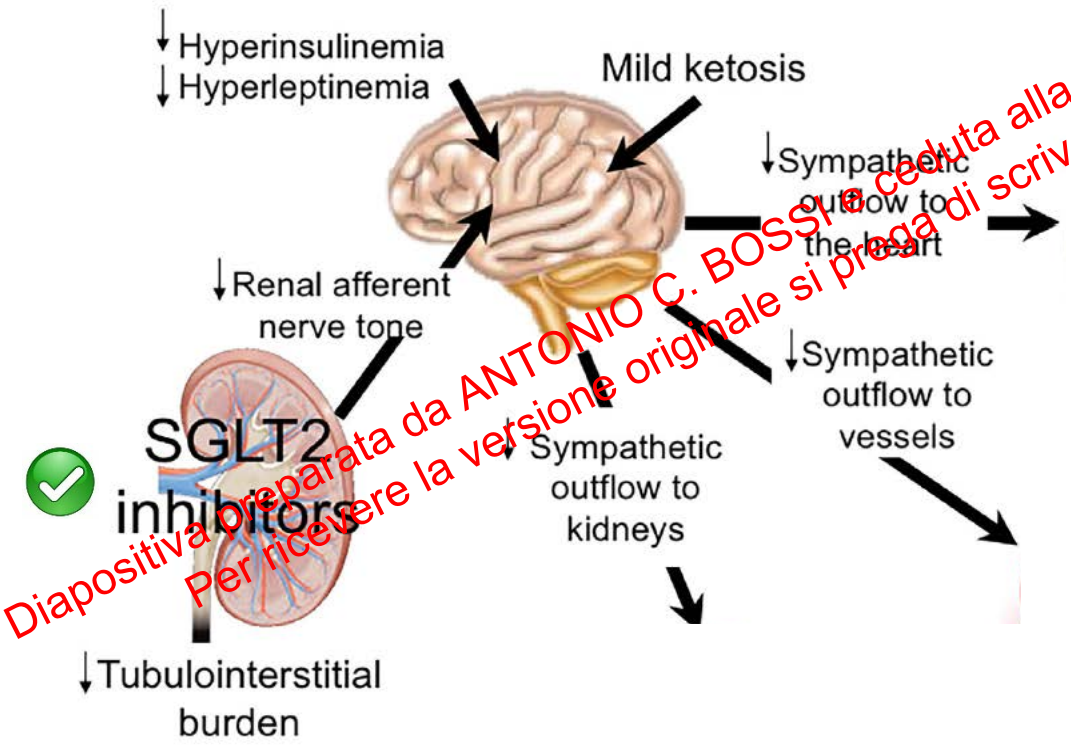
Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

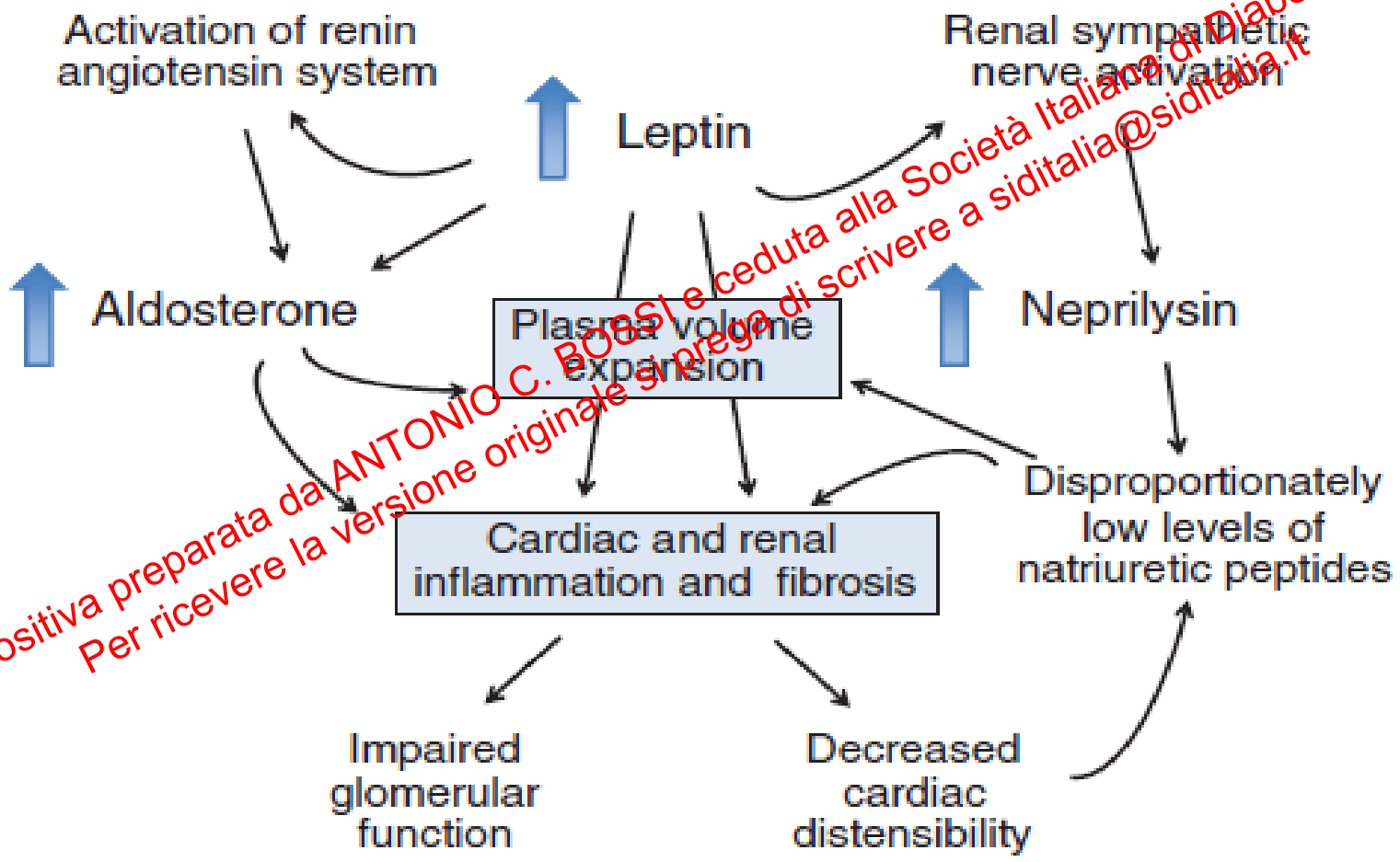
A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity

Proposed mechanism of cardiovascular protection by SGLT2 inhibitors.



