Il giusto posto delle gliflozine nel trattamento del diabete di tipo 2
SGLT2i e chetogenesi: vantaggi e rischi

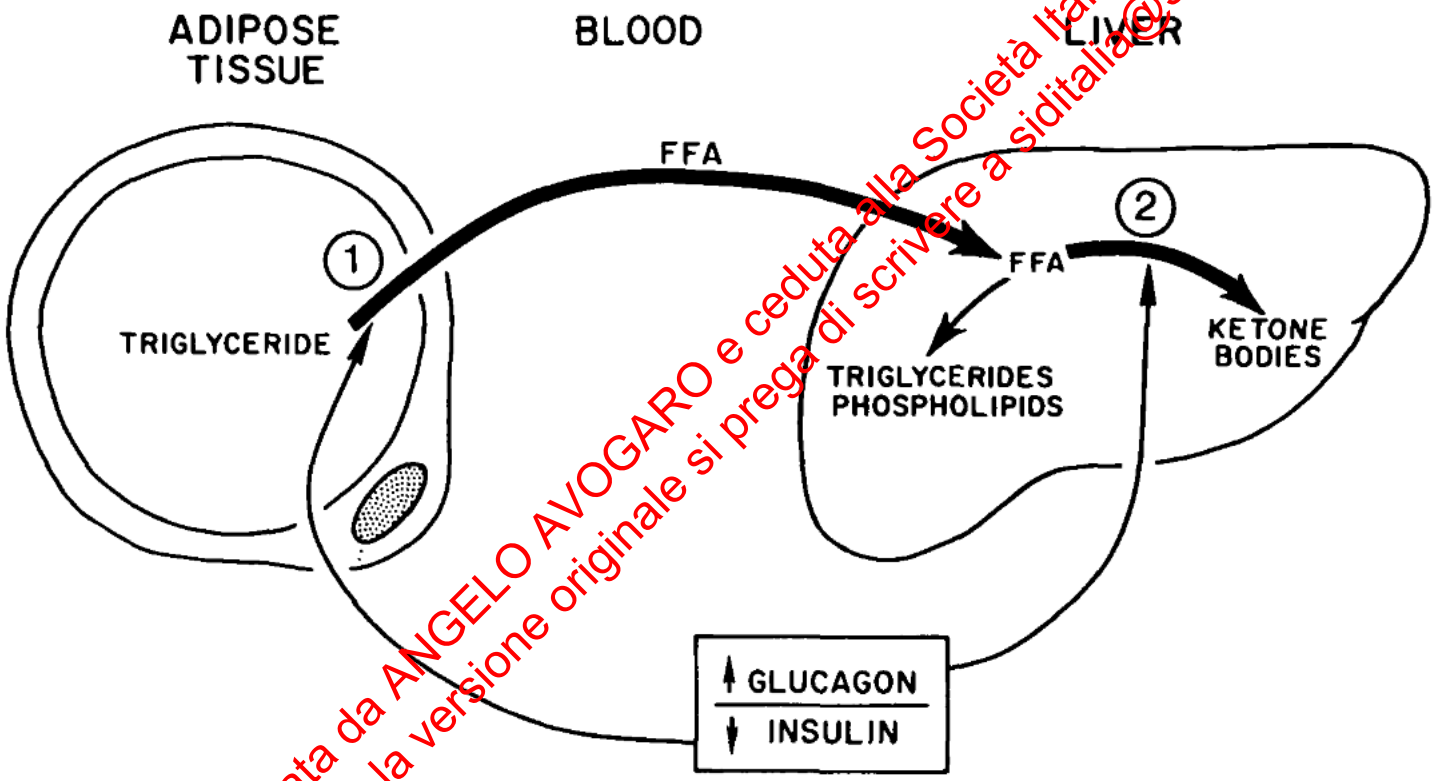
Angelo Avogaro

Università di Padova

Conflitti di Interesse di Angelo Avogaro

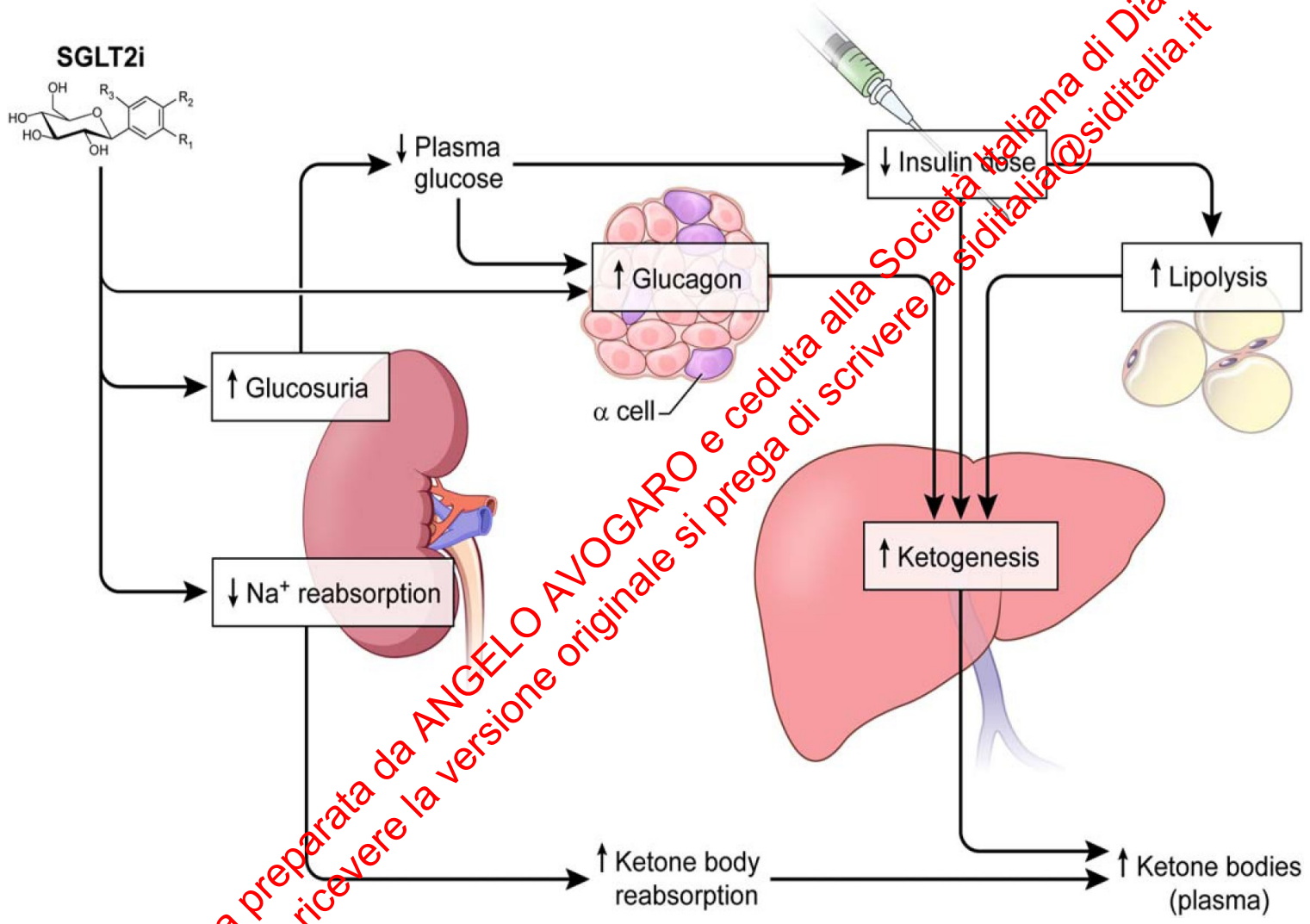
Dichiaro che negli ultimi 5 anni ho ricevuto compensi per advisory board e relazioni dalle seguenti aziende:

AstraZeneca, Boehringer Ingelheim, Bayer, Eli Lilly, Mundipharma, Neopharmed, Amgen, Servier, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Takeda, Amarin



