
# *Effetti non-glicemici e prospettive future*



Marco Giorgio Baroni

*Endocrinologia e Metabolismo*

Dipartimento di Medicina Sperimentale

Sapienza Università di Roma

Il Prof Marco Giorgio Baroni dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Novo Nordisk
- Abbott
- Takeda

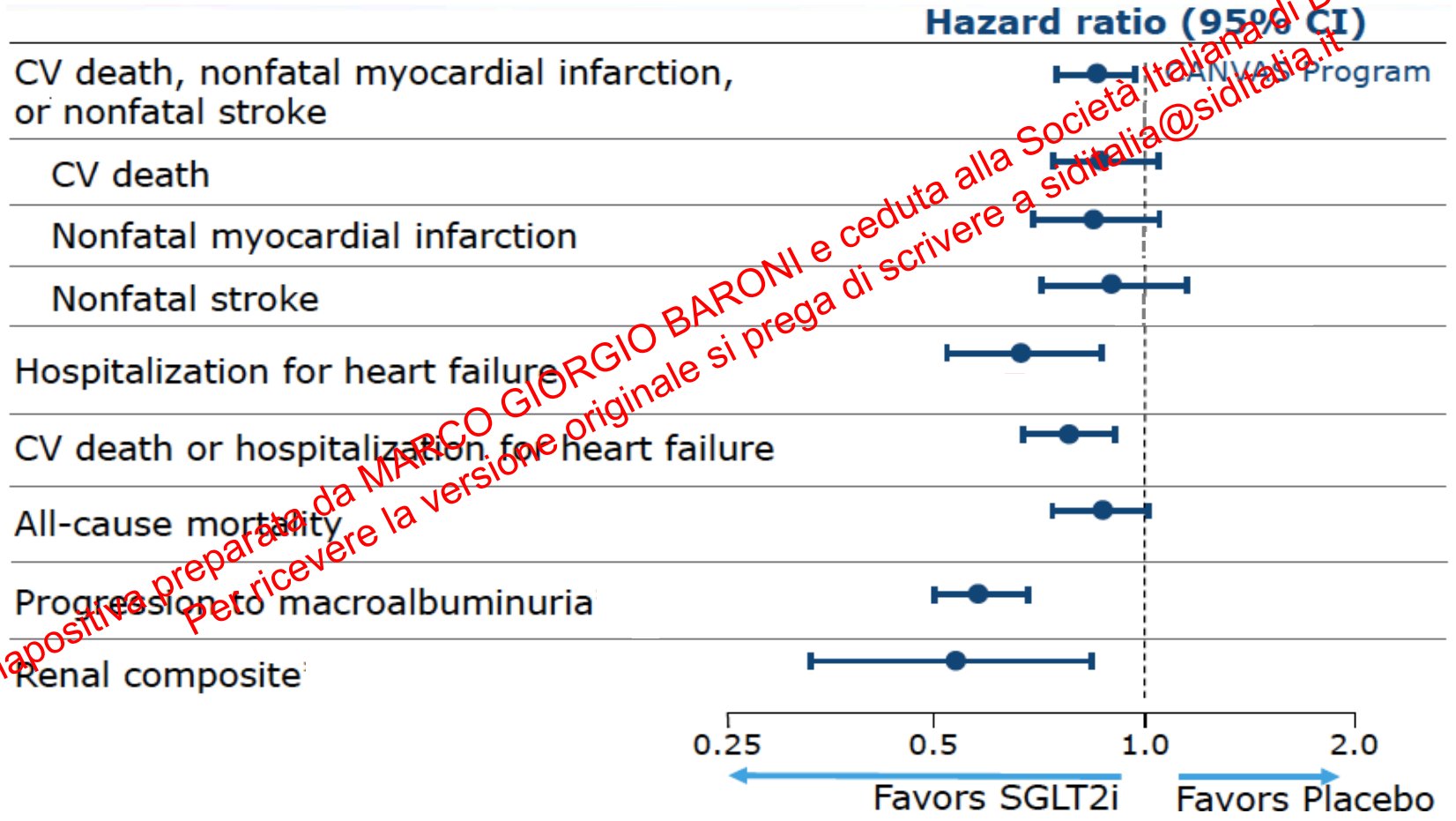


*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

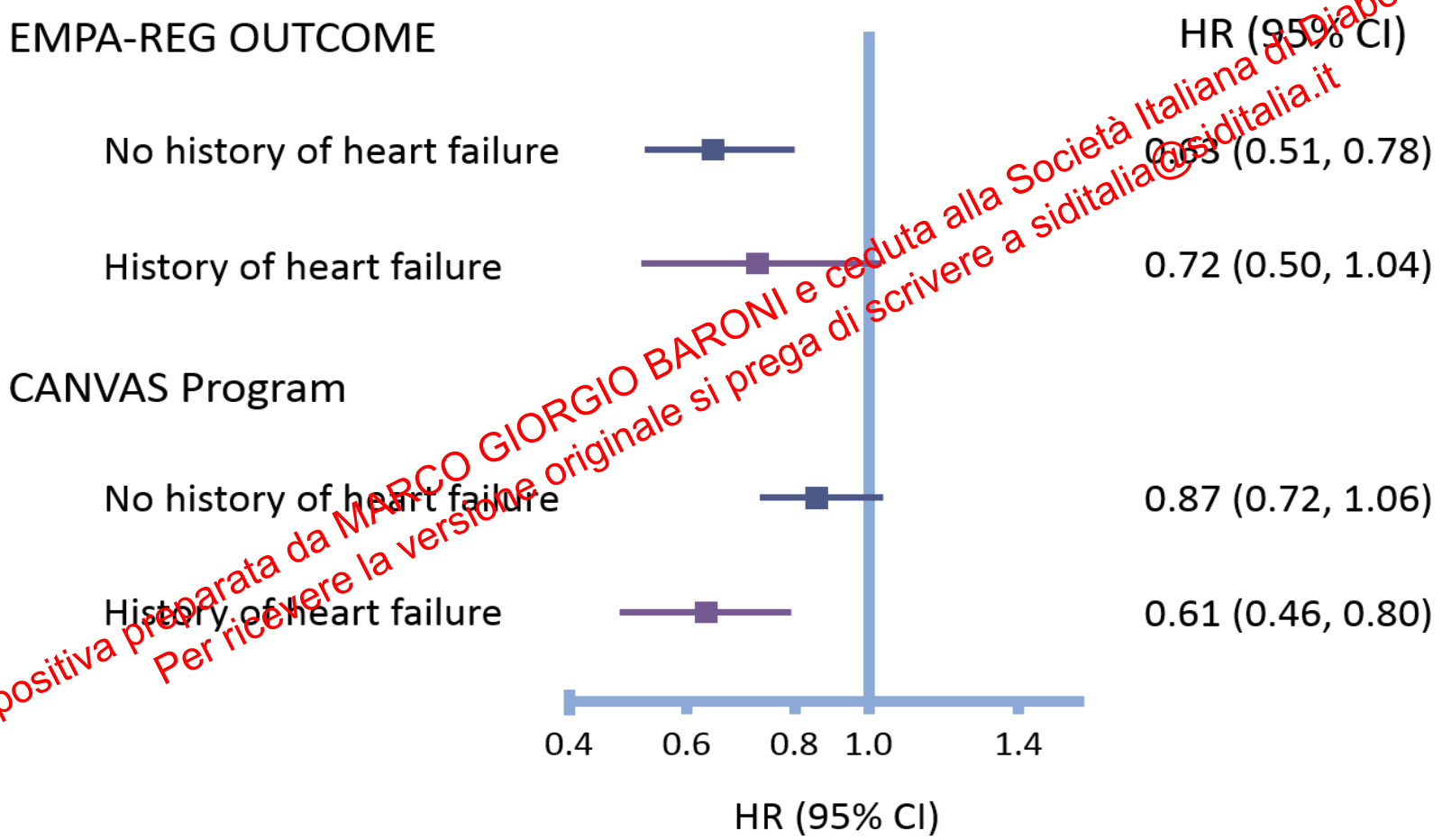
# Outline

- Effetti non glicemici degli SGLT2i
  - Cardiovascolari (SGLT2 indipendenti)
  - Metabolici (SGLT2 dipendenti e indipendenti)

# Key Outcomes in the CANVAS Program



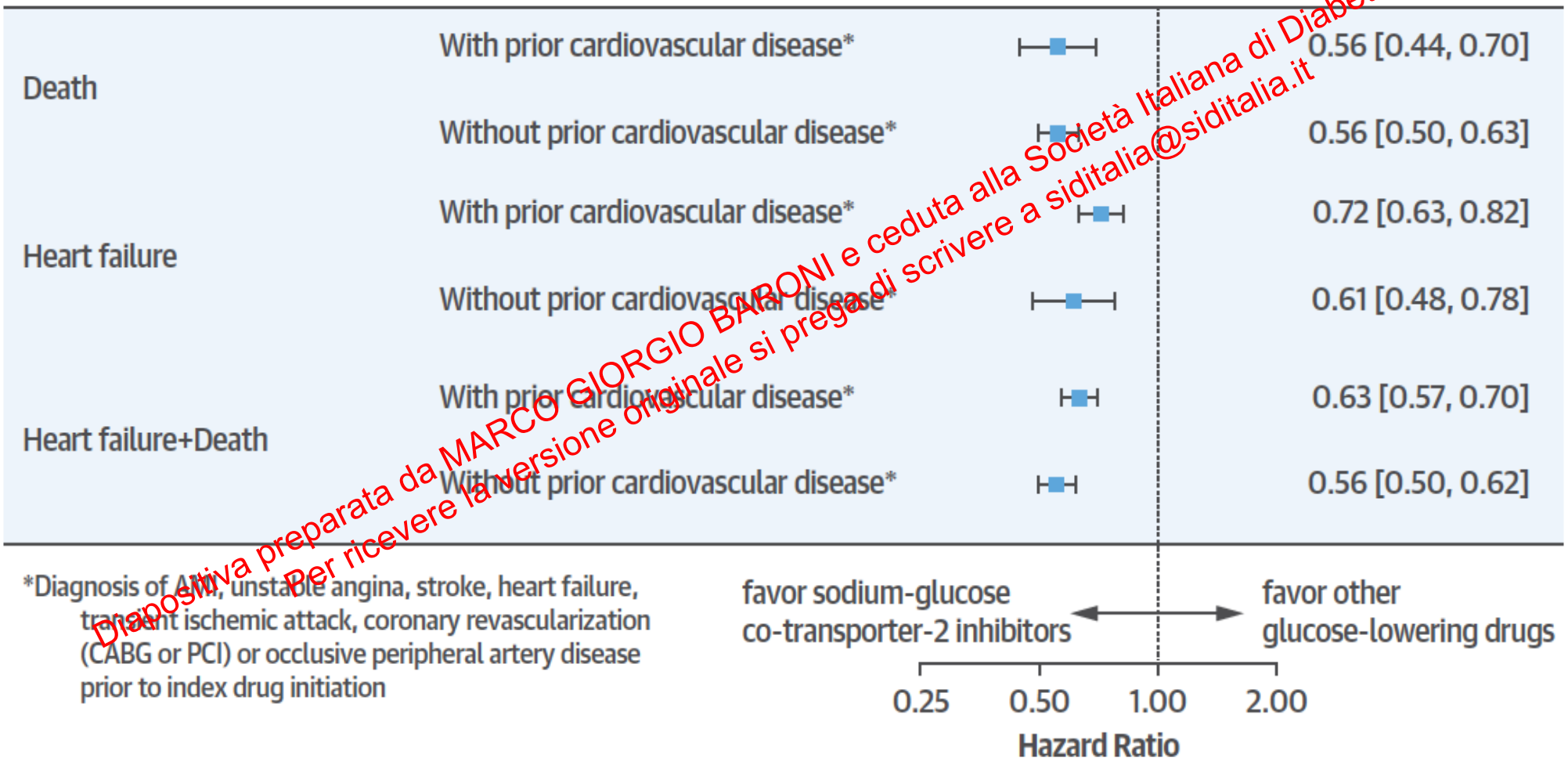
# The cardiovascular benefits with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) in participants with and without a history of heart failure