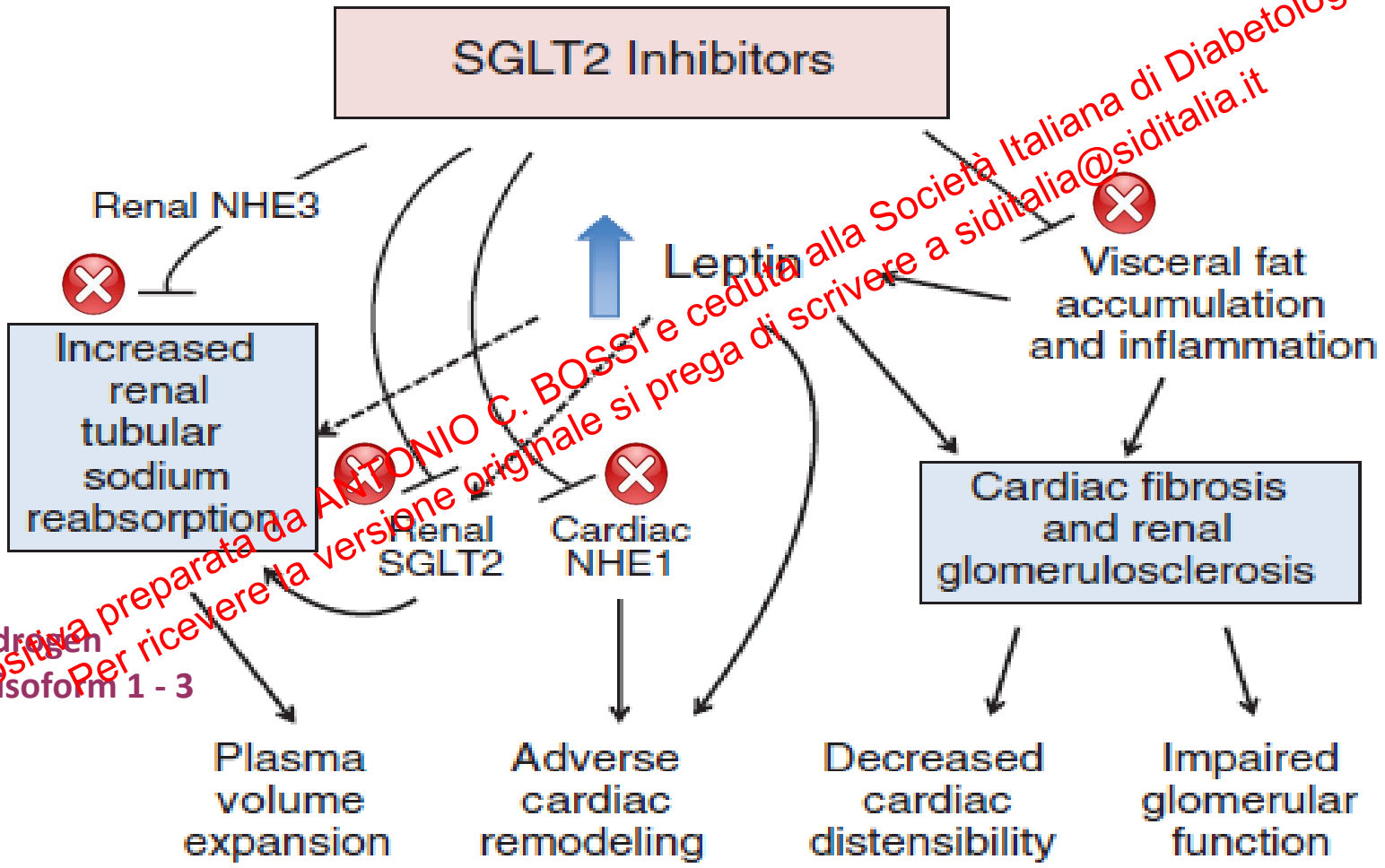
Motoaki Sano
Journal of Cardiology 71 (2018) 471–476

Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis



Milton Packer. Diabetes Obes Metab. 2018;1–6.

Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis



NHE1-3:
sodium-hydrogen exchanger isoform 1 - 3

Milton Packer. Diabetes Obes Metab. 2018;1–6.

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Journal of Cardiology

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Review

A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity

Clinical trials currently investigating the cardiovascular effects of SGLT2 inhibitors.

SGLT2 inhibitor	Abbreviated study title	Full study title	Diabetes status	Trial identification number
Dapagliflozin	DEFINE-HF	Dapagliflozin Effect on Symptoms and Biomarkers in Diabetes Patients With Heart Failure	All T2DM	NCT02653482
Dapagliflozin	PRESERVED HF	Dapagliflozin in Type 2 Diabetes or Pre-diabetes and Preserved Ejection Fraction Heart Failure	T2DM or prediabetes	NCT03030235
Dapagliflozin	DAPA-HF	Study to Evaluate the Effect of Dapagliflozin on Incidence of Worsening Heart failure or Cardiovascular Death in Patients with CHF	Nondiabetic and T2DM (T1DM excluded)	NCT03036124
Empagliflozin	EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction	Nondiabetic, T1DM, and T2DM eligible	NCT03057951
Empagliflozin	EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction	Nondiabetic, T1DM, and T2DM eligible	NCT03057977
Empagliflozin	EMBRACE-F	Empagliflozin Impact on Hemodynamics in Patients With Diabetes and Heart Failure	All T2DM	NCT03030222
Dapagliflozin	REFORM	Study and Effectiveness of SGLT-2 Inhibitors in Patients with Heart Failure and Diabetes	All T2DM	NCT02397421
Empagliflozin	EMPA	Empagliflozin in Heart Failure: Diuretic and Cardio-Renal Effects	All T2DM	NCT03027960