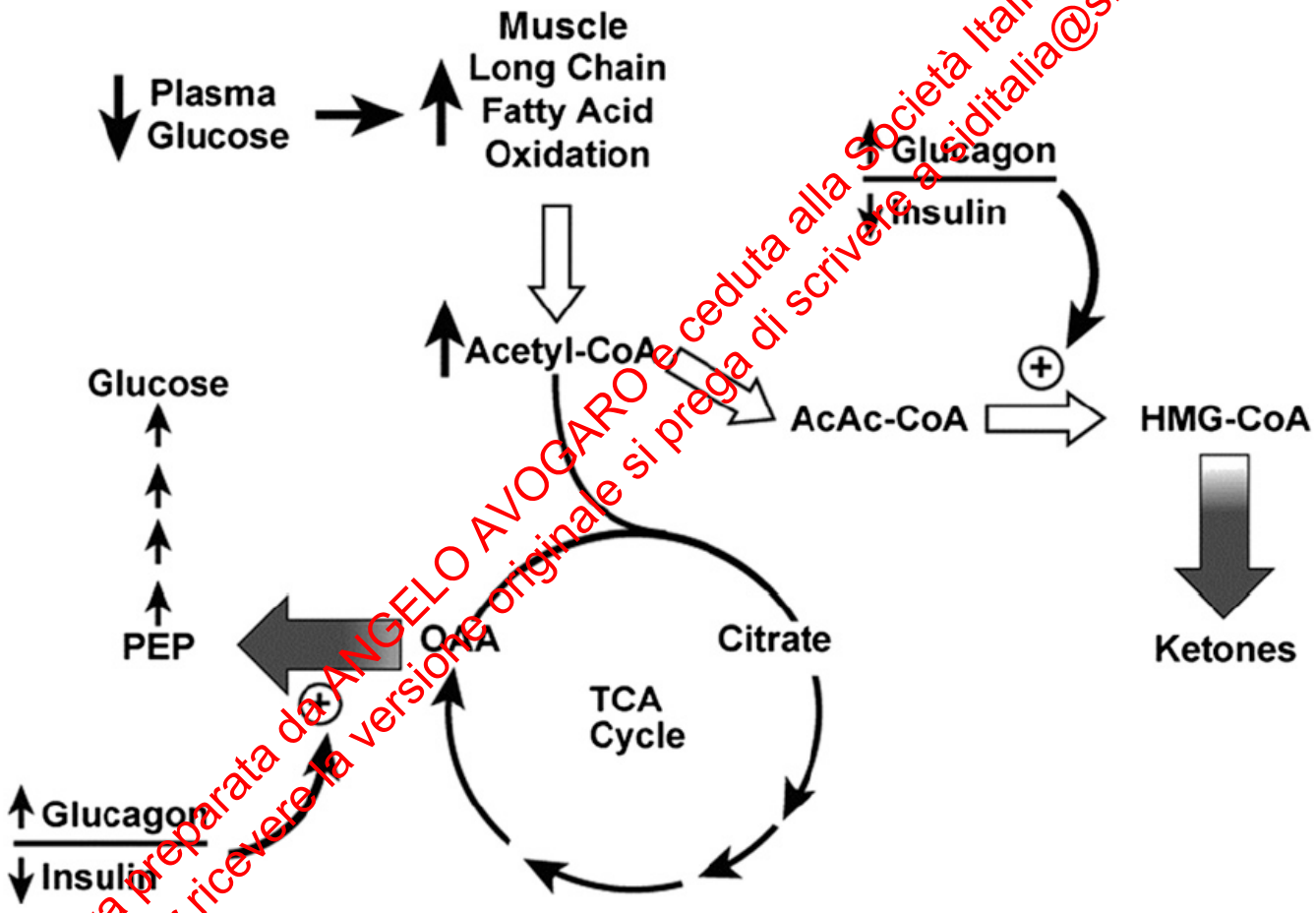
McGarry Diabetes 1978

Potential mechanisms whereby adjunctive therapy with SGLT2 inhibitors may promote ketosis



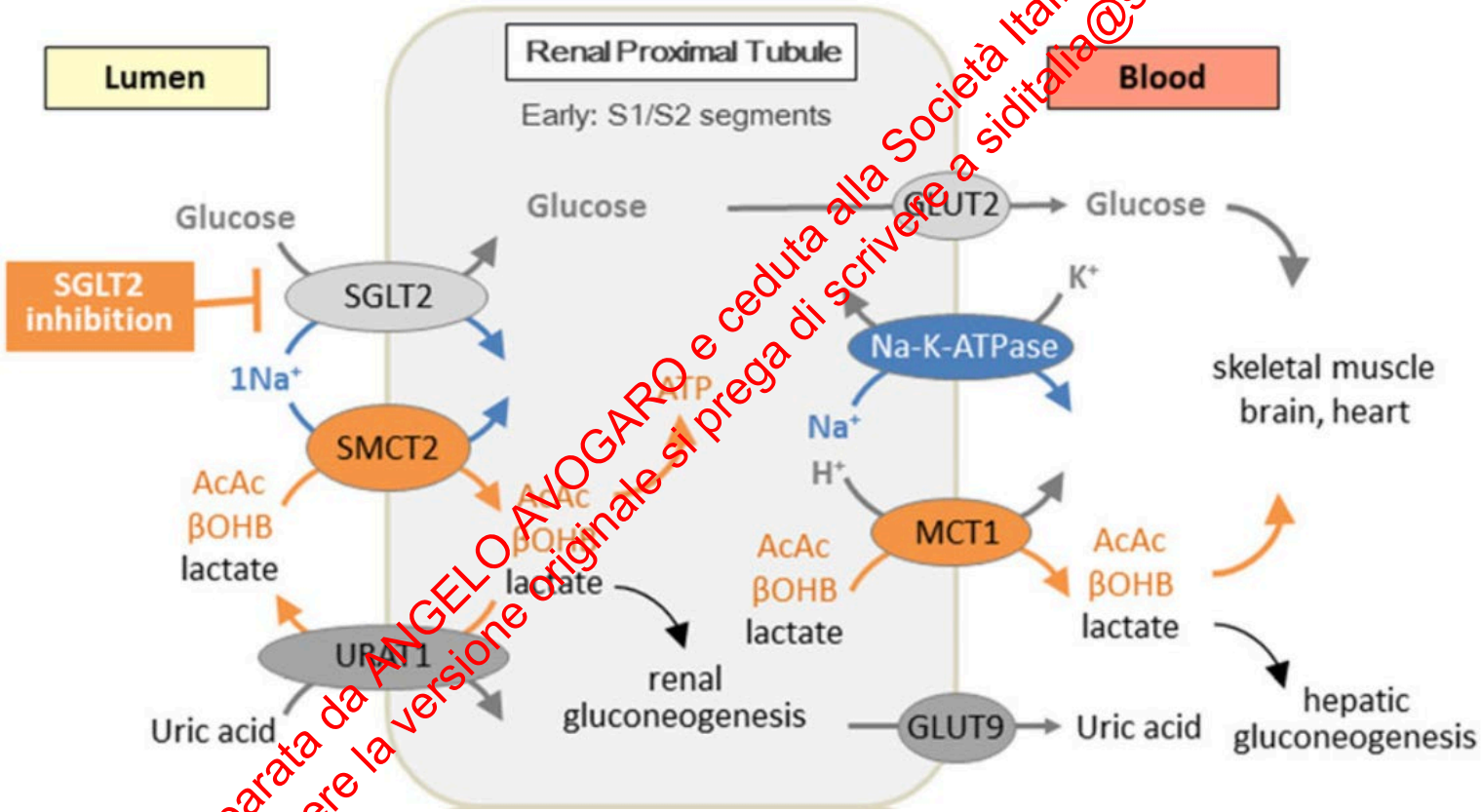
J Clin Endocrinol Metab, Volume 100, Issue 8, 1 August 2015, Pages 2849–2852,

Schematic representation of the effect of SGLT2 inhibition on the stimulation of hepatic ketogenesis

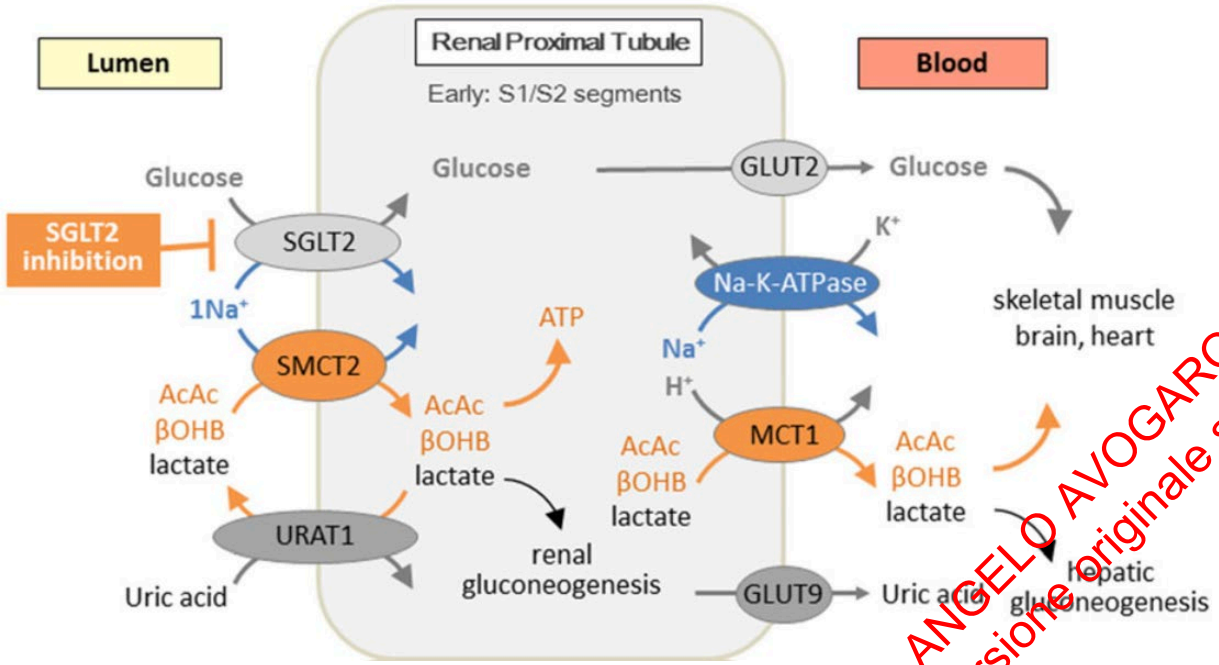


Daniele et al. Diabetes Care 2016

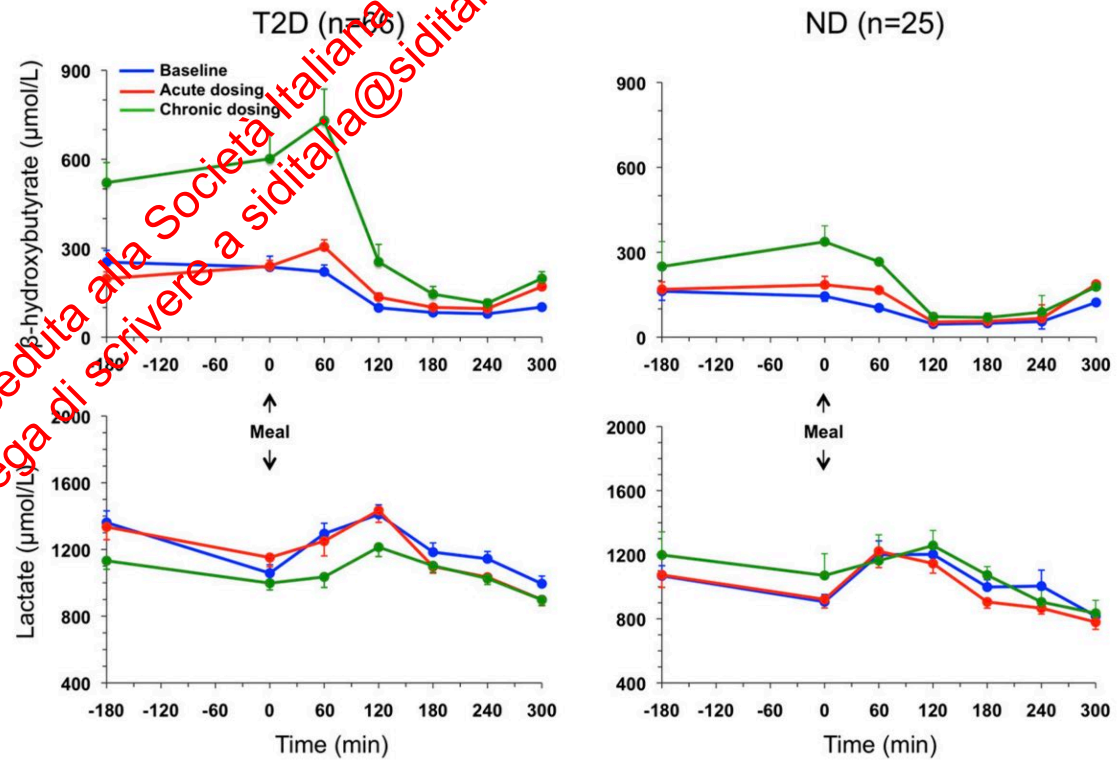
SGLT2i activate sodium-dependent monocarboxylate transporters