Verma and McMurray (2018) Diabetologia

# CVD-Real: outcomes in patients with and without cardiovascular disease at baseline





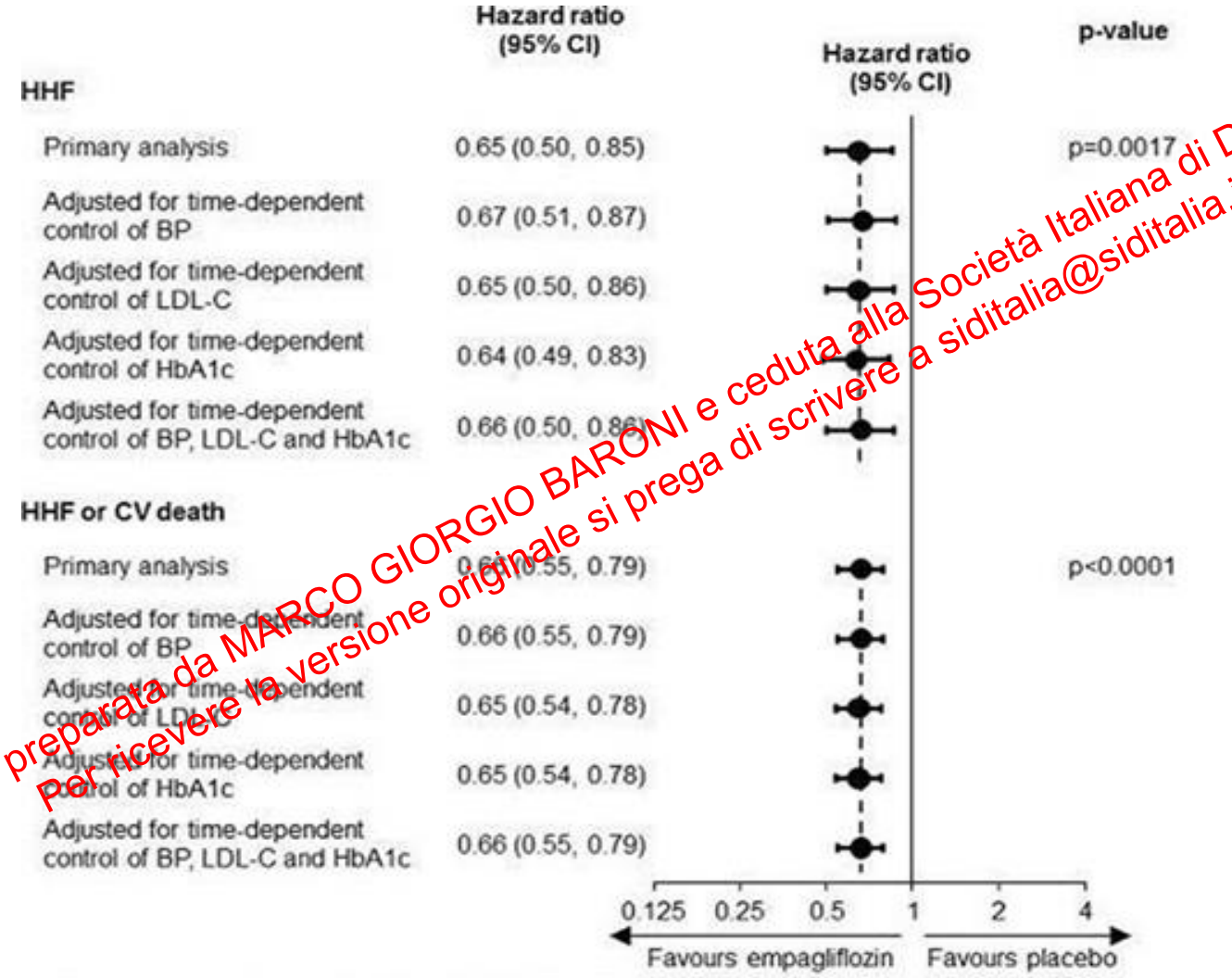

Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497–506

# SGLT2 inhibitor-associated cardiovascular benefits

- The concept that SGLT2 inhibitors reduced cardiovascular events primarily through prevention of heart failure (vs atherothrombotic events) has gained broad acceptance.

- But the most important question remained unanswered, being: 'how'?

# Empagliflozin, heart failure and control of blood pressure, LDL-cholesterol and HbA1c

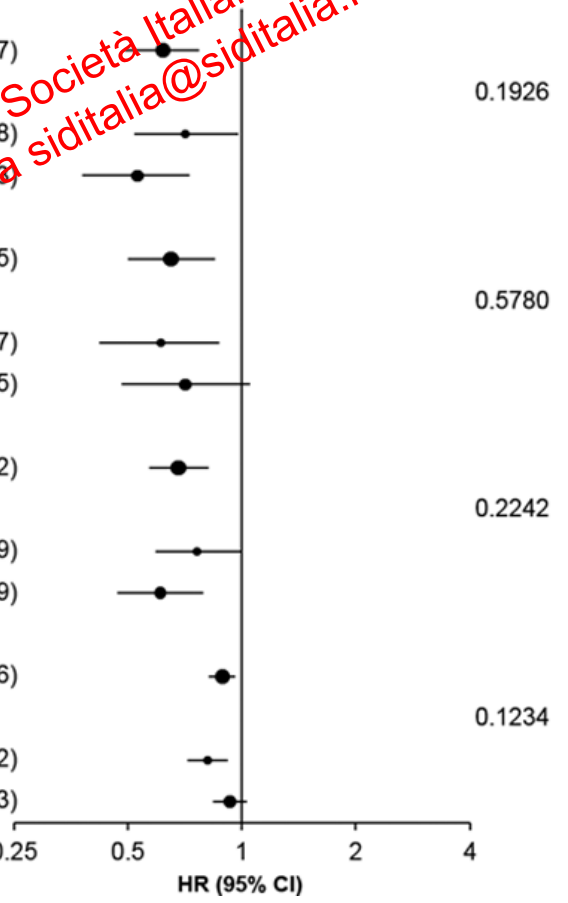



Cox regression analysis in patients treated with ≥1 dose of study drug.
Control of BP, LDL-C and HbA1c were defined as systolic BP <140 mmHg and diastolic BP <90 mmHg, LDL-C <100 mg/dL, and HbA1c <7.5%.

Fitchett D et al. Eur Heart J. 2017; 38 (suppl_1)

# CVD Clinical Outcomes and Chronic Kidney Disease in Empa-Reg Trial

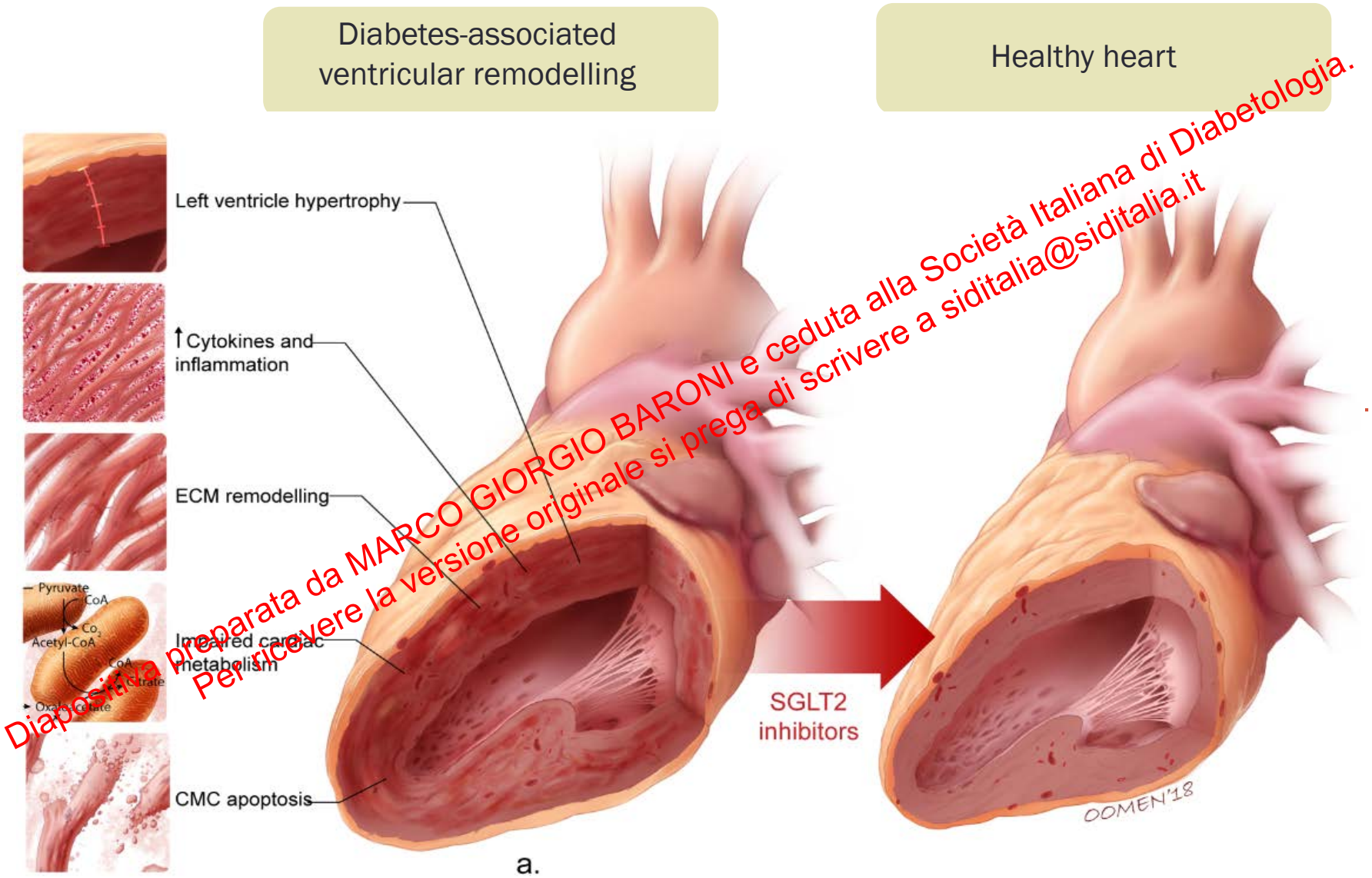
| | Empagliflozin | | Placebo | | | Interaction |
|---|---|---|---|---|---|---|
| | n with event/N (%) | Rate/ 1000 pt-yr | n with event/N (%) | Rate/ 1000 pt-yr | HR (95% CI) | p-value |
| Cardiovascular death | | | | | | |
| All patients | 172/4687 (3.7) | 12.4 | 137/2333 (5.9) | 20.2 | 0.62 (0.49, 0.77) | |
| Prevalent kidney disease* | | | | | | 0.1926 |
| Yes | 94/1498 (6.3) | 21.4 | 65/752 (8.6) | 30.1 | 0.71 (0.53, 0.98) | |
| No | 77/3149 (2.4) | 8.3 | 72/1569 (4.6) | 15.7 | 0.53 (0.38, 0.73) | |
| Hospitalization for heart failure | | | | | | |
| All patients | 126/4687 (2.7) | 9.4 | 95/2333 (4.1) | 14.5 | 0.65 (0.50, 0.85) | |
| Prevalent kidney disease* | | | | | | 0.5780 |
| Yes | 66/1498 (4.4) | 15.5 | 53/752 (7.0) | 25.9 | 0.61 (0.42, 0.87) | |
| No | 60/3149 (1.9) | 6.6 | 42/1569 (2.7) | 9.4 | 0.71 (0.48, 1.05) | |
| All-cause mortality | | | | | | |
| All patients | 269/4687 (5.7) | 19.0 | 194/2333 (8.3) | 28.6 | 0.68 (0.57, 0.82) | |
| Prevalent kidney disease* | | | | | | 0.2242 |
| Yes | 143/1498 (9.5) | 32.5 | 92/752 (12.2) | 42.5 | 0.76 (0.59, 0.99) | |
| No | 126/3149 (4.0) | 13.4 | 102/1569 (6.5) | 22.2 | 0.61 (0.47, 0.79) | |
| All-cause hospitalization | | | | | | |
| All patients | 1725/4687 (36.8) | 161.9 | 925/2333 (39.6) | 183.3 | 0.89 (0.82, 0.96) | |
| Prevalent kidney disease* | | | | | | 0.1234 |
| Yes | 663/1498 (44.3) | 208.4 | 375/752 (49.9) | 258.9 | 0.81 (0.72, 0.92) | |
| No | 1046/3149 (33.2) | 141.8 | 549/1569 (35.0) | 154.1 | 0.93 (0.84, 1.03) | |