SGLT2, sodium glucose cotransporter 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Motoaki Sano
Journal of Cardiology 71 (2018) 471–476

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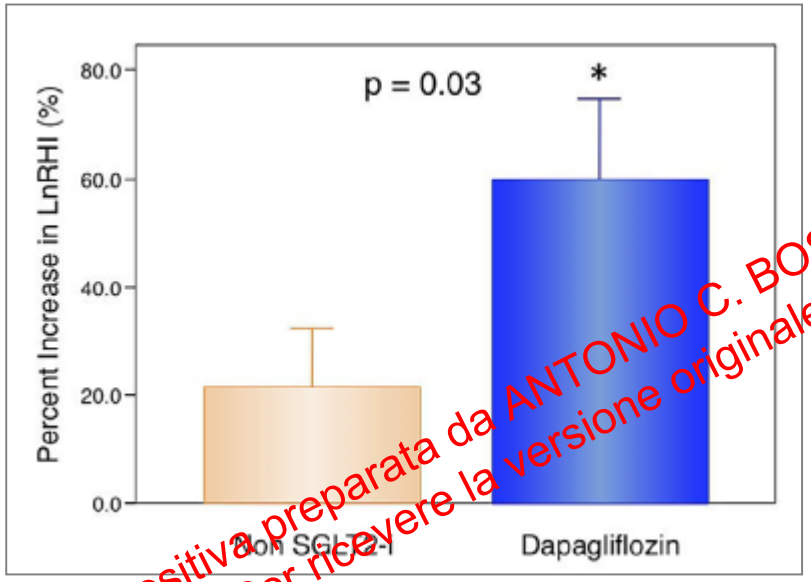
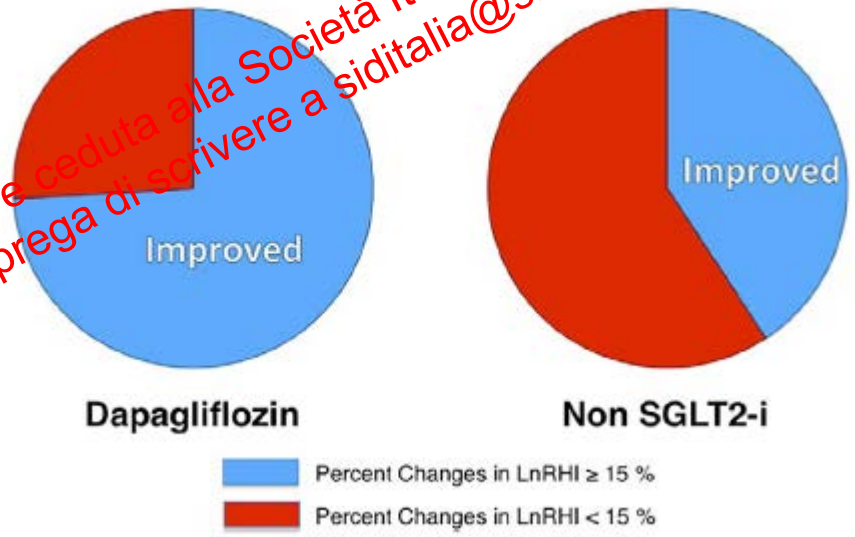
Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0701-17
Intern Med Advance Publication
http://internmed.jp

The SGLT2 Inhibitor Dapagliflozin Significantly Improves the Peripheral Microvascular Endothelial Function in Patients with Uncontrolled Type 2 Diabetes Mellitus





LnRHI, natural logarithmic transformation of the reactive hyperemia index

Sugiyama S et Al.
Intern Med Advance Publication
DOI: 10.2169/internalmedicine.0701-17

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SCIENTIFIC REPORTS

OPEN

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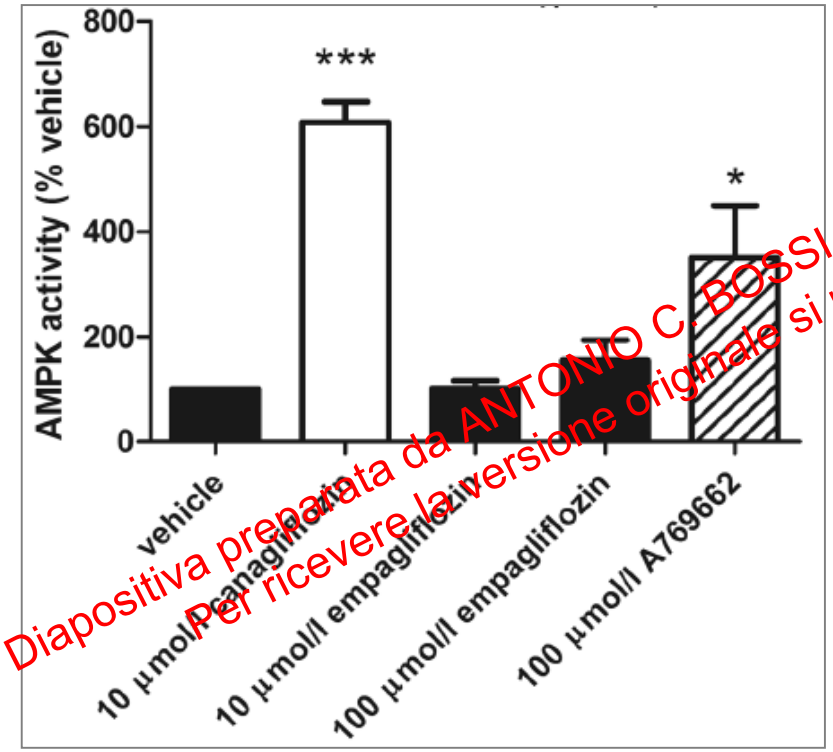
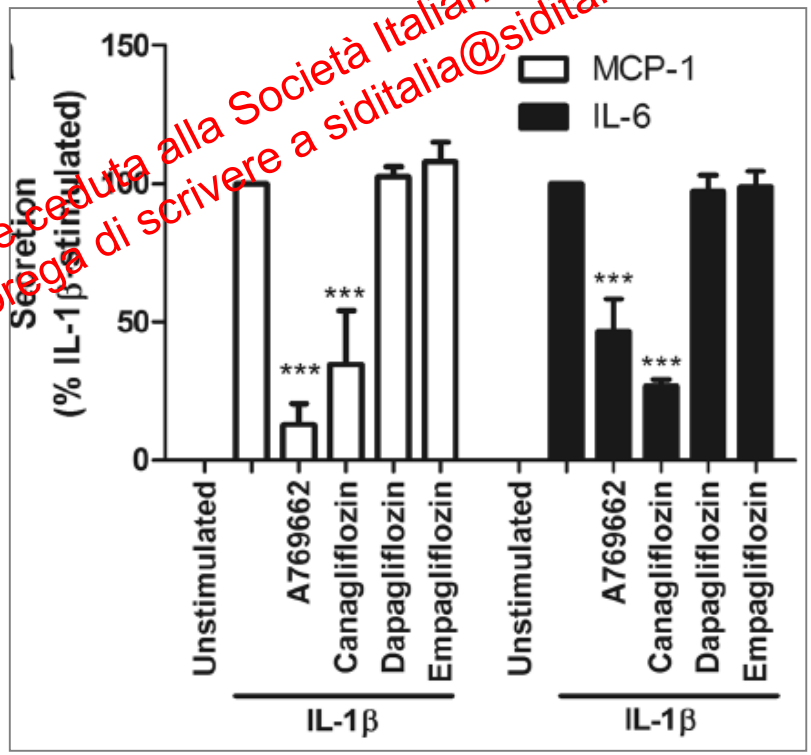
Published online: 27 March 2018