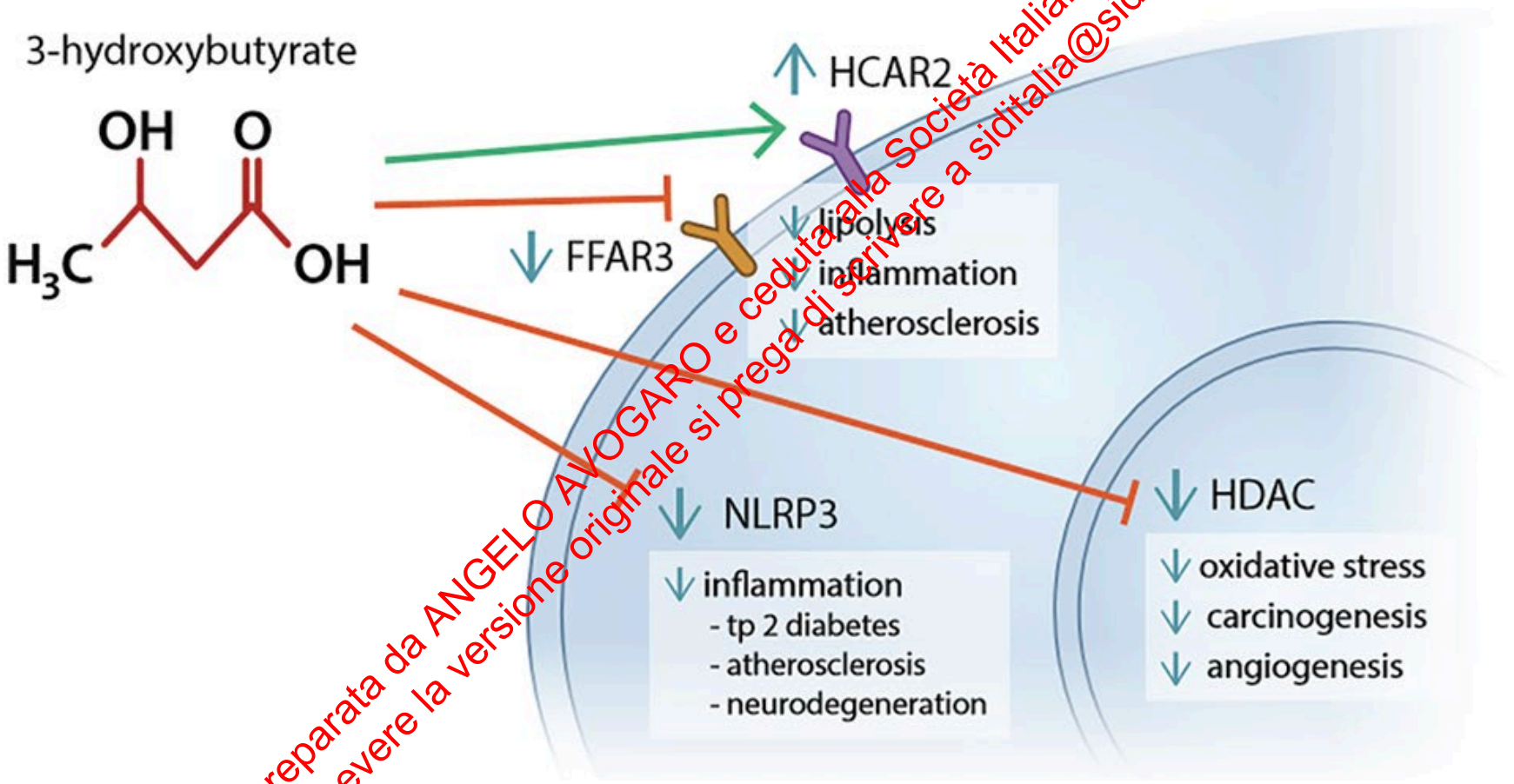
Honoyu Qiu et al. DMMR 2017



Hongyu Qiu et al. DMMR 2017

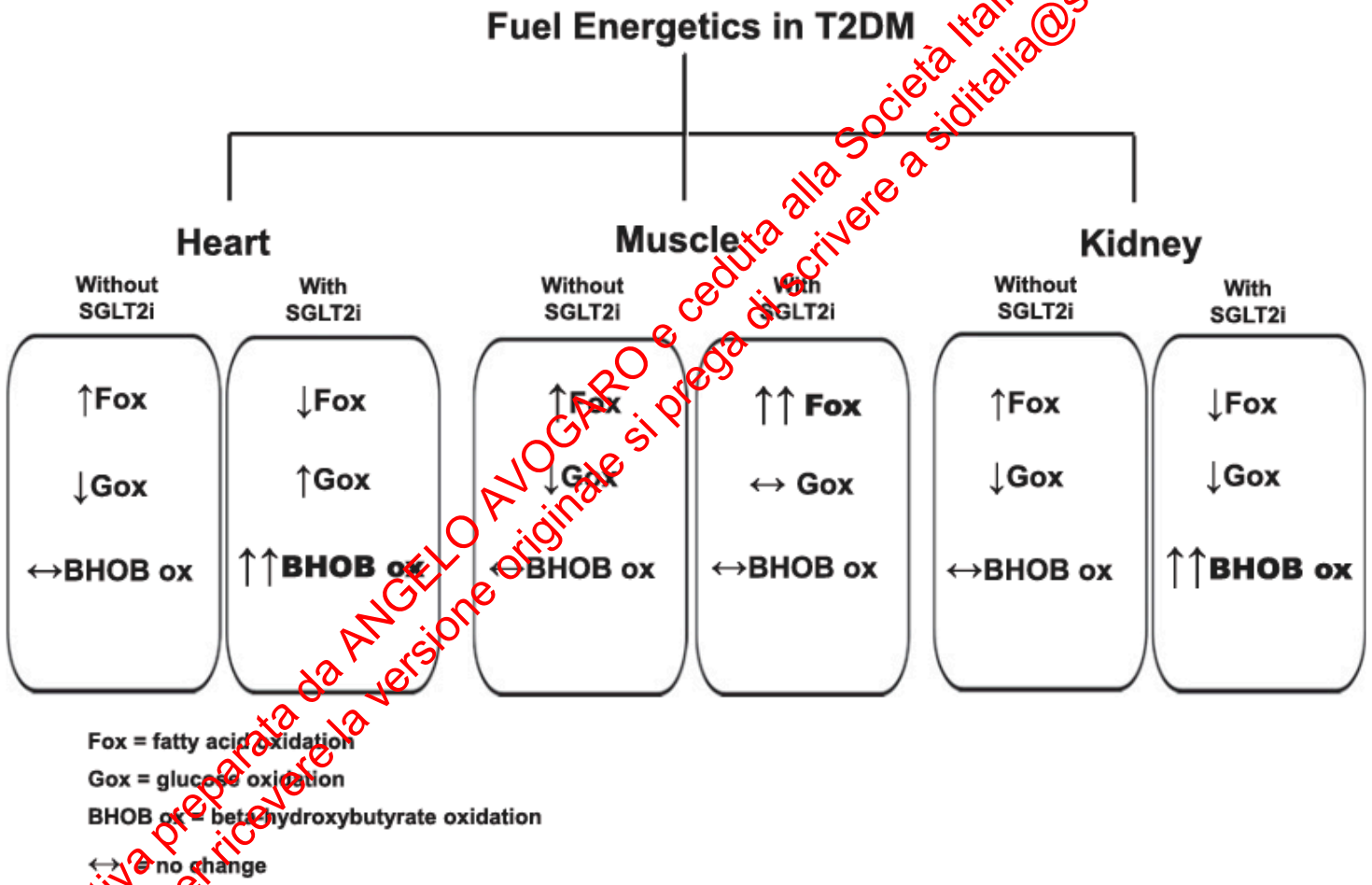


Ferrannini et al. Diabetes 2016



Moeller JCEM 2020

Postulated changes in whole-body and organ fuel energetics in T2DM before and after SGLT2 inhibitor (SGLT2i) therapy.