Wanner C et al. Circulation. 2017;137:119–129

# Cardiovascular protection by SGLT2 inhibitors






Verma and McMurray (2018) Diabetologia

# Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

1. Improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function)
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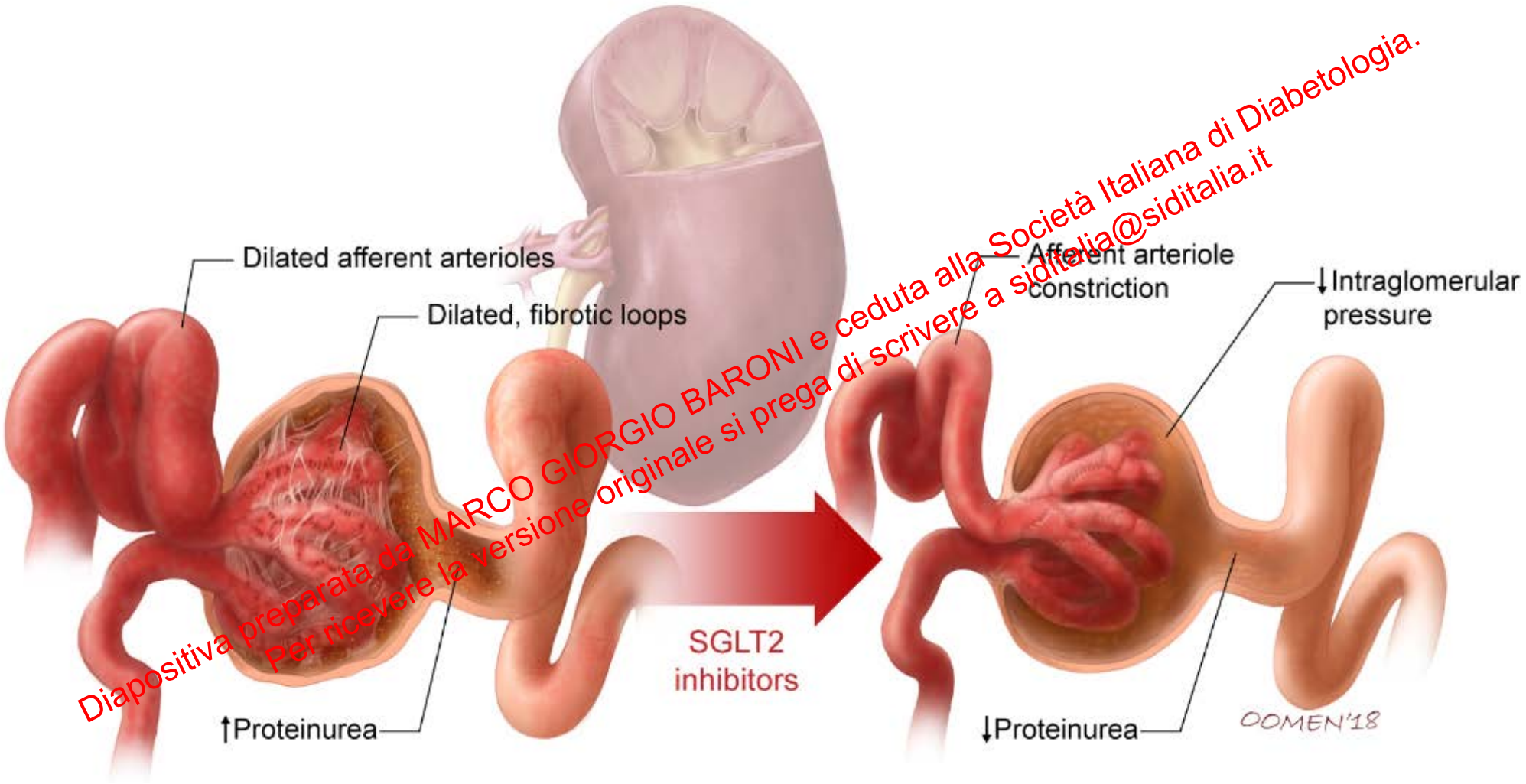
# SGLT2 inhibitors improve ventricular loading conditions

- SGLT2 inhibitors exert their beneficial actions via improvement of ventricular loading conditions, secondary to a reduction in preload primarily due to the diuretic and natriuretic effects

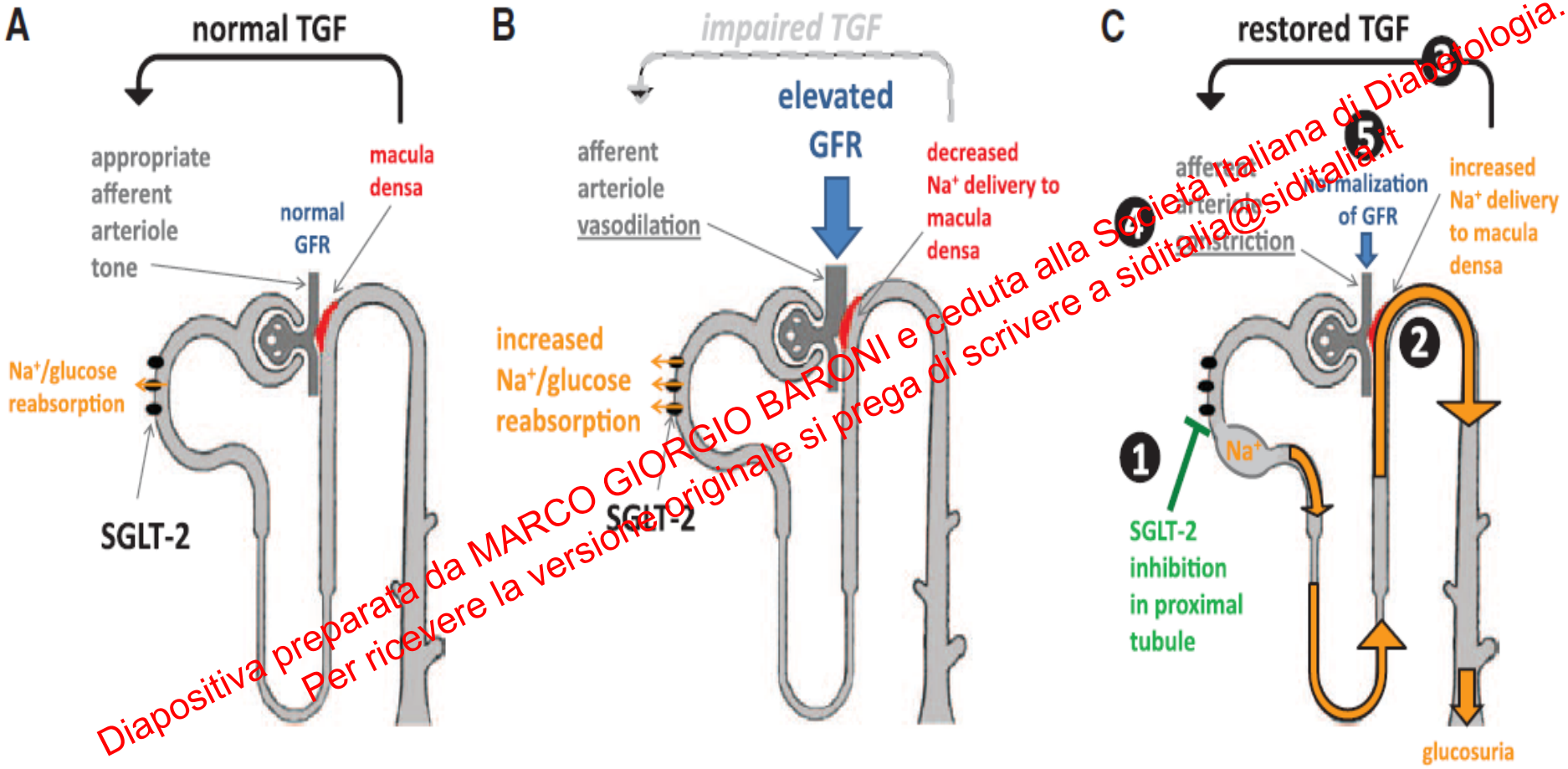
# SGLT2 inhibitors improve ventricular loading conditions






Verma and McMurray (2018) Diabetologia

# Postulated tubuloglomerular feedback (TGF) mechanism




Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

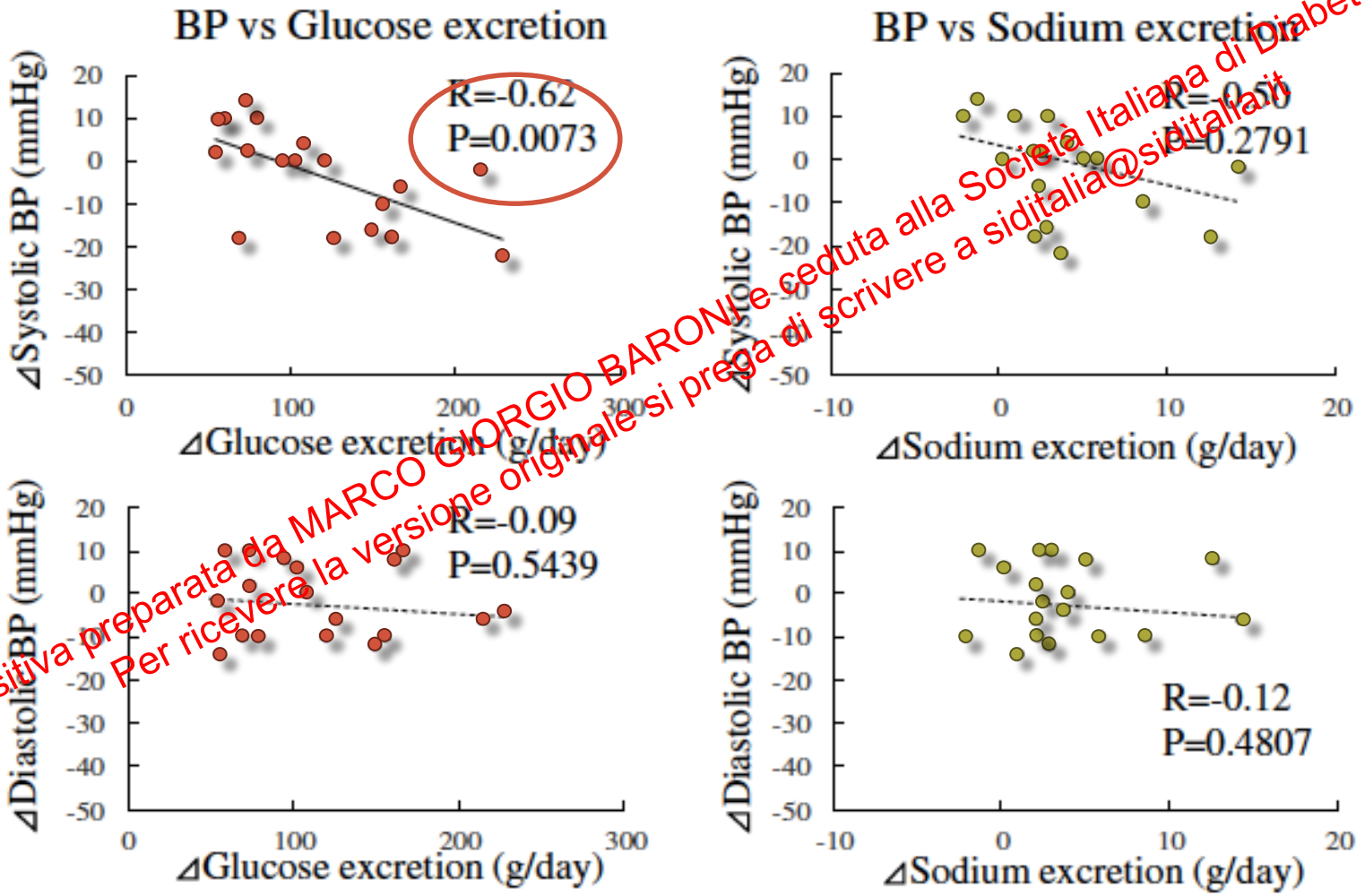
SGLT-2 inhibition reduces hyperfiltration via TGF

*Circulation*. 2014;129:587-597.