Canagliflozin inhibits interleukin-1β-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-activated protein kinase-dependent and -independent mechanisms

Sarah J. Mancini[1], Daria Boyd[1], Omar J. Katwan[1,2], Anastasiya Strembitska[1], Tarek A. Almabrouk[1,3], Simon Kennedy[1], Timothy M. Palmer[4] & Ian P. Salt[1]





Clinically-relevant canagliflozin concentrations directly inhibit endothelial pro-inflammatory chemokine/cytokine secretion by AMPK-dependent and -independent mechanisms without affecting early IL-1β signalling.

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SGLT2-i: protezione microvascolare

SGLT2-i: molteplici aspetti renali

The Tubuloglomerular Feed-Back

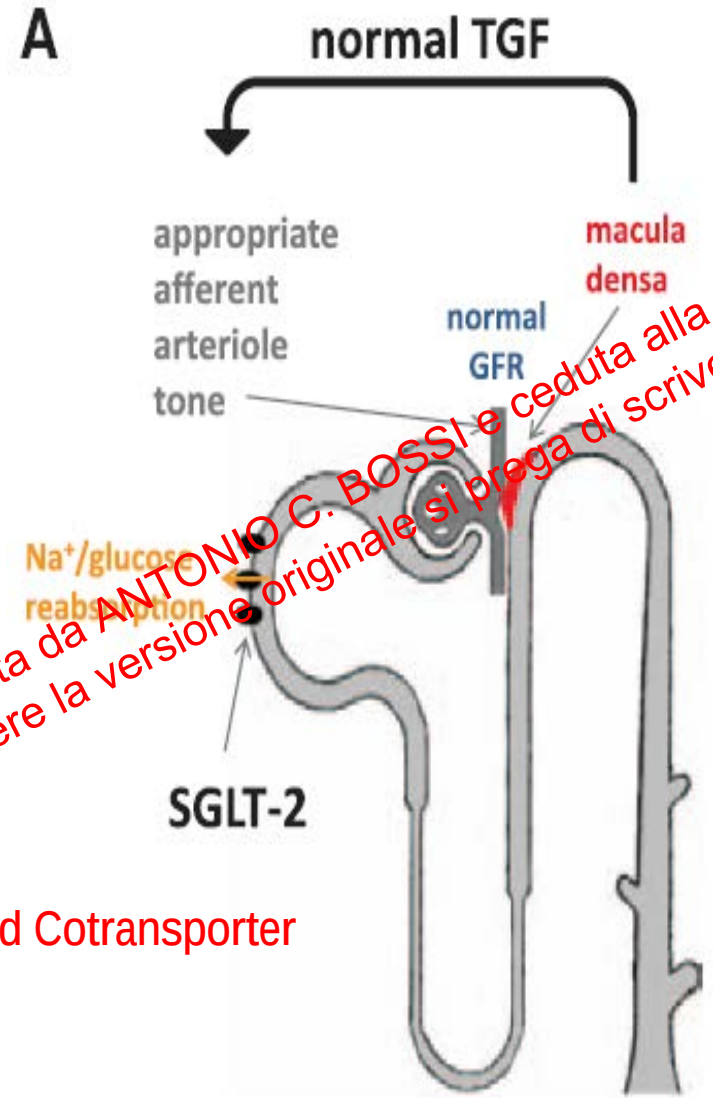
- ***Single Nephron GFR is modulated by sodium delivery to the macula densa***