Mudaliar et. Diabetes Care 2016

Heart Energetics

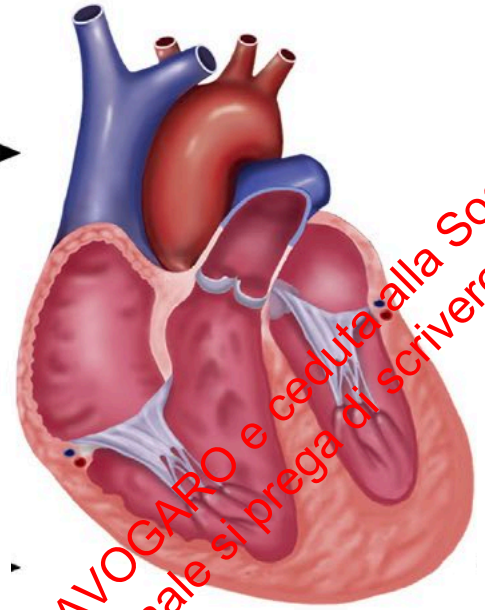
TABLE 1 Substrate Energetics in Mitochondrial Oxidative Phosphorylation

Substrate	*Per* 1 Molecule of Substrate: Molecules of ATPs Produced	*Per* 1 Molecule of Substrate: Atoms of Oxygen Consumed	P/O Ratio	O_2 Use (l/mol)	Energy Released (kcal/mol): *Per* Molecule	Energy Released (kcal/mol): *Per* C_2 Moiety
Glucose	31	12	2.58	134	671	224
Pyruvate	12.5	5	2.50	56	279	186
Ketones	20	8	2.50	101	487	244
Palmitate	105	46	2.33	515	2384	298

B Improved Myocardial Function

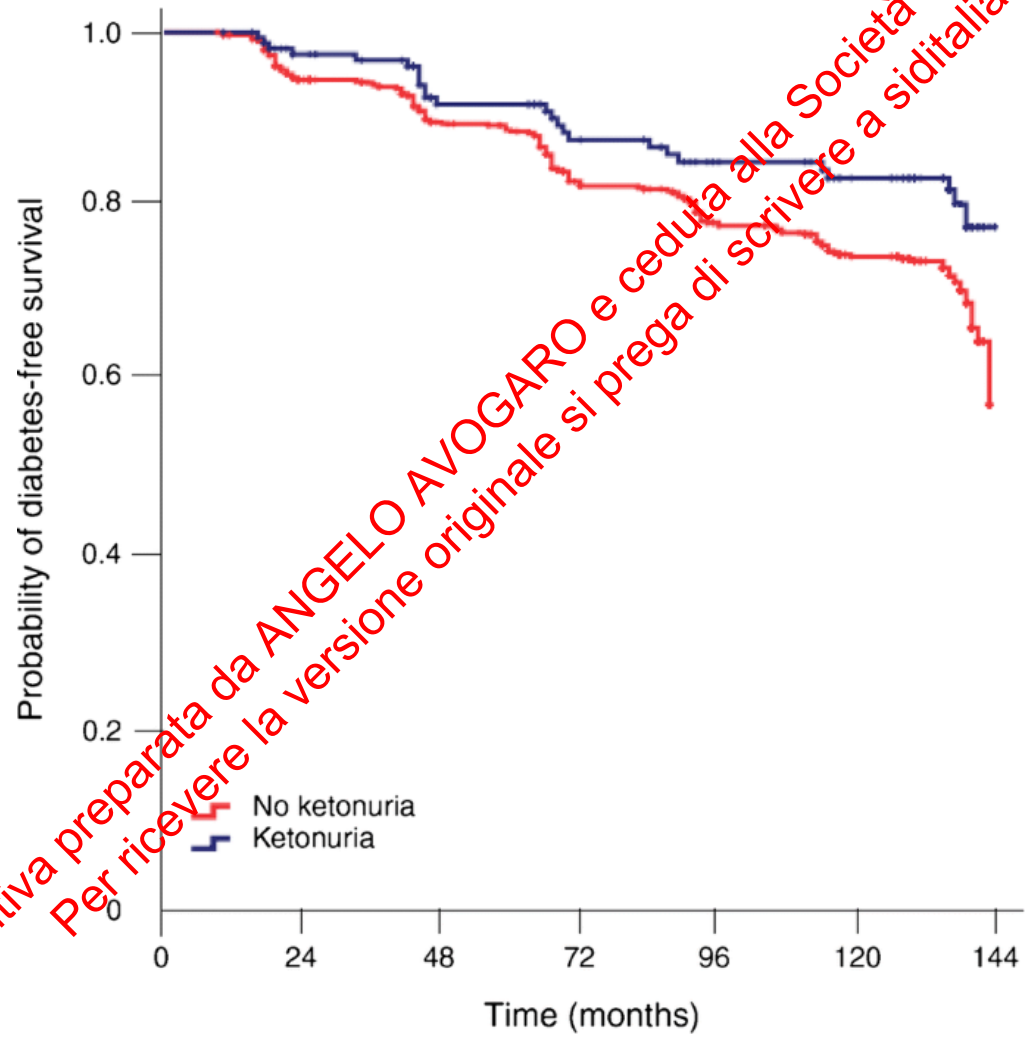
SGLT-2 Inhibitors

- SGLT-2 not expressed in the heart; connected to NHE3
- Increase in FA, ketone and BCAA oxidation
  - Provision of extra fuel for the energy-starved heart
  - ↑ Myocardial ATP content