# SGLT2 inhibitors improve ventricular loading conditions

- Volume contraction as a key determinant of benefit noted

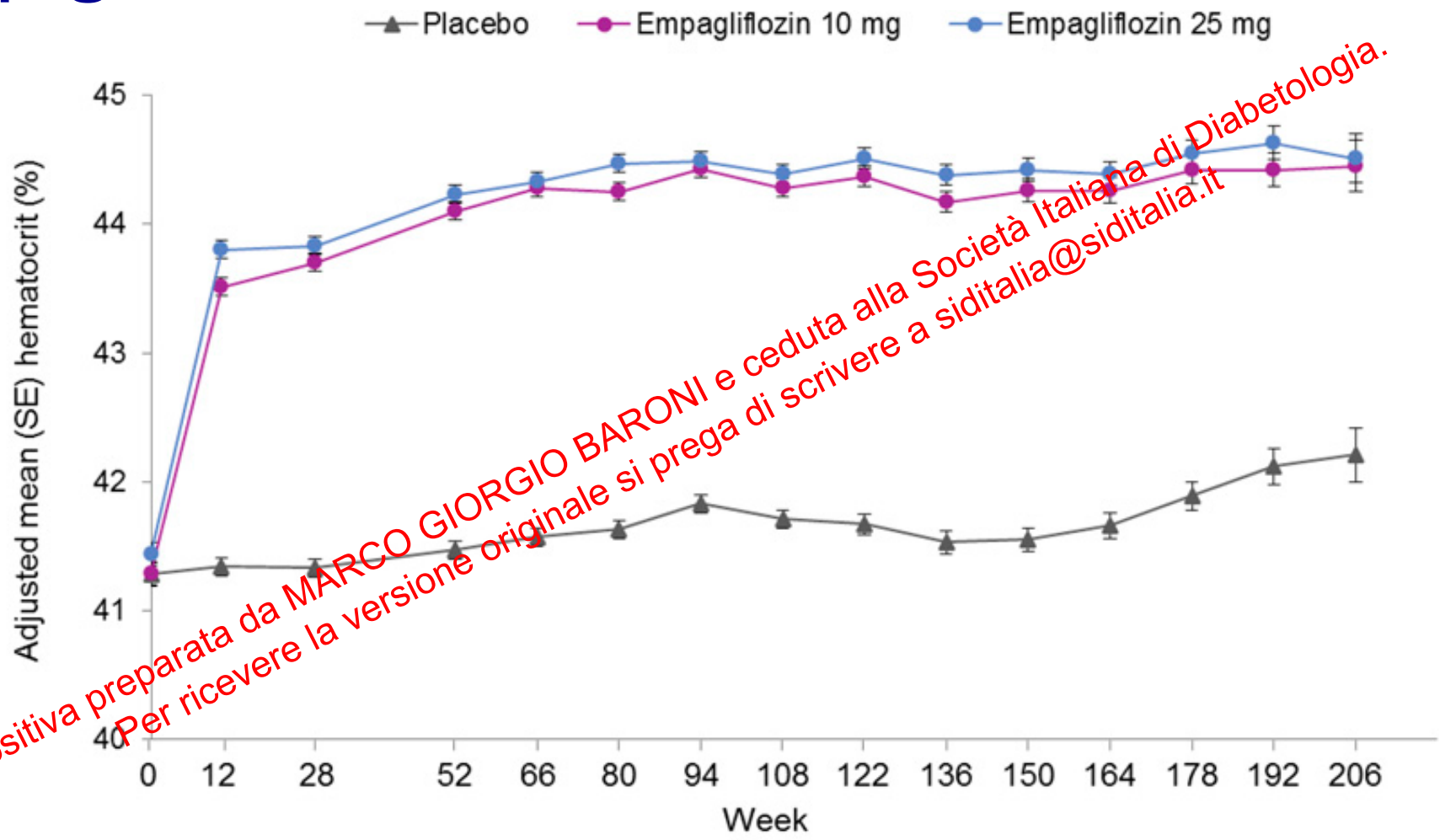
# Relationship between Changes in BP and Urinary $Na^+$ and Glucose Excretion after 2-week SGLT2 inhibitors






Kawasoe et al. *BMC Pharmacol Toxicol* 2017;18:23-33

# Hematocrit over time in patients treated with empagliflozin

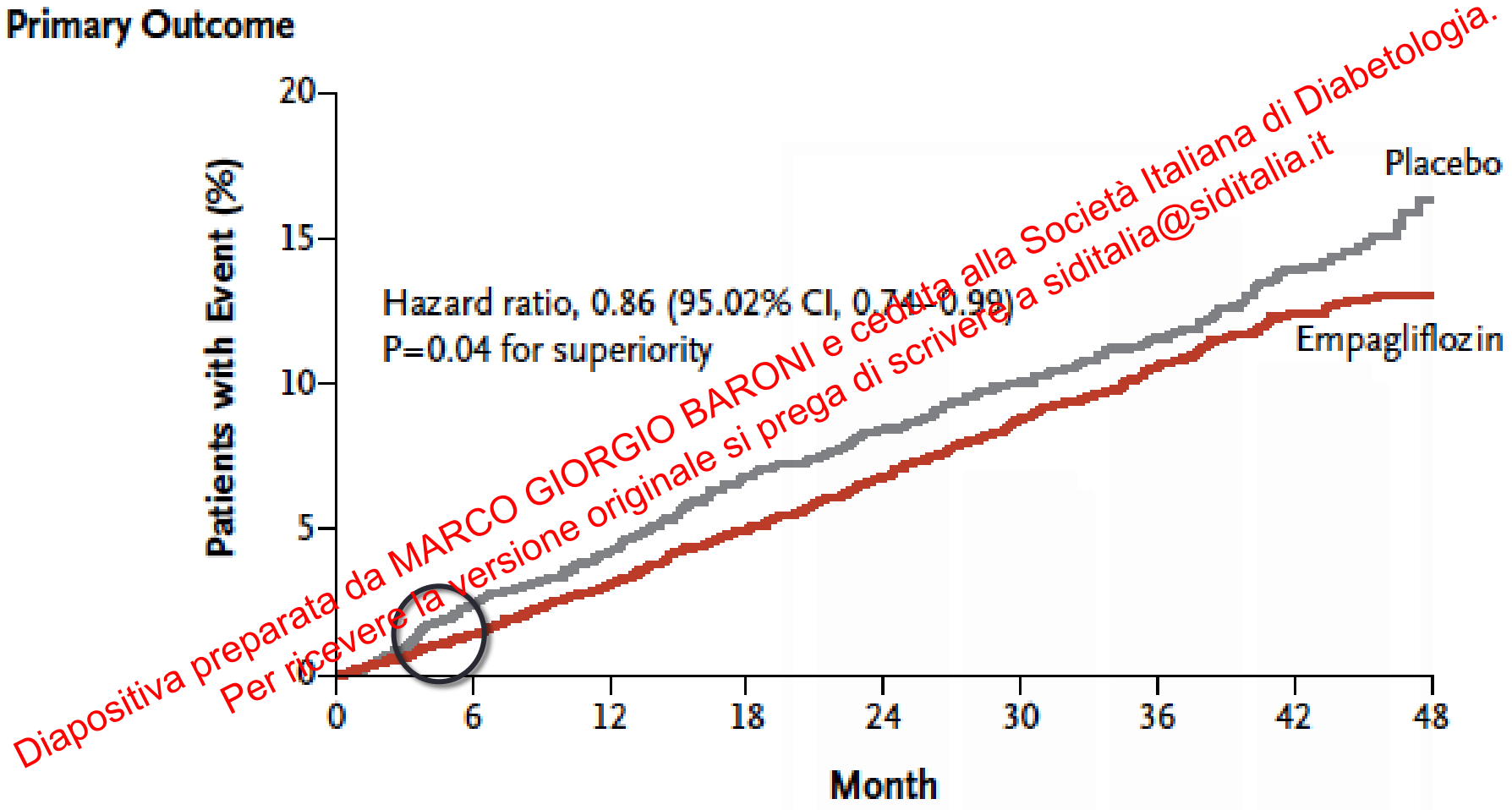





| No. of patients | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2288 | 2241 | 2170 | 2082 | 2023 | 1961 | 1928 | 1738 | 1440 | 1236 | 1094 | 955 | 716 | 442 | 168 |
| Empagliflozin 10 mg | 2288 | 2236 | 2187 | 2112 | 2077 | 2042 | 2020 | 1799 | 1508 | 1290 | 1142 | 994 | 762 | 498 | 185 |
| Empagliflozin 25 mg | 2289 | 2244 | 2183 | 2122 | 2066 | 2029 | 2008 | 1837 | 1519 | 1301 | 1178 | 1033 | 810 | 513 | 211 |