***Glomerular Hyperperfusion; °Glomerular Hypoperfusion**

Courtesy of P. Ruggenenti

Gilbert R et al, ***Kidney Intern*** 2014

Tubuloglomerular Feedback (TGF) Mechanisms in Normal Physiology

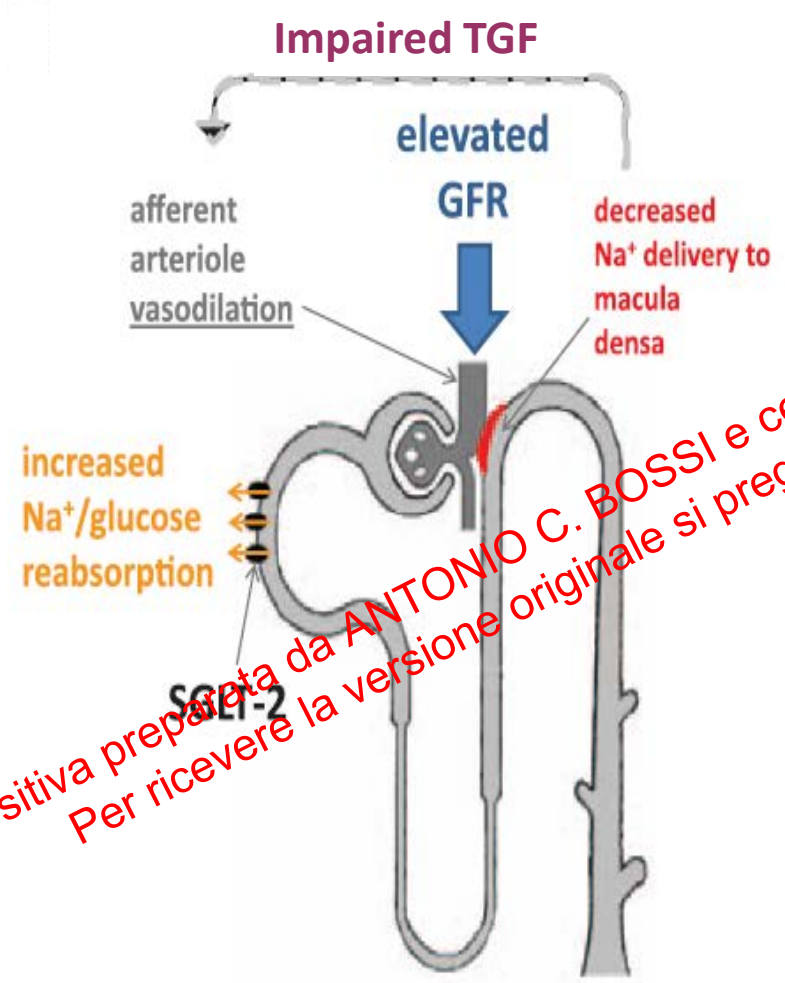


SGLT:
Sodium-Glucose Linked Cotransporter

Courtesy of P. Ruggenenti

Mod. from Cherney, ***Circulation*** 2014

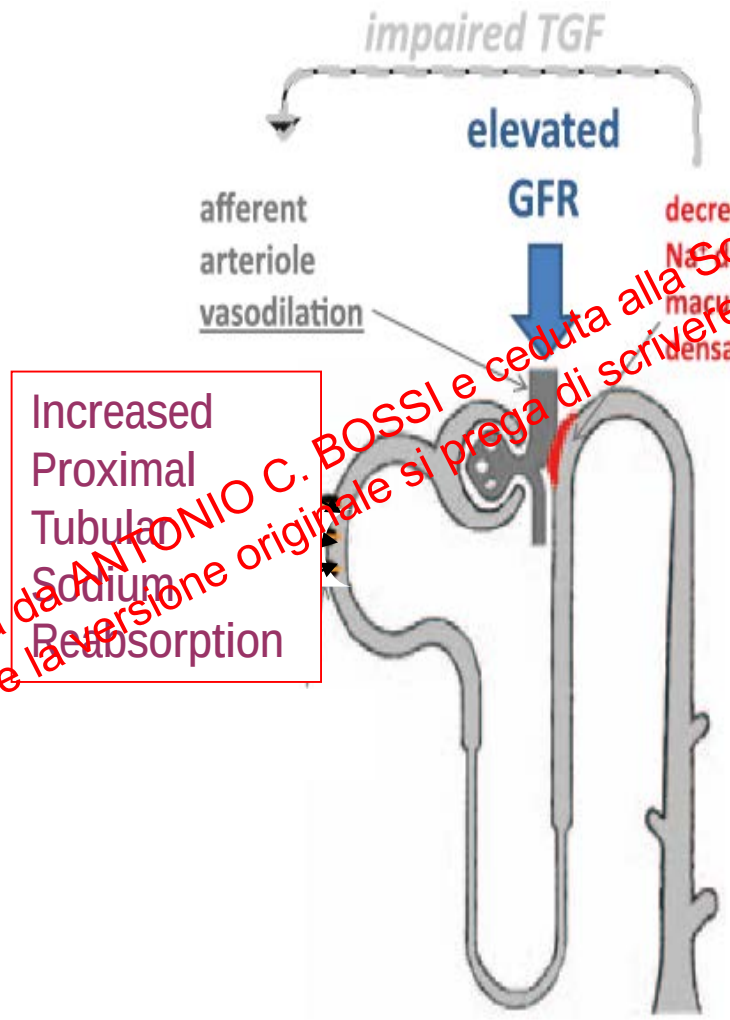
Tubuloglomerular Feedback (TGF) Mechanisms in Diabetes and during SGLT 2 Inhibition