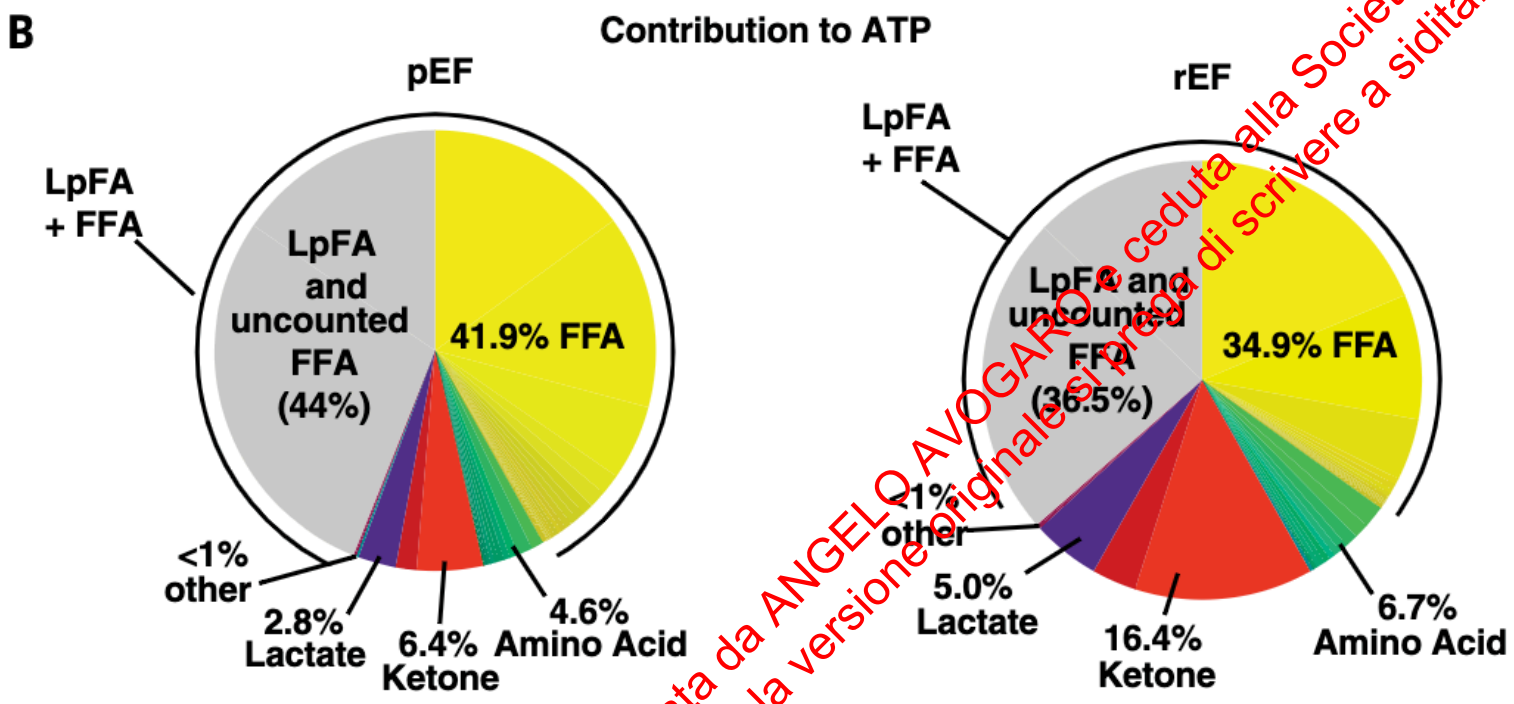


Honka, H. et al. J Am Coll Cardiol. 2021

Twelve year diabetes-free survival according to baseline ketonuria

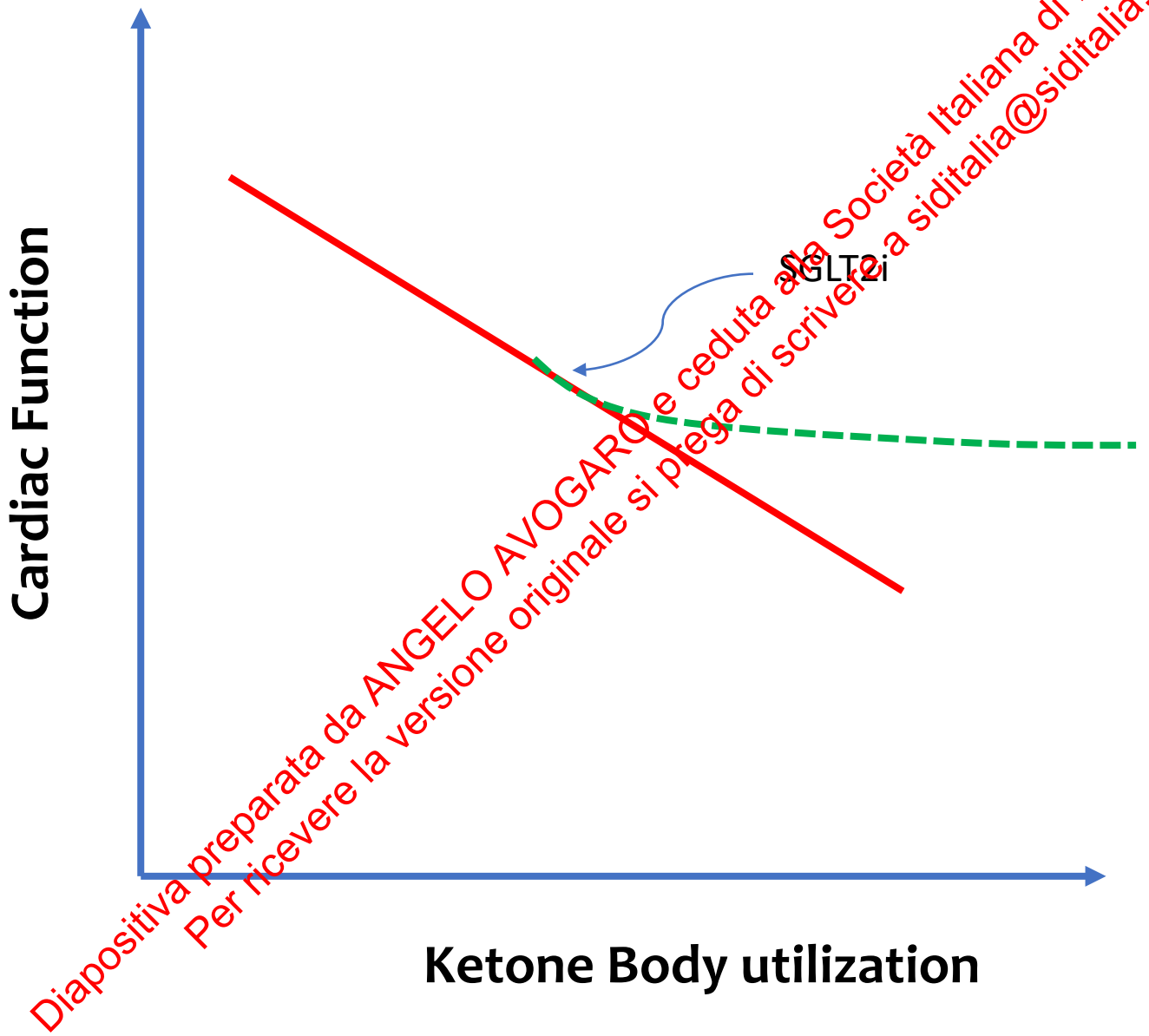


Gyuri Kim et al. 2019

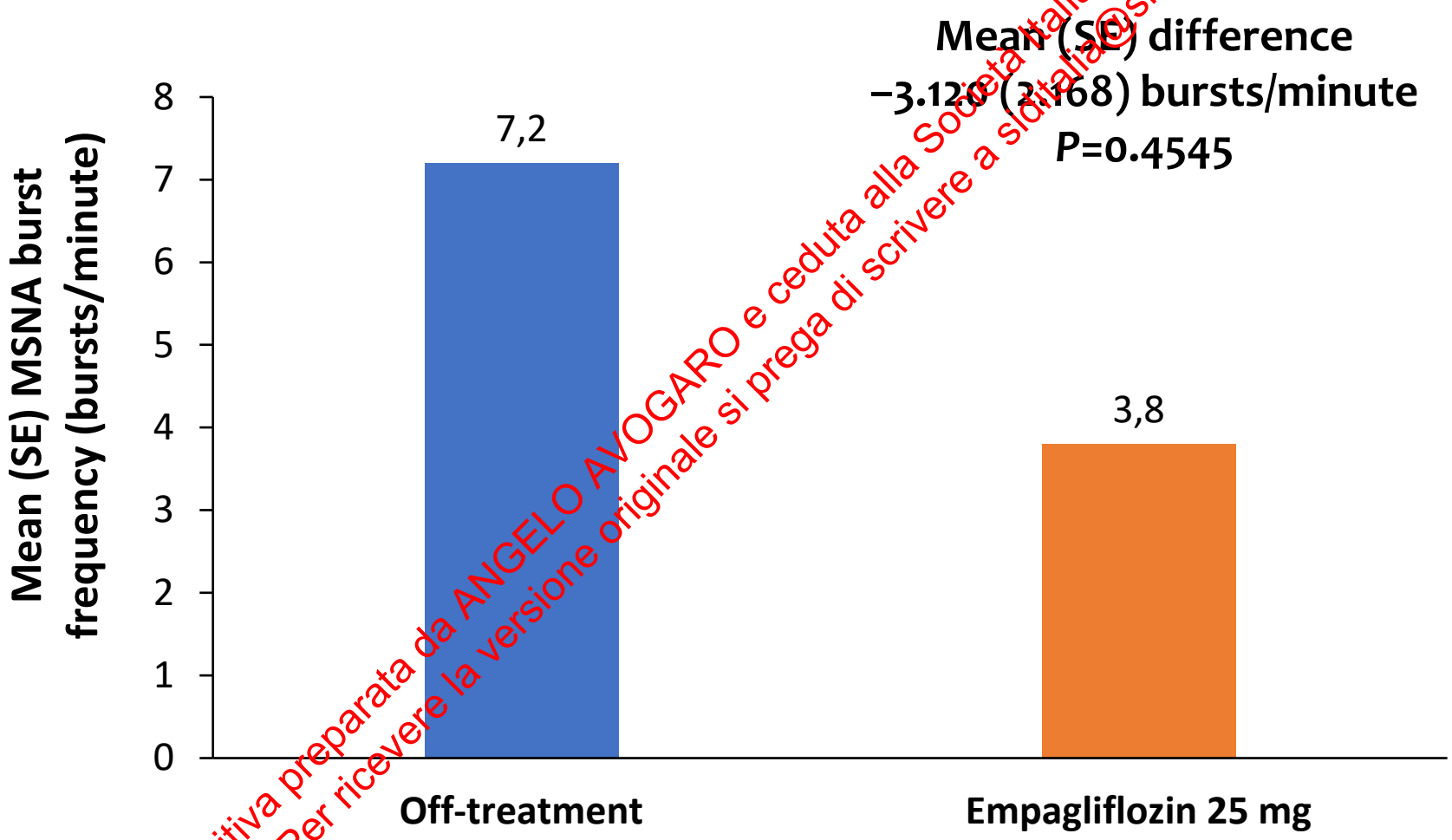


Substrate-specific contribution to cardiac ATP generation in patients with preserved ejection fraction (pEF) versus reduced ejection fraction (rEF)

Murashige et al. Science 2020



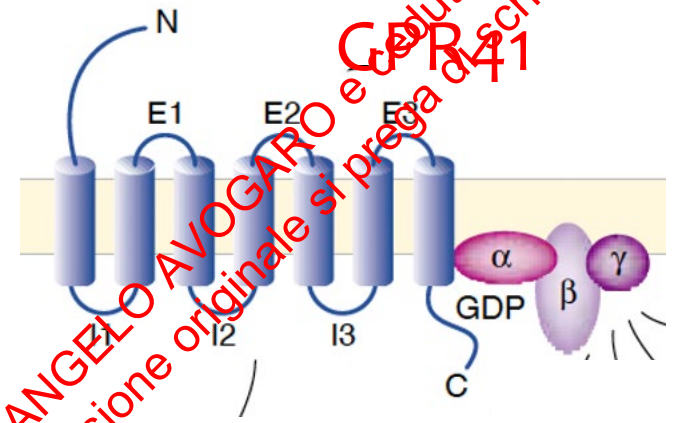
Effect of empagliflozin on muscle sympathetic nerve activity in patients with T2D



- MSNA, muscle sympathetic nerve activity; SE, standard error; T2D, Type 2 diabetes
- Jordan J, et al. *J Am Soc Hypertens* 2017;11:604–612

Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41

FFA

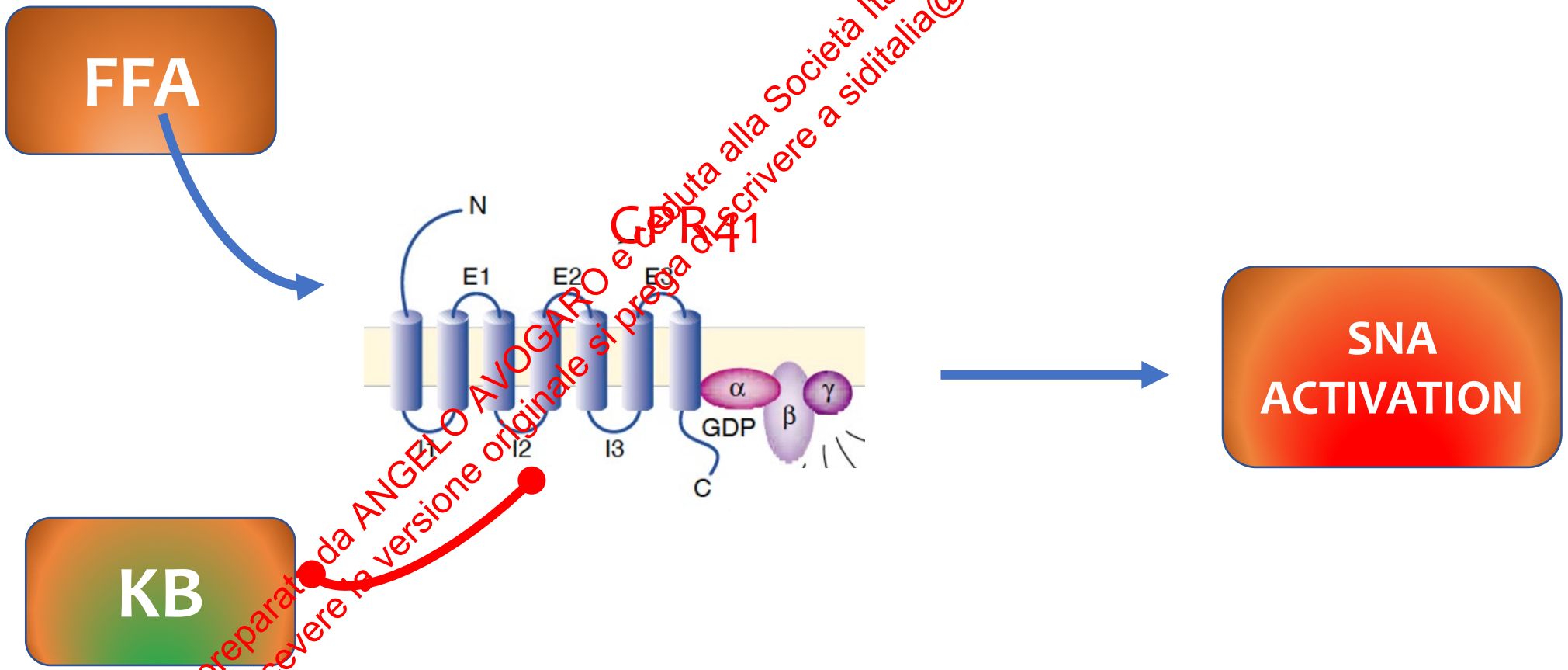


GPR 41

SNA ACTIVATION

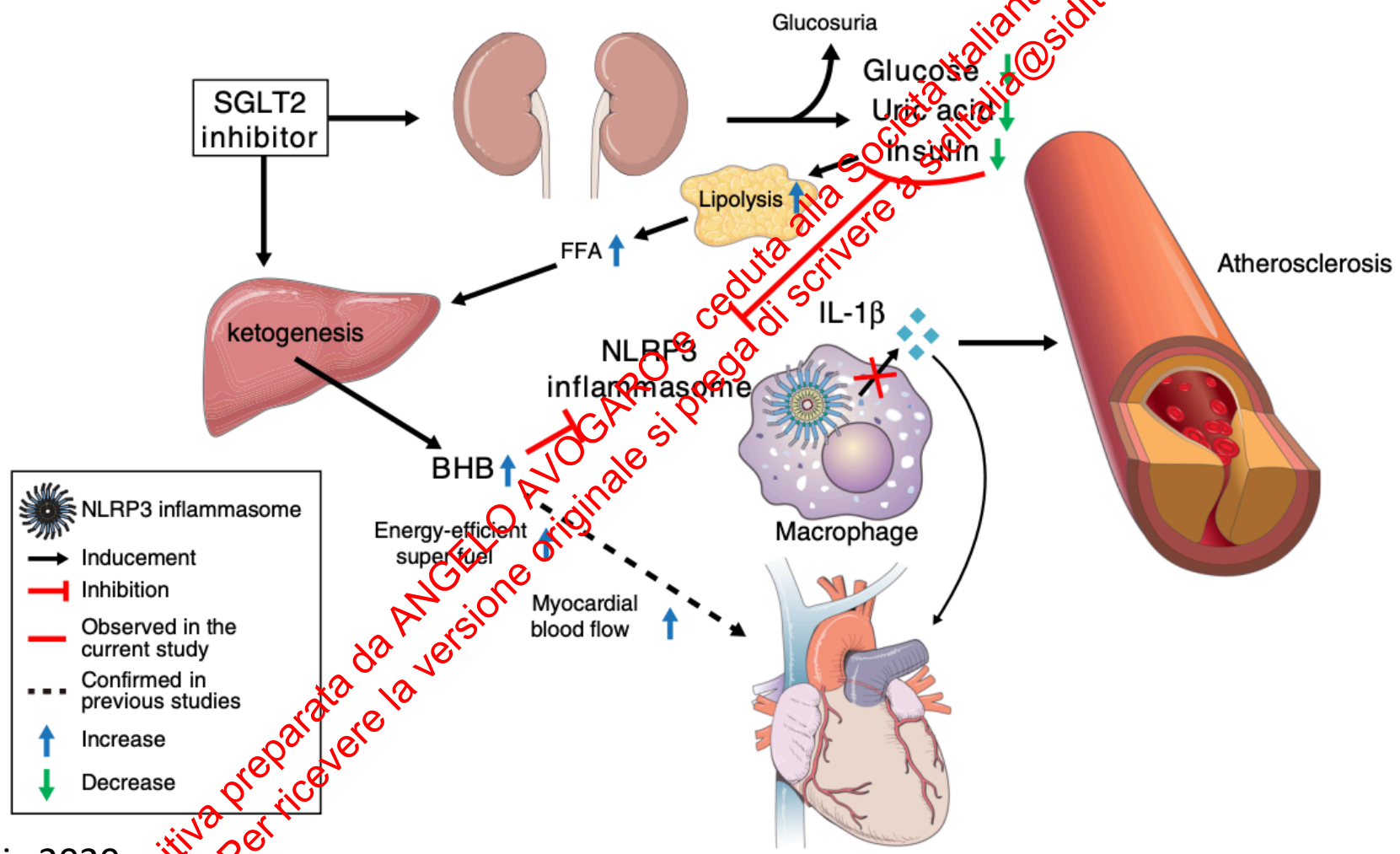
Redrawn from Kimura et al. PNAS 2011

Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41



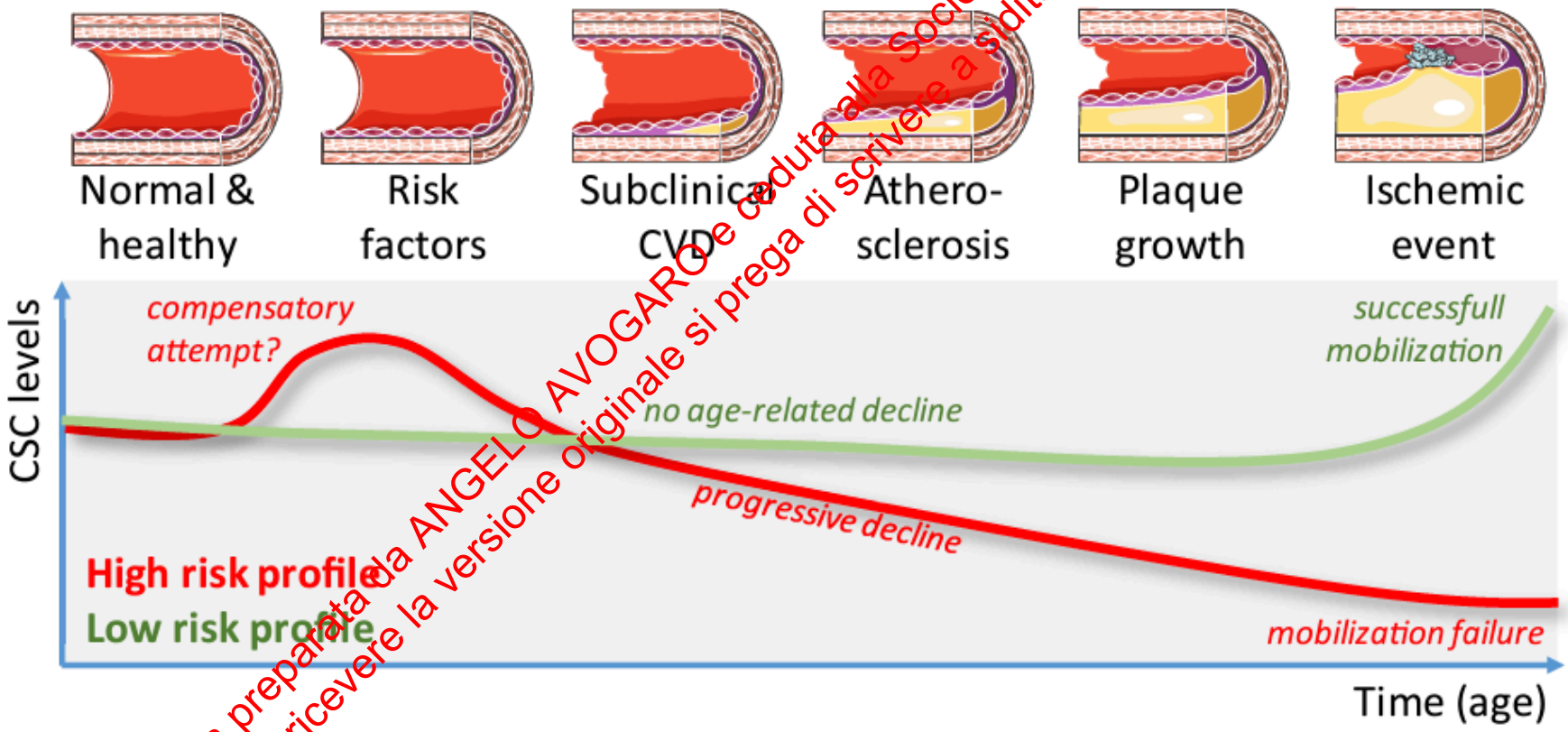
Redrawn from Kimura et al. PNAS 2011

Scheme representing the proposed effects of SGLT2 inhibitor on NLRP3 inflammasome activation



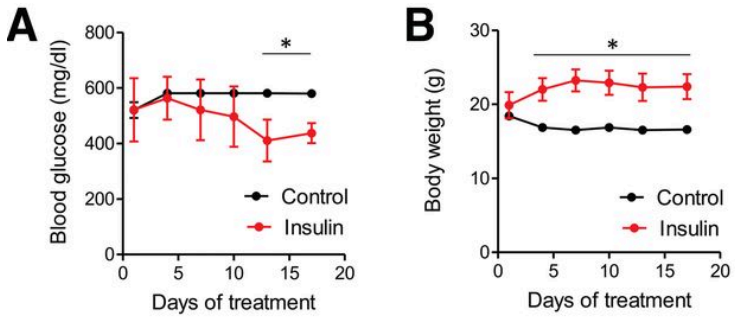
So Ra Kim Nat Communic 2020

Circulating stem cells and the natural history of atherosclerosis



Fadini et al. EHJ 2020

Inhibition of SGLT2 Rescues Bone Marrow Cell Traffic for Vascular Repair: Role of Glucose Control and Ketogenesis



Mattia Albiero et al. Diabetes 2021;70:1767-1779

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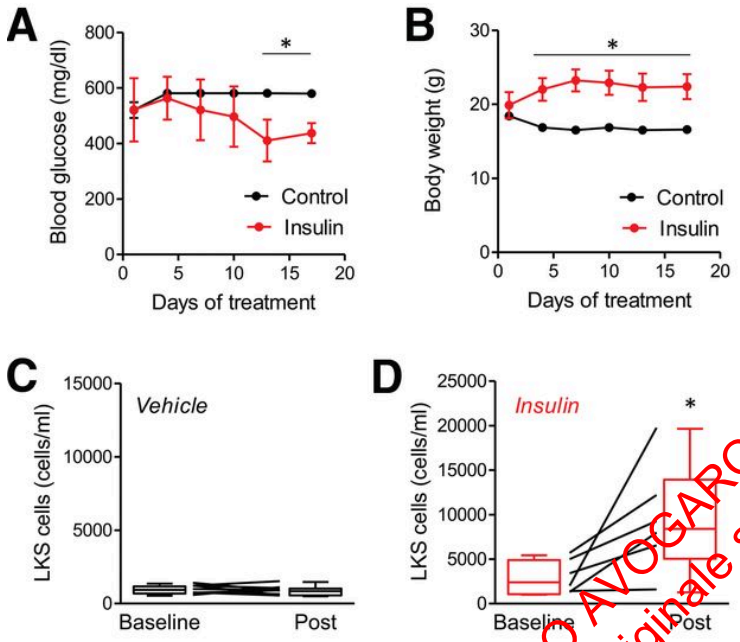