Inzucchi et al. Diabetes Care. 2018

# EMPA-REG CV OUTCOME – Main Results

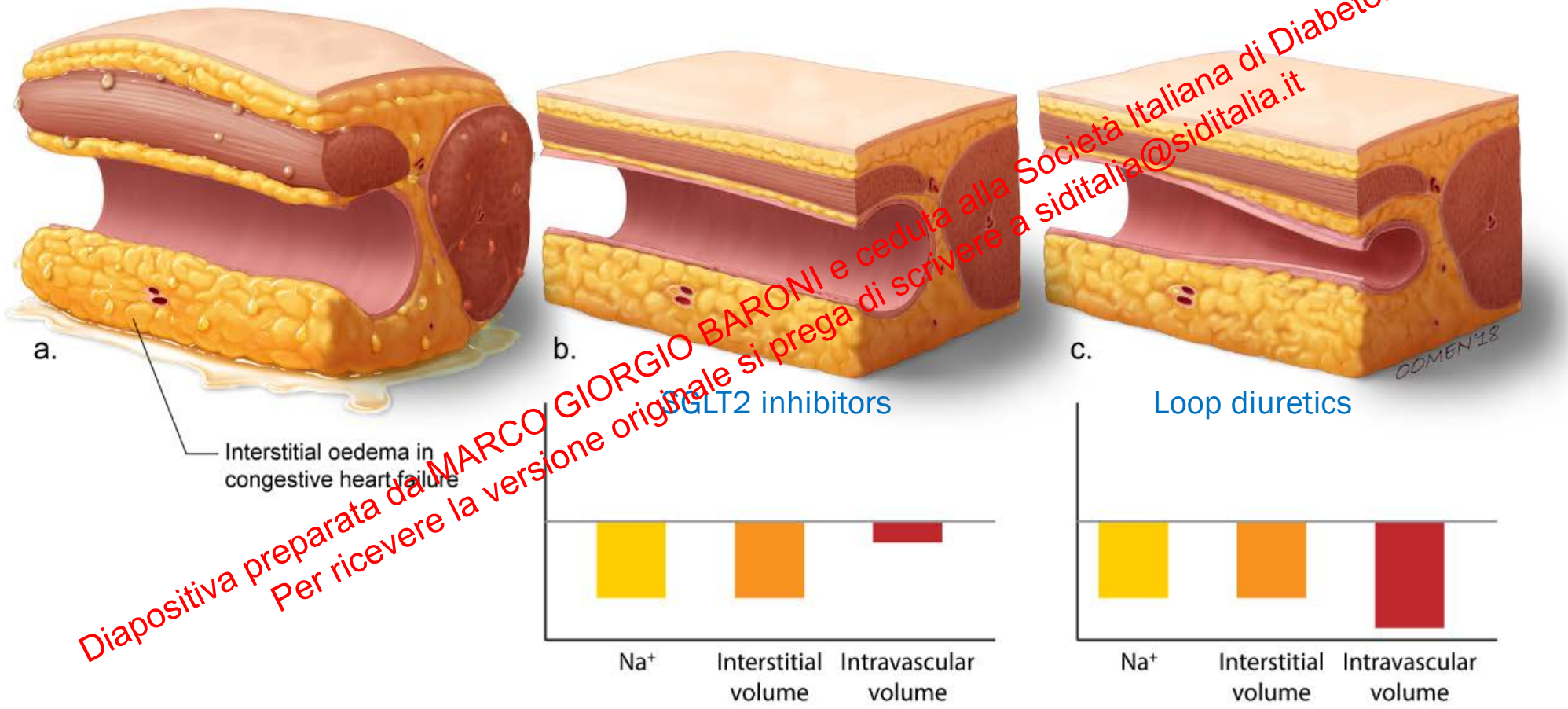





**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4687 | 4580 | 4455 | 4328 | 3851 | 2821 | 2359 | 1534 | 370 |
| Placebo | 2333 | 2256 | 2194 | 2112 | 1875 | 1380 | 1161 | 741 | 166 |

# SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics



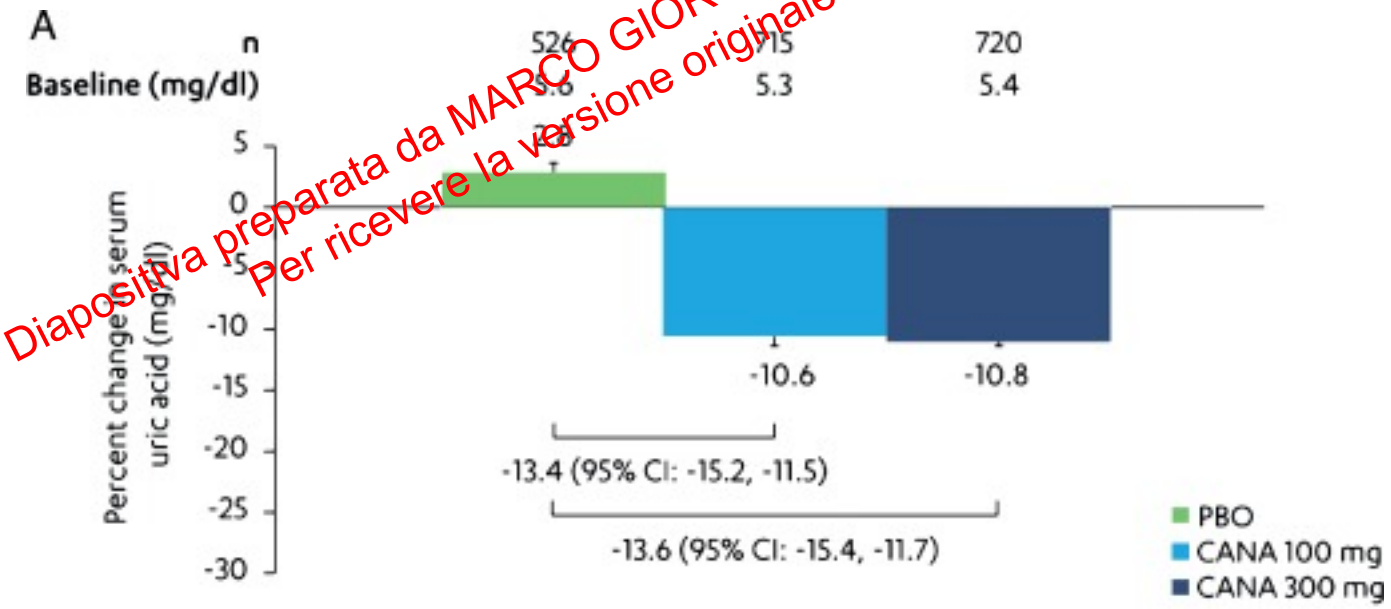



Hallow KM et al (2017) DOM

# SGLT2 inhibitors and Uric Acid

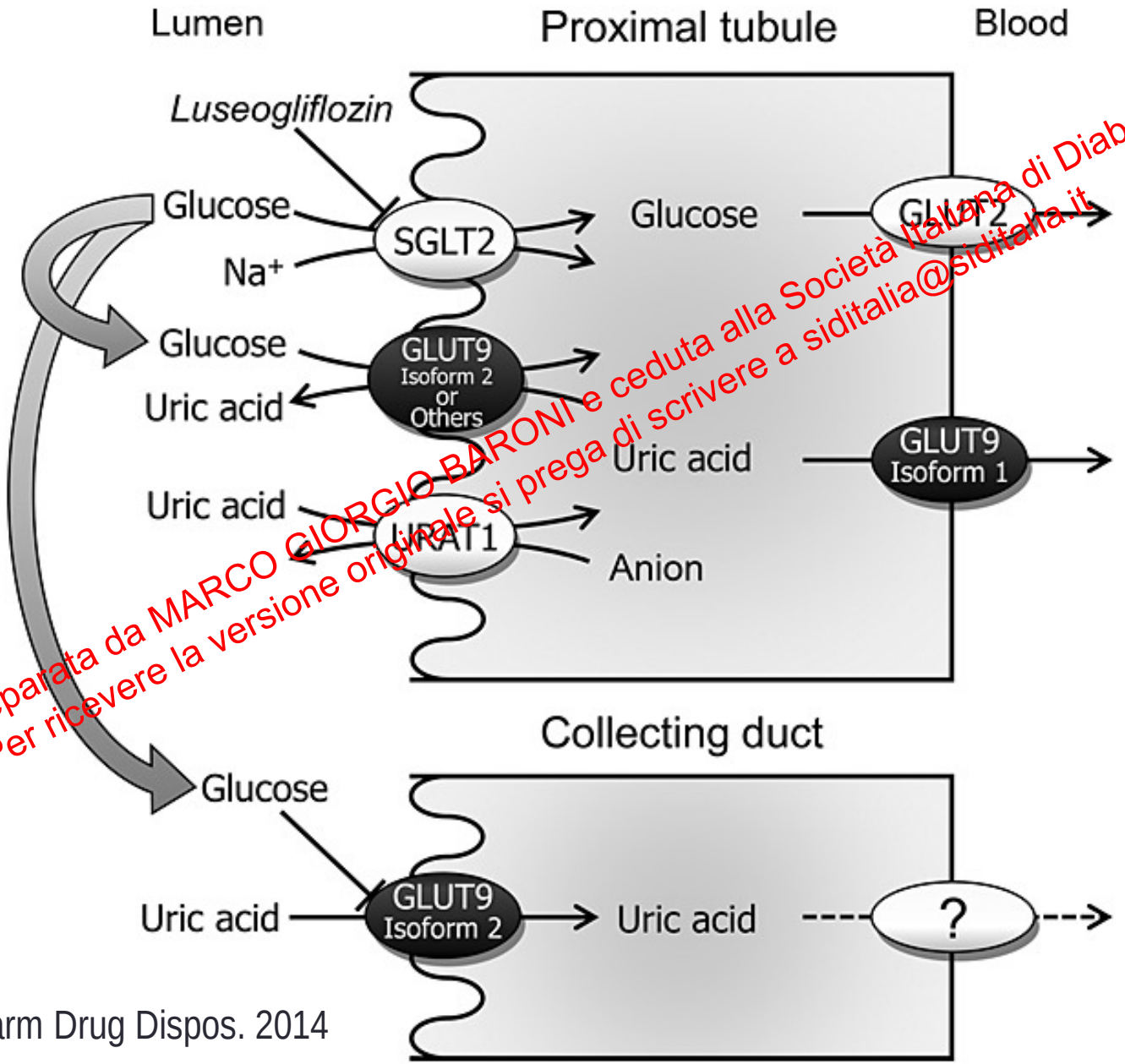
| Uric acid (μmol/L)† | Placebo group | Dapagliflozin 2·5 mg group | Dapagliflozin 5 mg group | Dapagliflozin 10 mg group |
|---|---|---|---|---|
| n | 136 | 137 | 136 | 132 |
| Baseline | 314·1 (79·0) | 322·4 (80·4) | 323·0 (88·3) | 323·0 (79·9) |
| Change at week 24 | −4·2 (4·2) | −30·9 (4·2) | −36·3 (4·2) | −47·6 (4·3) |