Courtesy of P. Ruggenenti

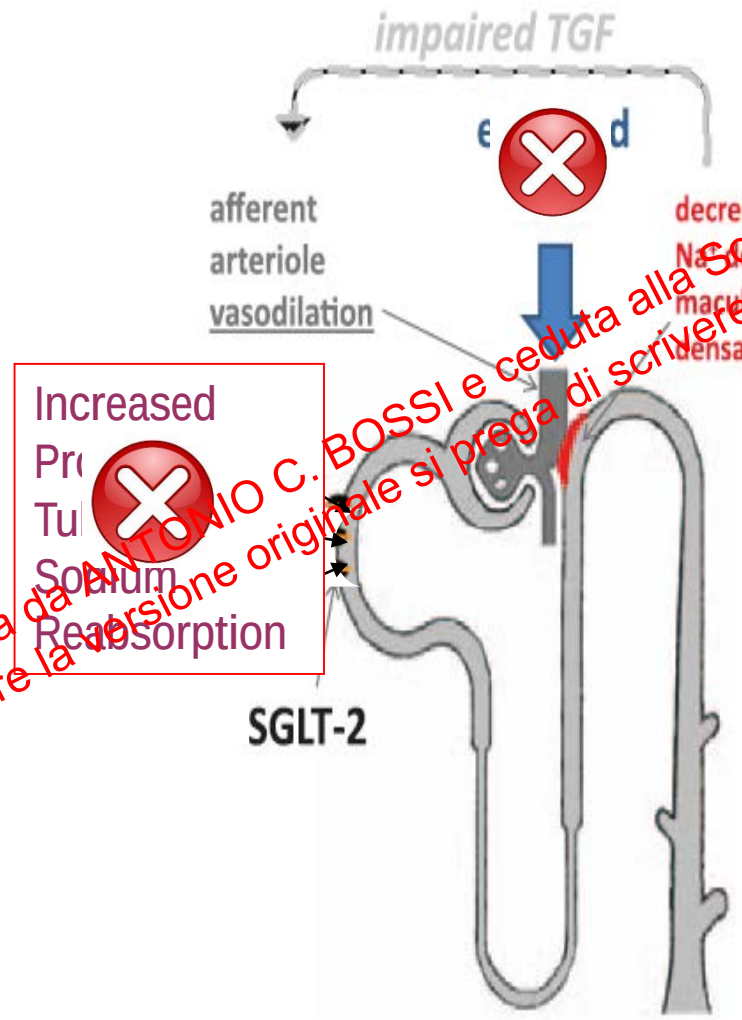
Diabetes

Obesity-associated increased proximal tubular sodium reabsorption and hyperfiltration



Courtesy of P. Ruggenenti

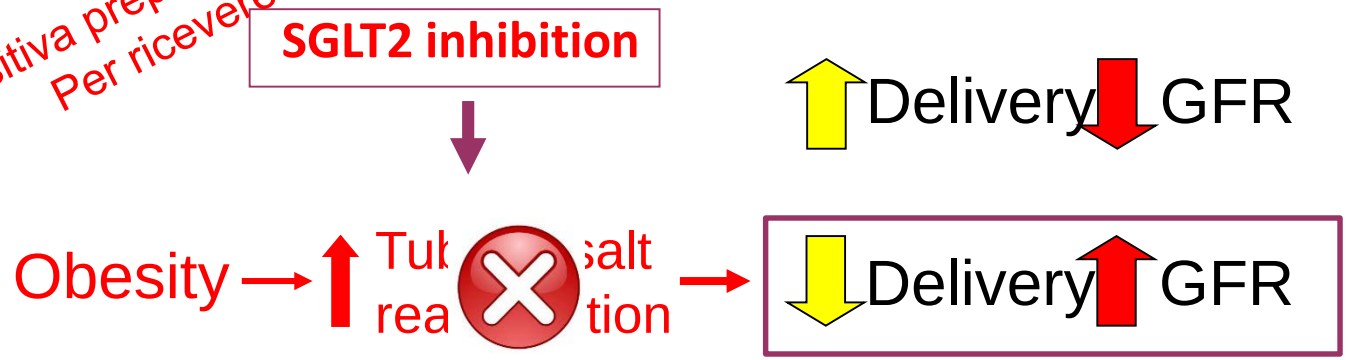
Weight loss in obesity-associated increased proximal tubular sodium reabsorption and hyperfiltration



Courtesy of P. Ruggenenti

The possible role of SGLT2 inhibition in Obesity, additional to the effects of weight loss

In obesity, SGLT2 inhibition might prevent single nephron GFR increase by restoring tubulo-glomerular feed back via inhibition of obesity-mediated proximal tubular salt reabsorption and decreased delivery to the macula densa.



Courtesy of P. Ruggenenti

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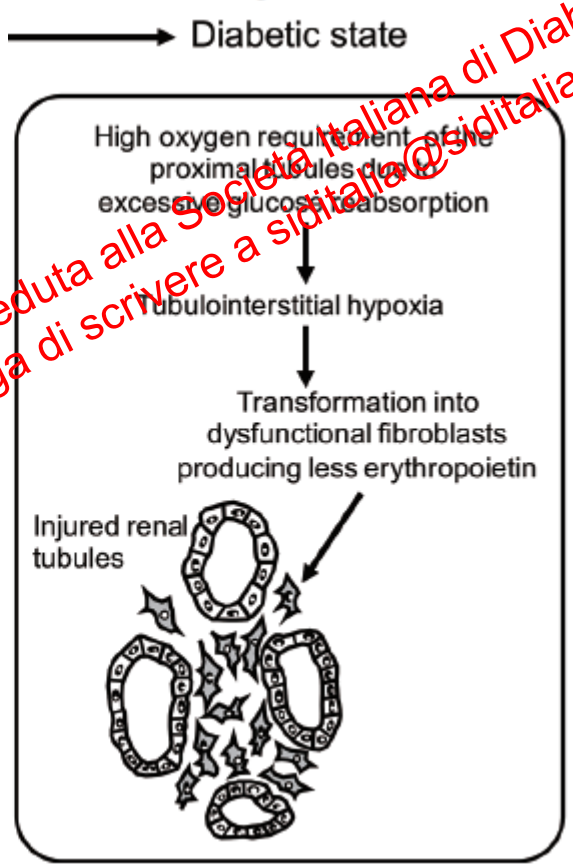
SGLT2-i: molteplici aspetti renali

SGLT2-i: ematocrito

Increased Hematocrit During Sodium-Glucose Cotransporter 2 Inhibitor Therapy Indicates Recovery of Tubulointerstitial Function in Diabetic Kidneys