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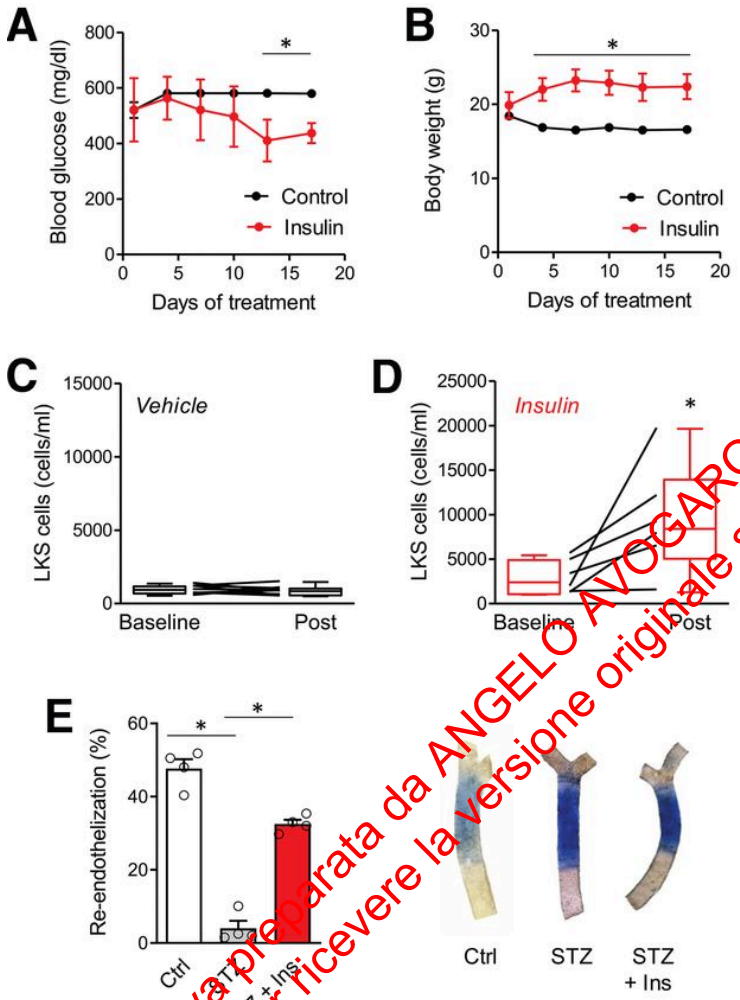

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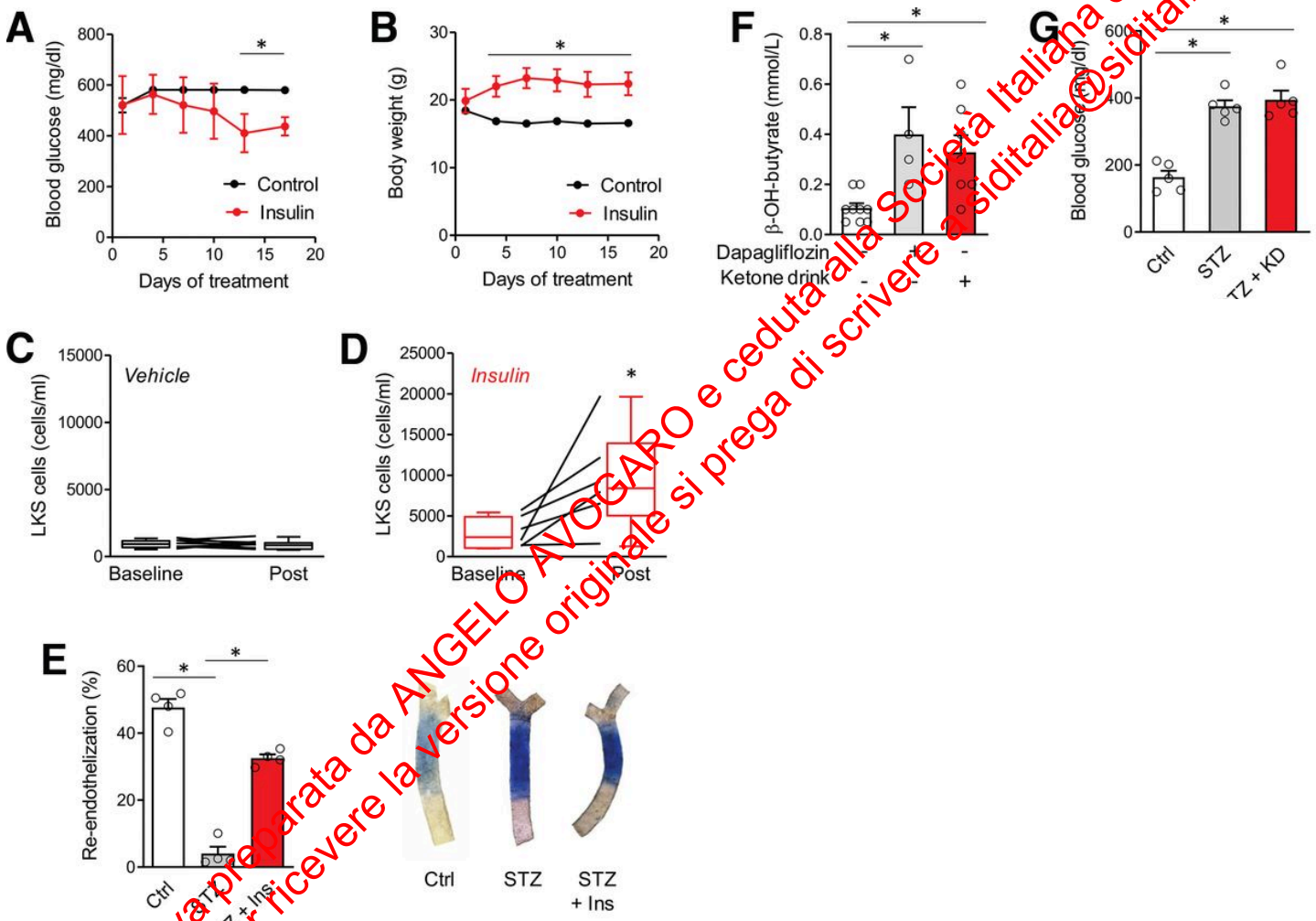

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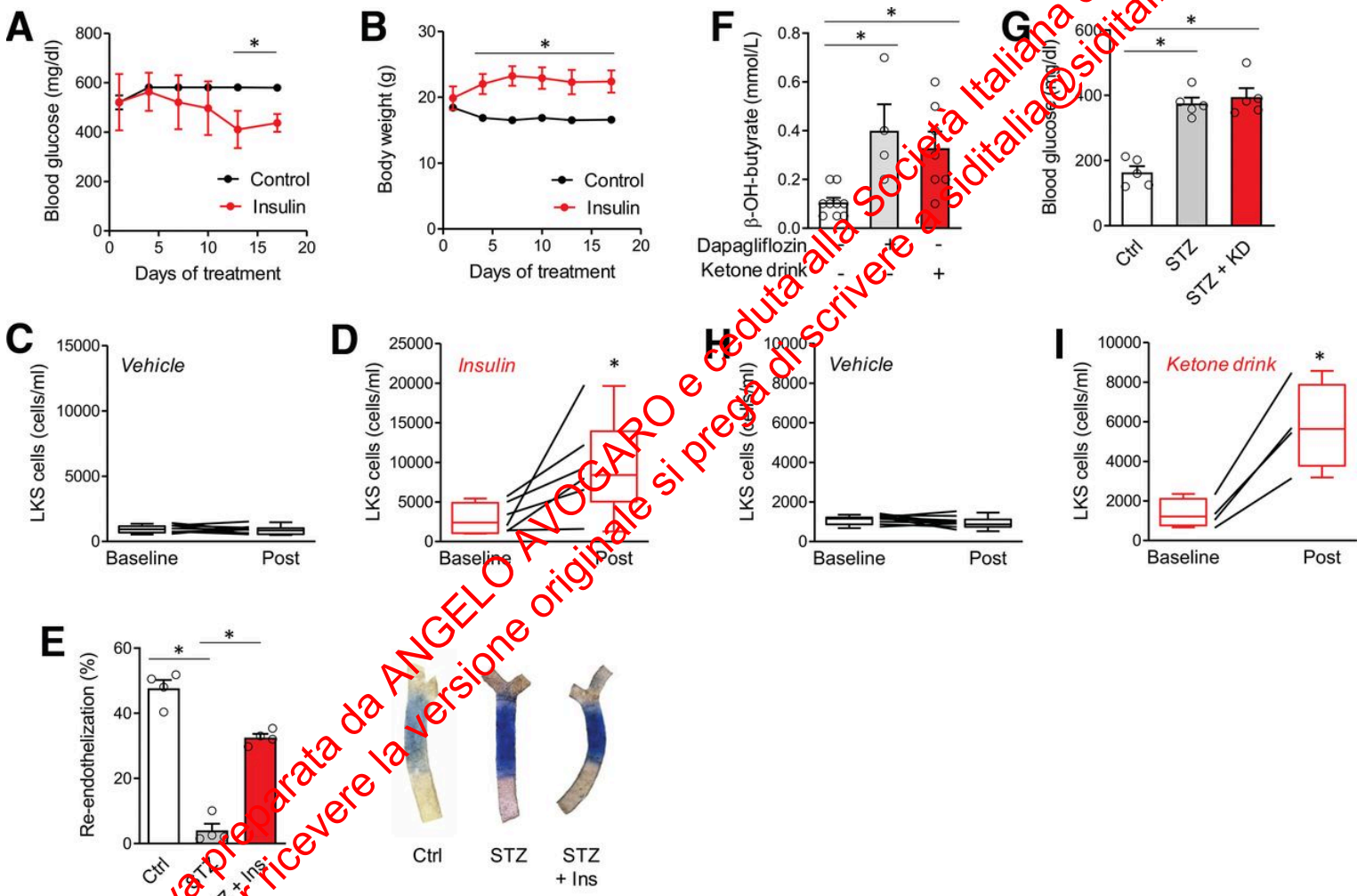