Bailey CJ Lancet 2010




Davis MJ et al. DOM 2015

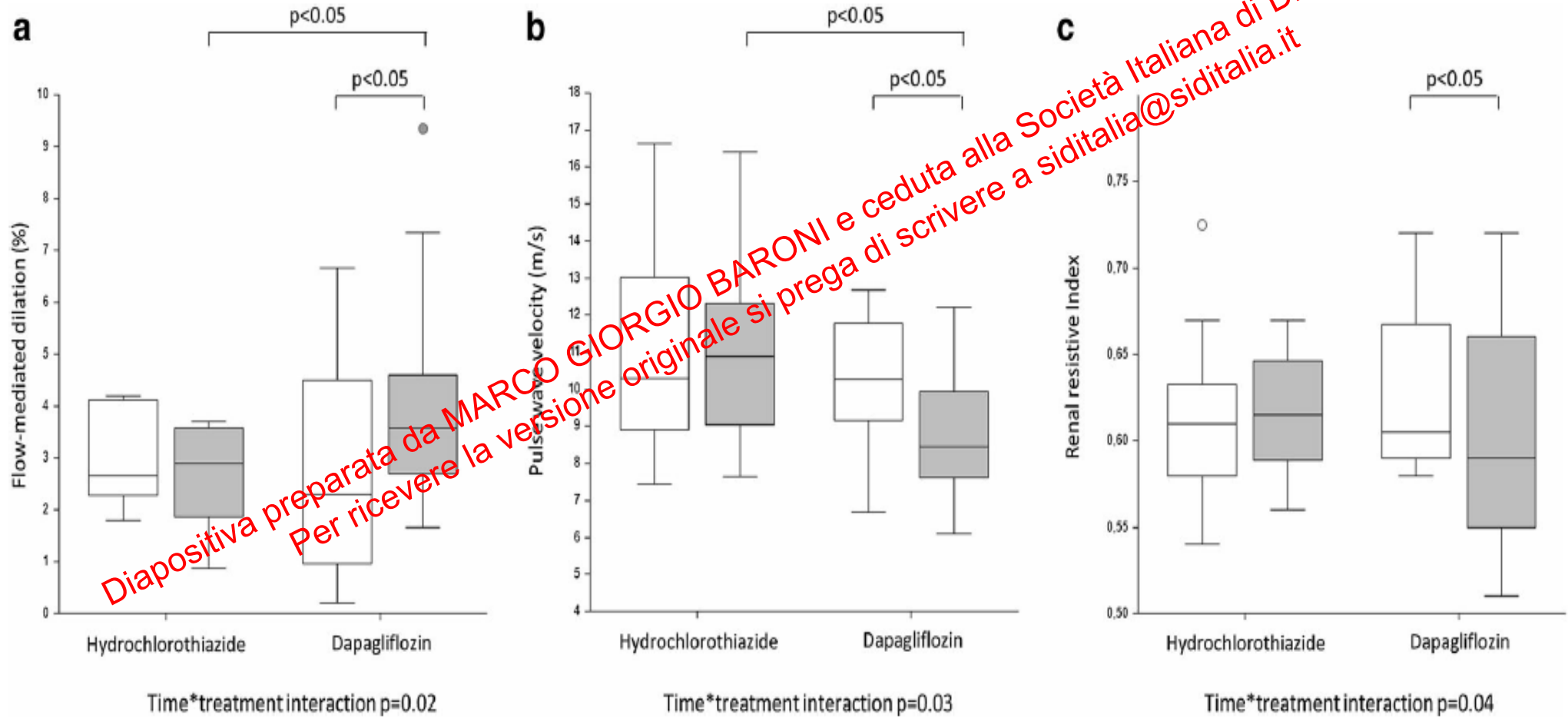
# Uricosuric effect of SGLT2 inhibitors






Chino Y et al. Biopharm Drug Dispos. 2014

# Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients






Solini et al. Cardiovasc Diabetol (2017) 16:138

# Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

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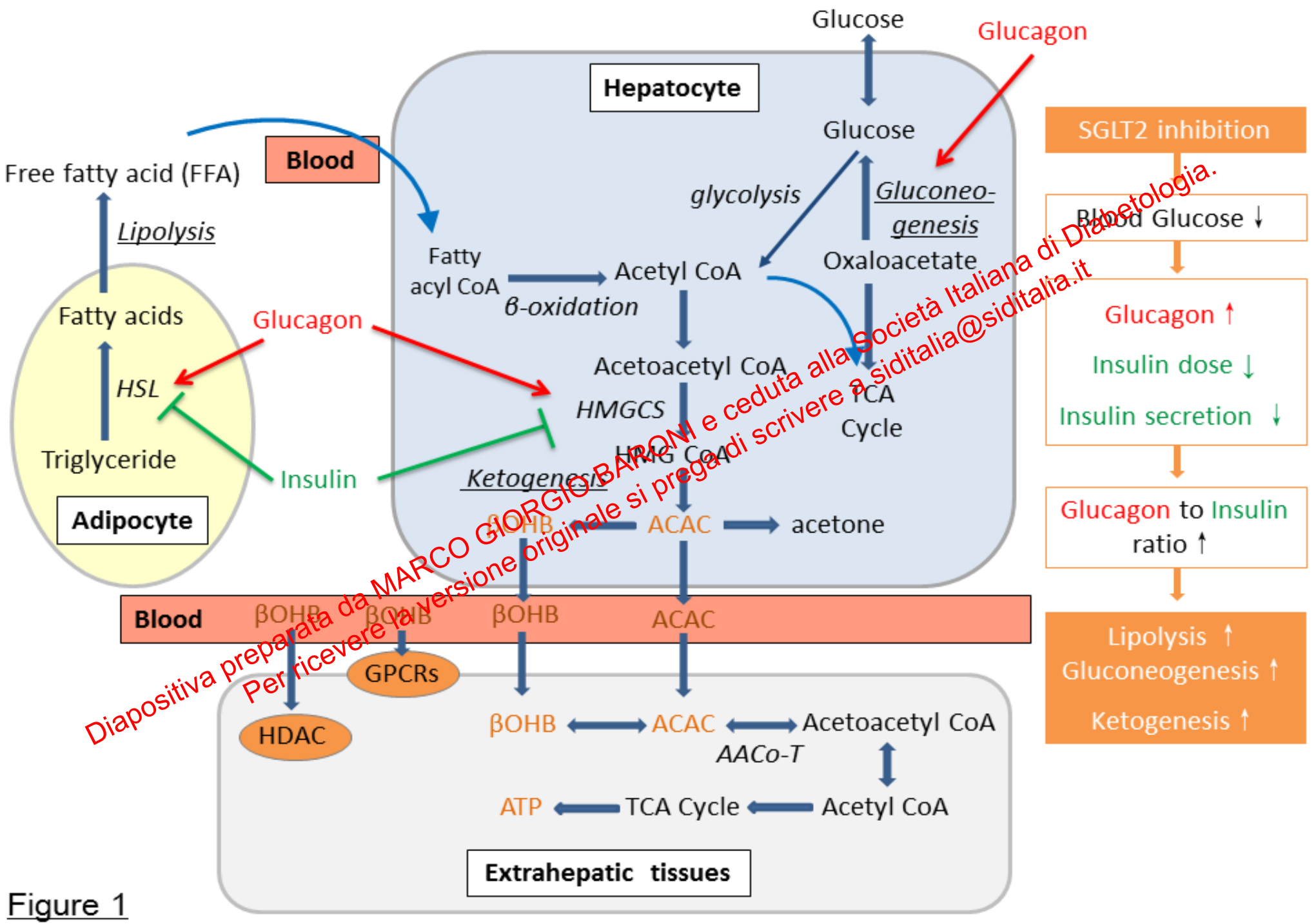
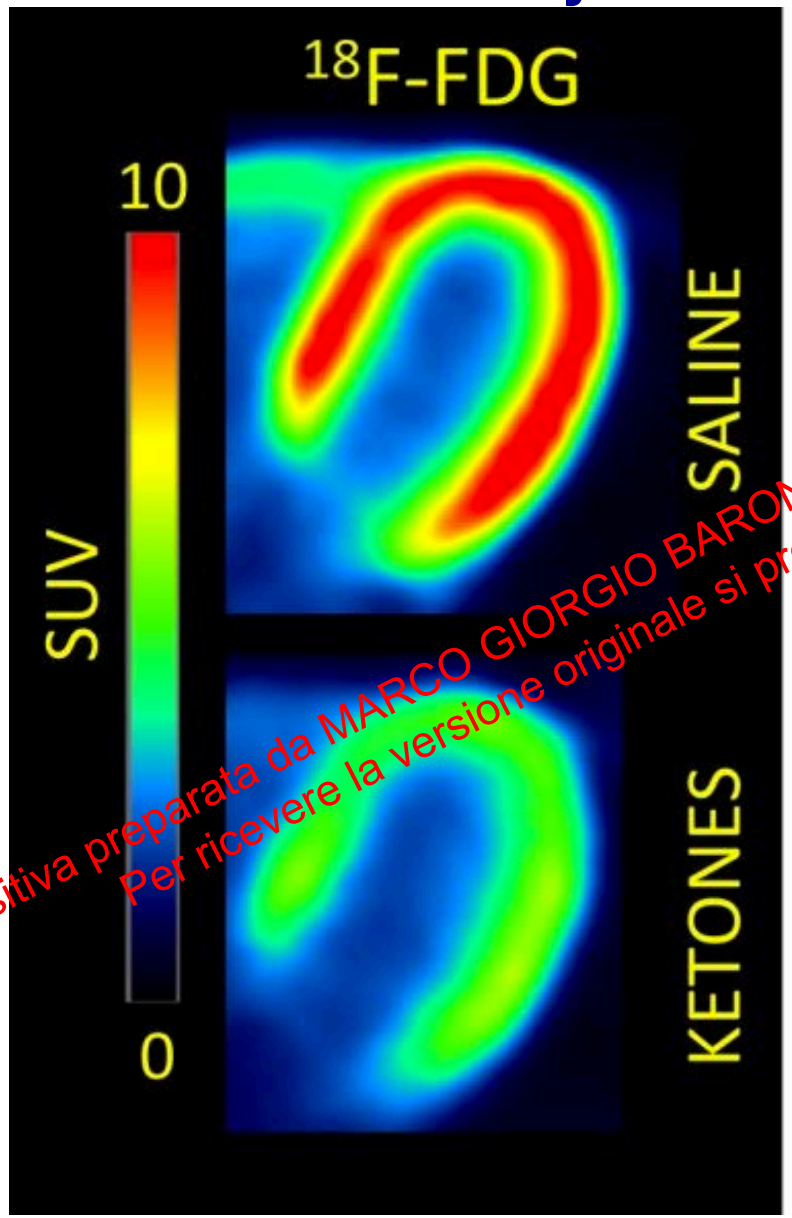
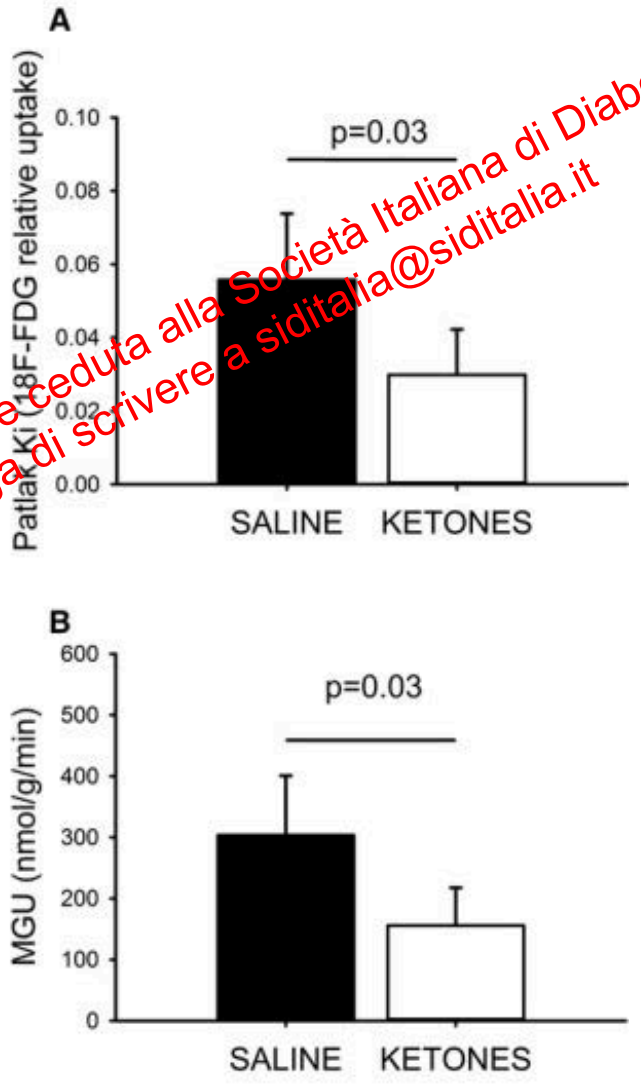