How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial

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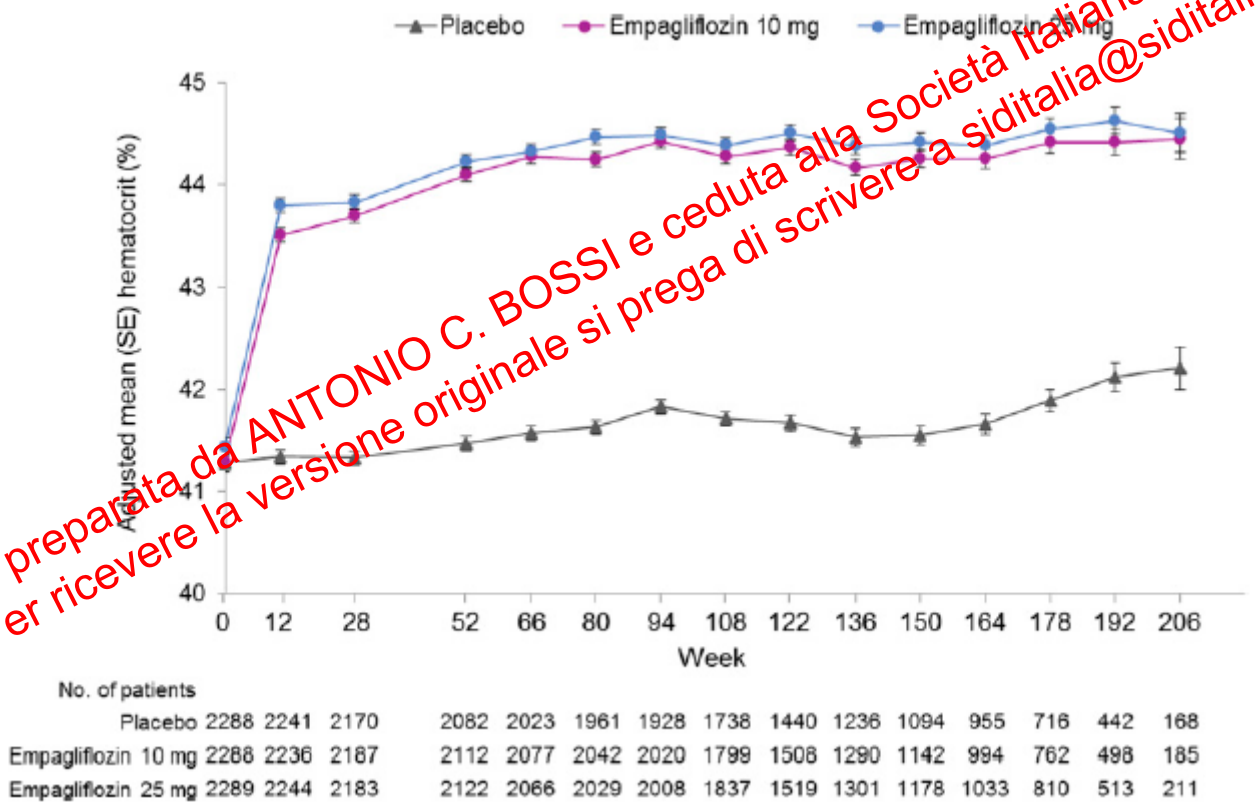

Hematocrit over time in patients treated with empagliflozin 10 mg, empagliflozin 25mg, and placebo.

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	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.687 (0.543, 0.868)	22.8
FPG	0.709 (0.559, 0.898)	29.3
SBP	0.610 (0.485, 0.766)	−1.7
DBP	0.618 (0.493, 0.774)	1.0
Heart rate	0.623 (0.497, 0.782)	2.7
LDL-C	0.591 (0.471, 0.741)	−8.2
HDL-C	0.629 (0.500, 0.789)	4.6
logTG	0.603 (0.481, 0.757)	−4.1
FFAs	0.587 (0.463, 0.743)	−9.6
logUACR	0.672 (0.536, 0.844)	18.2
eGFR (MDRD)	0.601 (0.480, 0.752)	−4.7
eGFR (CKD-EPI)	0.597 (0.477, 0.748)	−6.1
Weight	0.588 (0.466, 0.741)	−9.2
BMI	0.588 (0.466, 0.742)	−9.2
WC	0.602 (0.480, 0.755)	−4.4
Hematocrit	0.791 (0.620, 1.009)	51.8
Hemoglobin	0.768 (0.604, 0.978)	45.7
Albumin	0.717 (0.571, 0.900)	31.6
Uric acid	0.673 (0.536, 0.845)	18.5

Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

Come si potrebbe spiegare la riduzione di mortalità associata agli inibitori di SGLT2?

AGENDA

Introduzione

SGLT2-i: un approccio insulino-indipendente

SGLT2-i: ripristino metabolico diurno

SGLT2-i: protezione cardio-vascolare

SGLT2-i: protezione microvascolare

SGLT2-i: molteplici aspetti renali

Conclusioni

SGLT2i Effects on Cardiac Homeostasis

Hemodynamics

- ↓ Vascular resistance
- ↑ Osmotic diuresis
- ↓ Blood pressure
- ↓ Aortic stiffness
- ↓ SNS activity
- ↓ Preload

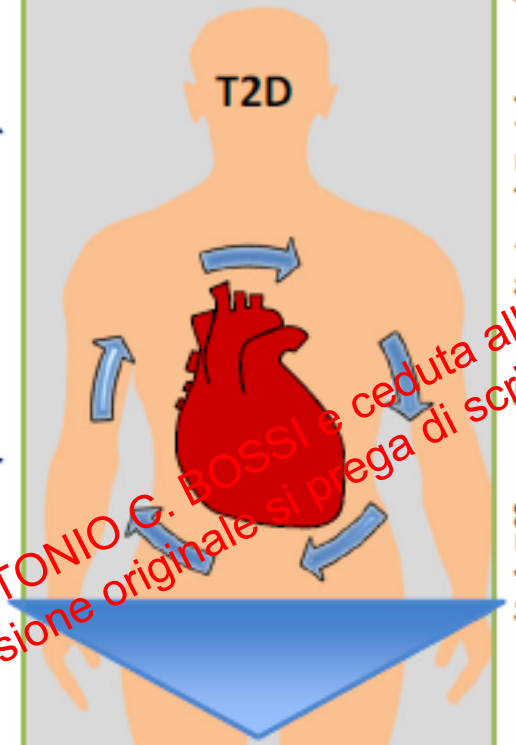
Plasma/Metabolism/Inflammation

- ↑ Ang1-7
- ↓ HbA1c
- ↓ hs-CRP
- ↓ Uric acid
- ↓ $NaCl/H_2O$
- ↑ Glucagon
- ↓ Glycaemia, insulin
- ↑ Ketone bodies, FFA