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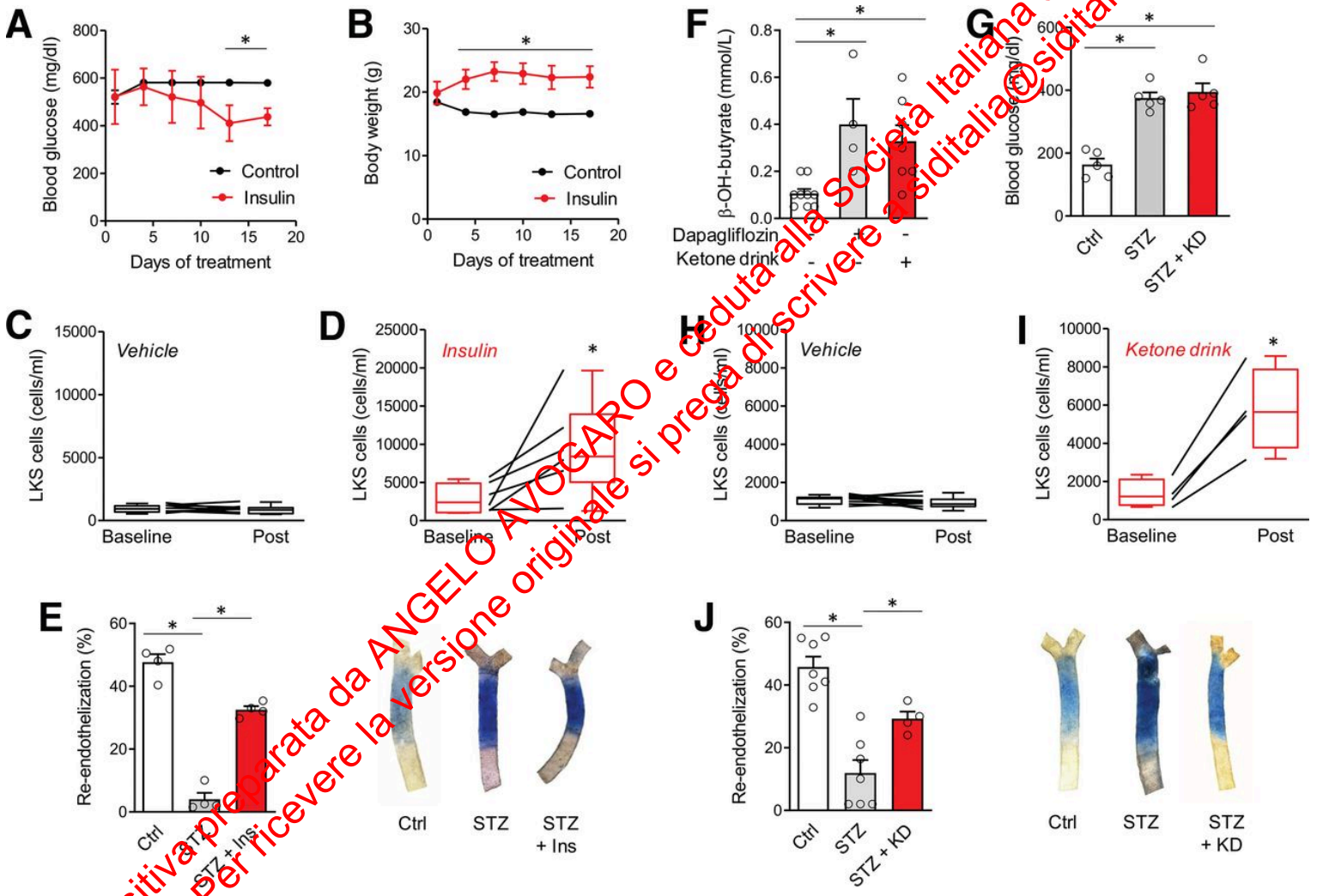

Mattia Albiero et al. Diabetes 2021;70:1767-1779

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium–Glucose Cotransporter 2 Inhibition

Anne L. Peters,[1] Elizabeth O. Buschur,[2] John B. Buse,[3] Pejman Cohan,[4] Jamie C. Diner,[3] and Irl B. Hirsch[5]

Table 1—Clinical characteristics of euDKA cases

Case patient	1	2	3	4	5	6	7	8	9
Age (years)	40	58	27	28	31	33	26	39	64
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female
T1/T2	T1	T2	T1	T1	T2	T1	T1	T1	T2
MDI/CSII	MDI	N/A	MDI	CSII	CSII	CSII	CSII	CSII	N/A
Duration (years)	17	2	25	6	15	18	13	26	6
BMI (kg/m^2)	26.5	26.5	24.3	25.9	33.2	22.0	22.0	26.1	32.8
Prior A1C [% (mmol/mol)]	11.4 (101.1)	9.8 (83.6)	7.8 (61.7)	8.0 (63.9)	7.0 (53.0)	7.2 (55.2)	6.6 (48.6)	7.0 (53.0)	7.8 (62.0)
Canagliflozin dose (mg)	300	300	300	100	300	100	300	300	300	150	300	300
Potential contributors	URI	Surgery 1 week prior	URI, alcohol	Alcohol	Alcohol	Exercise, alcohol	Exercise	GI	None	URI	Surgery 12 h prior
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Yes	Unknown	No	No	No	Yes	N/A
Presenting plasma glucose [mg/dL (mmol/L)]	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	~125 (~6.9)	203 (11.3)	190 (10.6)	150 (8.3)	233 (12.9)	169 (9.4)
pH	6.9	7.12	6.89						7.15				
P_{CO_2} (mmHg)	10								26				
Bicarbonate (mEq/L)	6	10	6	11	18	15	9	9	13 and then 5
Anion gap (mEq/L)	25	17	35	22	18	26	21	24	16 and then 19
Ketones*	Yes (serum and urine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	Outpt.	Outpt.	ICU	ICU

CSII, continuous subcutaneous insulin infusion; GI, gastrointestinal; Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

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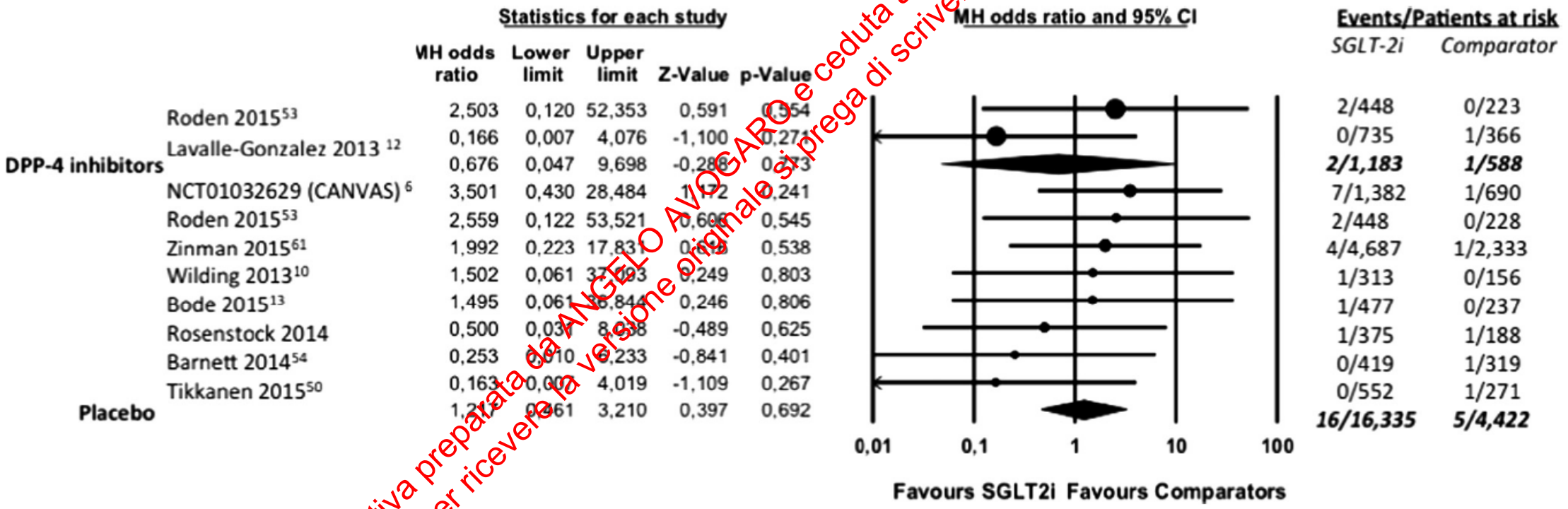
journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Effects of SGLT-2 inhibitors on diabetic ketoacidosis: A meta-analysis of randomised controlled trials

Matteo Monami[a,*], *Besmir Nreu*[b], *Stefania Zannoni*[a], *Carlotta Lualdi*[a], *Edoardo Mannucci*[a]



Conclusioni

1. Gli SGLT2 inibitori inducono un modesto incremento dei corpi chetonici circolanti
2. Tale aumento è determinato da un'aumentata produzione epatica e da un aumentato riassorbimento renale dei corpi chetonici
3. I corpi chetoni svolgono molteplici azioni positive, soprattutto a livello cardiaco
4. Una restrizione calorica, una dieta chetogenica o un' importante ingestione di alcool possono esporre al rischio di chetoacidosi in pazienti trattati con SGLT2i
5. Gli SGLT2i hanno modificato la percezione del significato fisiologico dei corpi chetonici