Figure 1

# Myocardial 18F-FDG uptake after hydroxybutyrate infusion in 80 healthy humans






Gormesen LC et al. J Am Heart Assoc. 2017

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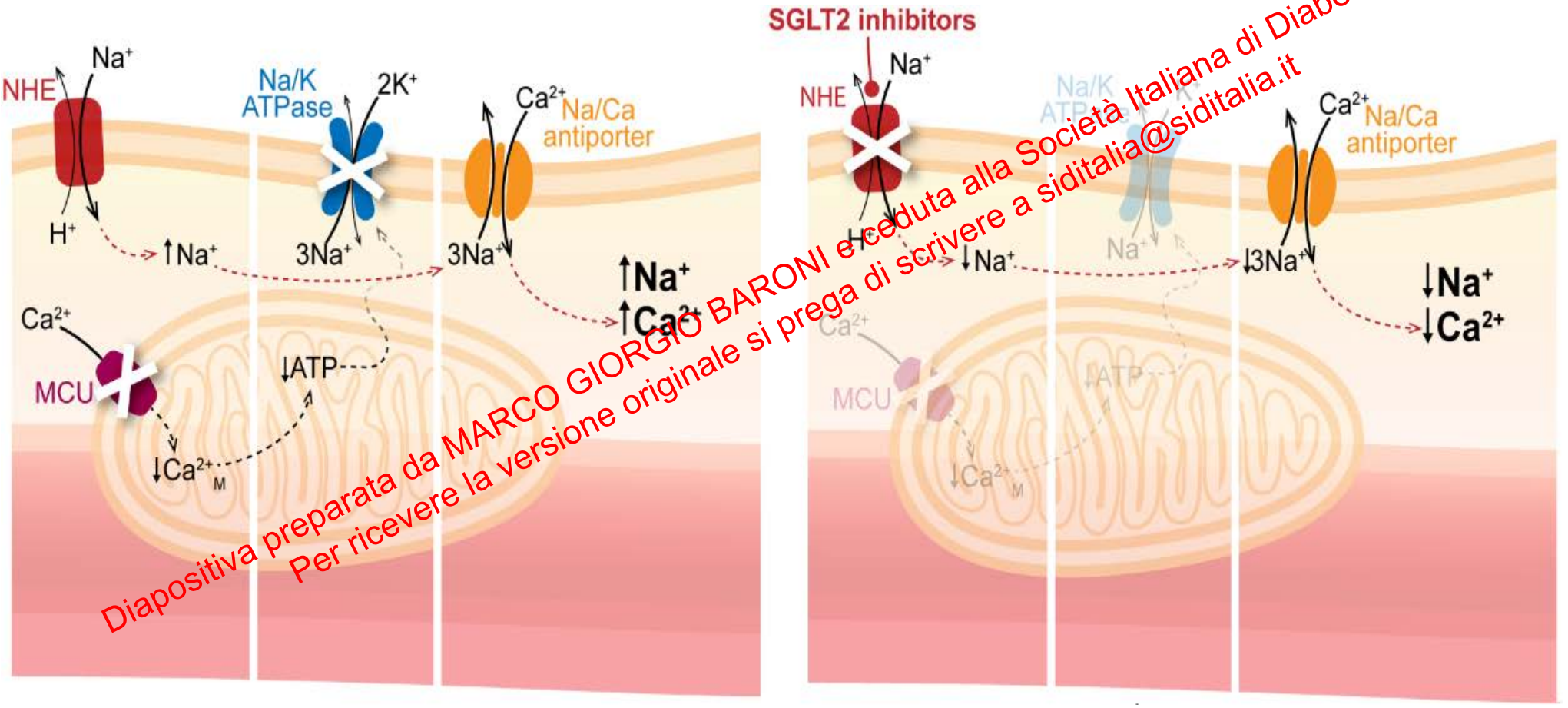
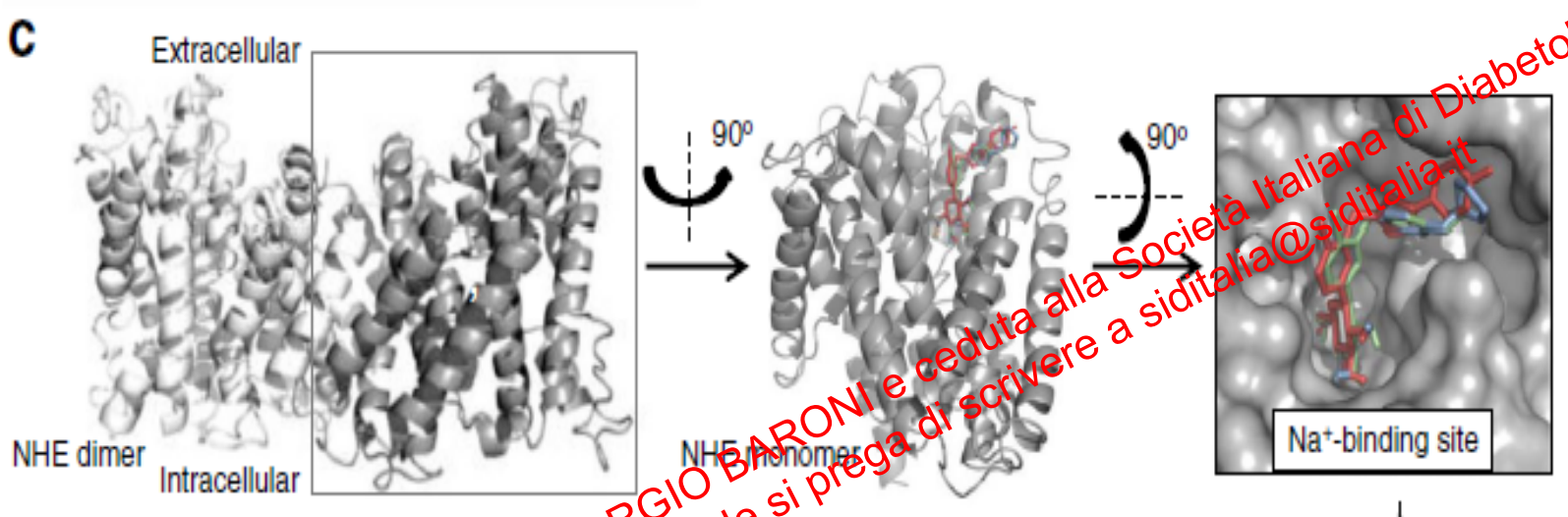
# SGLT2 inhibition and direct effects on Na+/H+ exchange in the myocardium

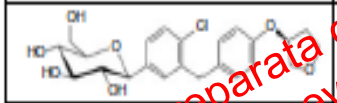
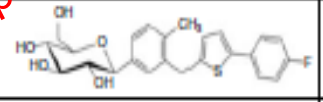
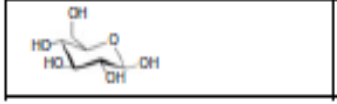





Verma and McMurray (2018) Diabetologia

# *In silico* analysis of SGLT2i binding to homology model of NHE




| Molecular structure | Compound | Binding energy (kJ/mol) |
|---|---|---|
|  | EMPA | -34.3 (-8.2 kcal/mol) |
|  | DAPA | -32.2 (-7.7 kcal/mol) |
|  | CANA | -37.2 (-8.9 kcal/mol) |
|  | Glucose | -24.3 (-5.8 kcal/mol) |



Diabetologia (2018) 61:722–726

# Impact of sodium-hydrogen exchange inhibition by cariporide on death or myocardial infarction in high-risk CABG surgery patients: Results of the CABG surgery cohort of the GUARDIAN study

EV every 8 hrs for 2-7 days

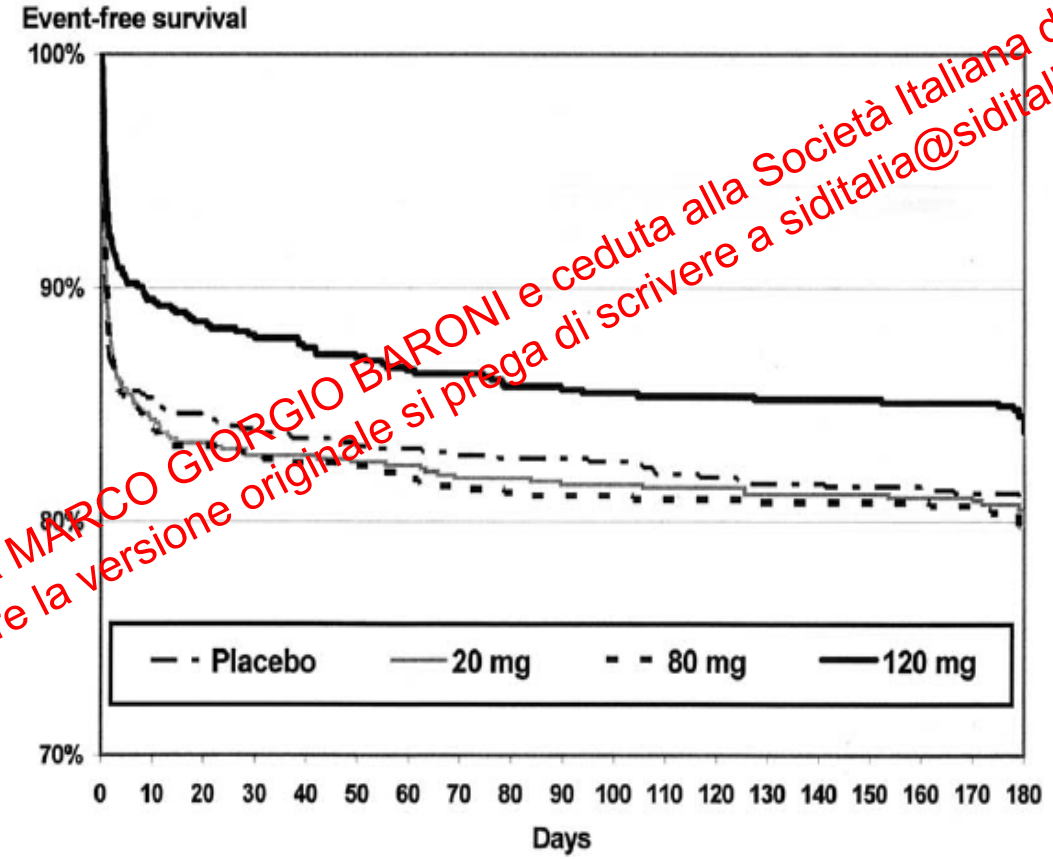


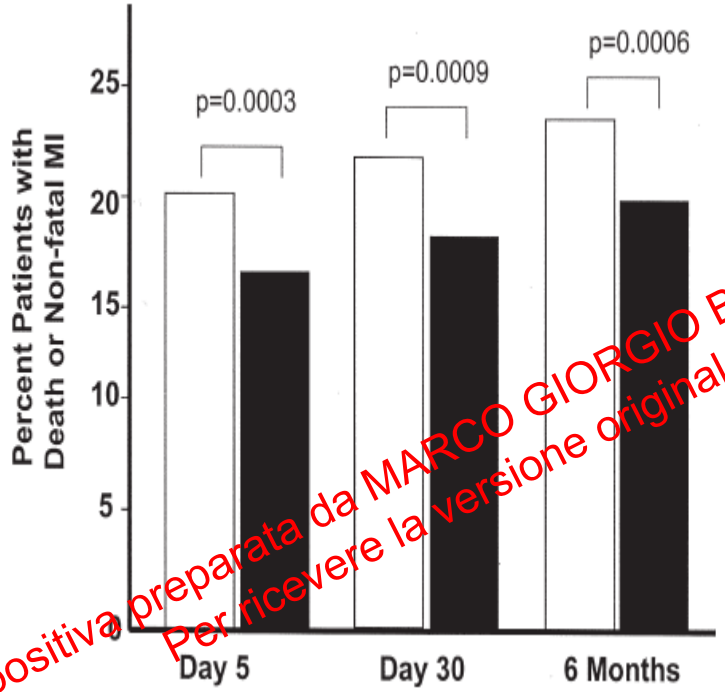

Figure 1. Event-free survival up to 6 months by treatment group. $P = .0334$.