Composition

- ↓ Epicardial Fat Volume
- ↓ Visceral adiposity
- ↓ Body weight

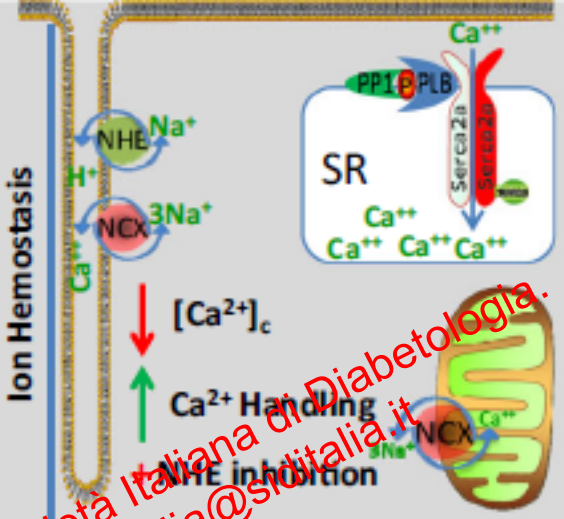
Systemic Effects (*Clinical Evidence*)



- ↓ Fibrosis/Steatosis (Myocardial)
- ↓ Cardiac/Vascular Inflammation
- ↑ Systolic/Diastolic Cardiac Function
- ↓ Major Adverse CV Events

Direct Myocardial Effects (*Preclinical Evidence*)

Ion Hemostasis



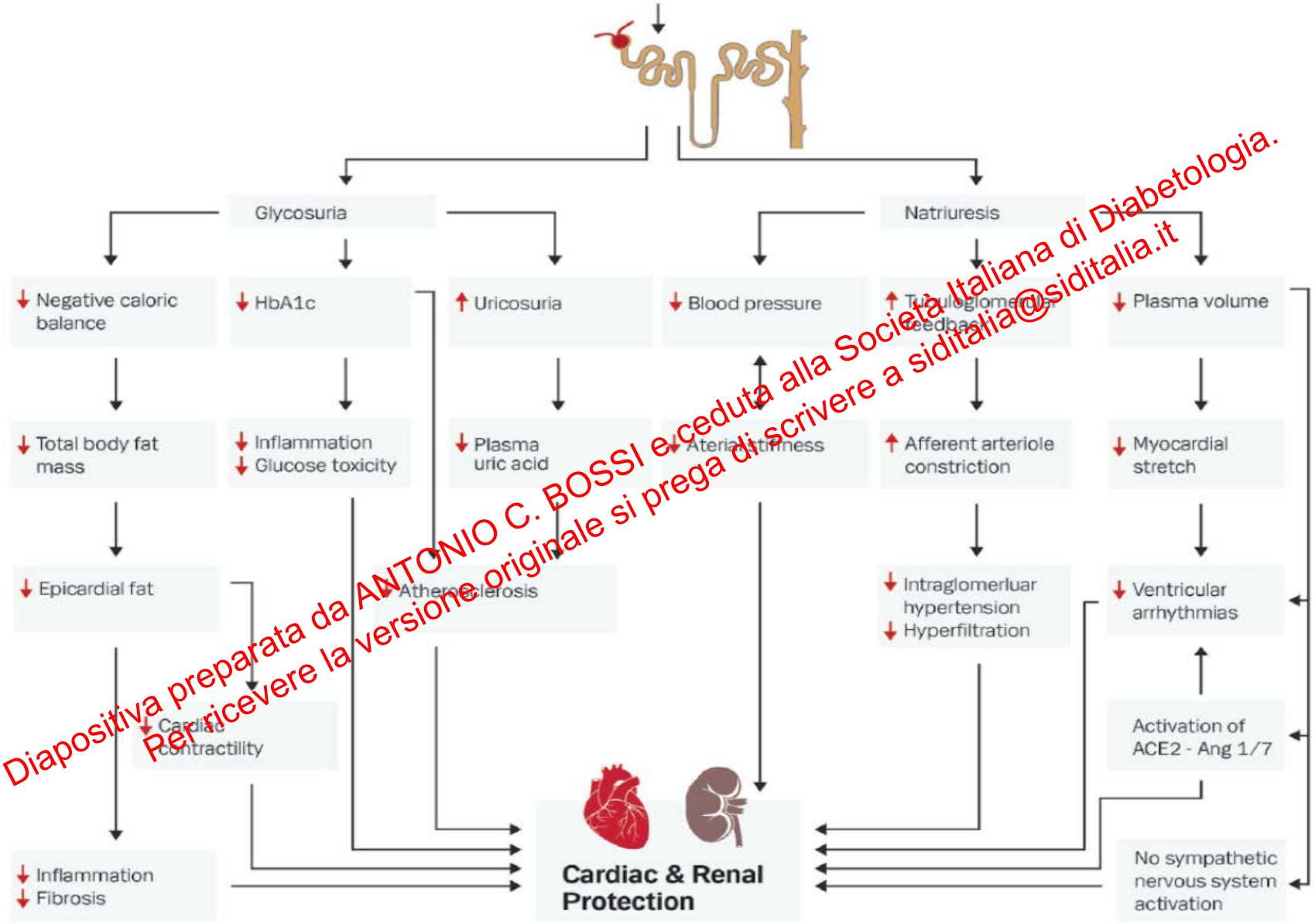
Inflammation/oxidation

- ↓ RONS production
- ↑ Anti-inflammatory cytokines
- ↓ NLRP-3 inflammasome activation

Metabolism

- ↓ AGEs formation
- ↑ Insulin sensitivity
- ↓ TG accumulation
- ↓ Glucose accumulation
- ↑ FA, Ketone bodies oxidation

Overview of the proposed effects of SGLT2-inhibitors on different organ systems.



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Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

		Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ
					ASCVD	CHF		
Metformin		High	No	Neutral Modest Loss)	Potential Benefit	Neutral	Low	Oral
SGLT-2 inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral
GLP-1 RAs		High	No	Loss	Neutral lixisenatide, exenatide extended release	Neutral	High	SQ
					Benefit: liraglutide†			
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral
Insulin	**Human insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ
	Analogs						High	SQ

GRAZIE
per la Vostra Attenzione!

Come si potrebbe spiegare la riduzione di mortalità associata agli inibitori di SGLT2?

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