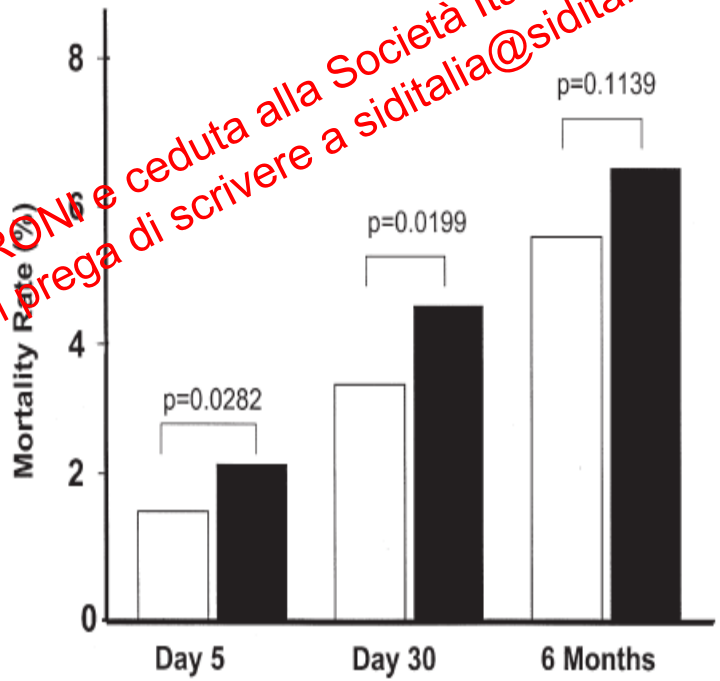


The Journal of Thoracic and Cardiovascular Surgery ● Volume 126, Number 2 2003

# Sodium-Hydrogen Exchange Inhibition by Cariporide to Reduce the Risk of Ischemic Cardiac Events in Patients Undergoing Coronary Artery Bypass Grafting: Results of the EXPEDITION Study

N=5791






Cariporide (■) ev (180 mg in a 1-hour preoperative loading dose, then 40 mg per hour over 24 hours and 20 mg per hour over the subsequent 24 hours) vs placebo (□)

(Ann Thorac Surg 2008;85:1261–70)

# Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

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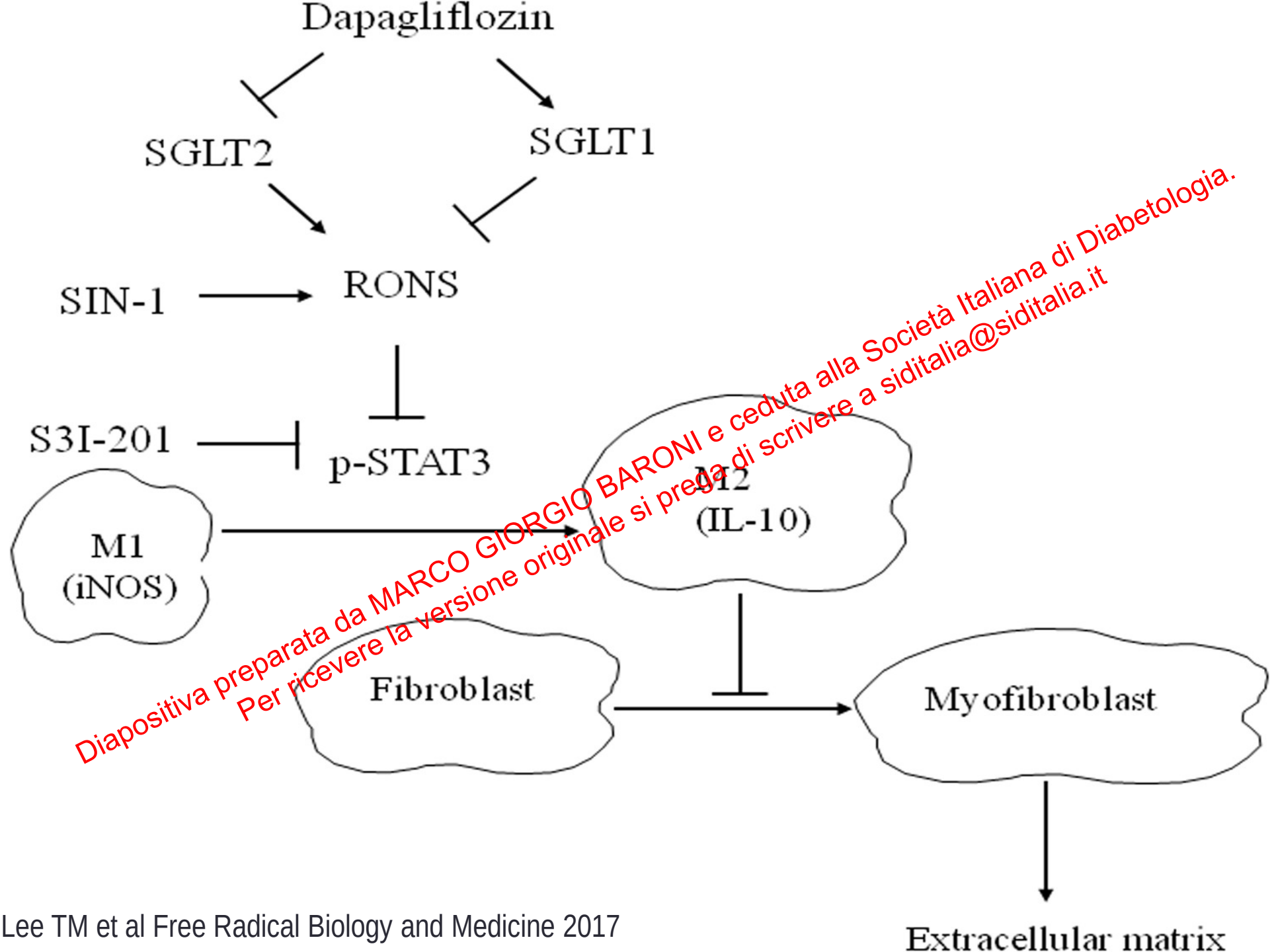
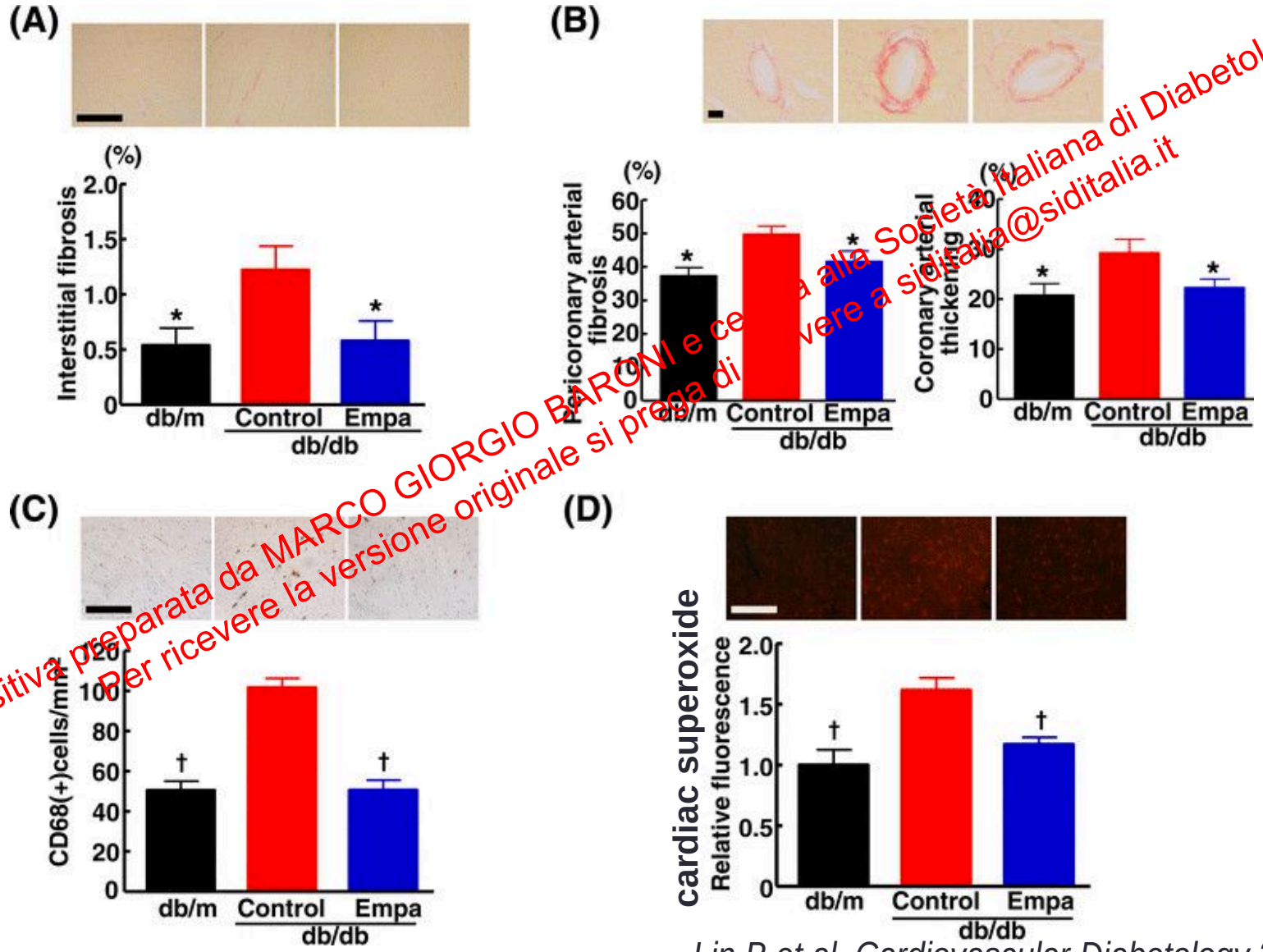





Lee TM et al Free Radical Biology and Medicine 2017

# Effects of empagliflozin on cardiac injuries in db/db mice






*Lin B et al. Cardiovascular Diabetology* 2014, 13:148

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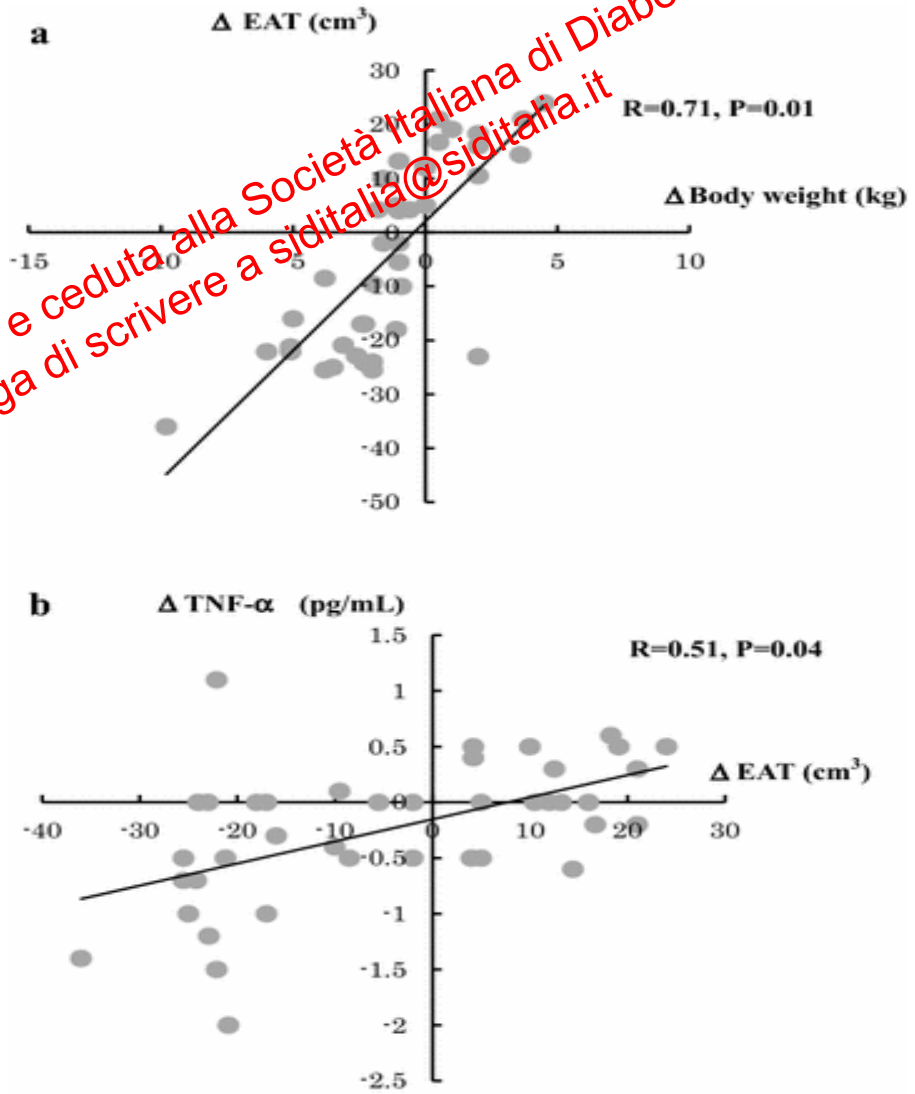
# The effect of dapagliflozin treatment on epicardial adipose tissue volume

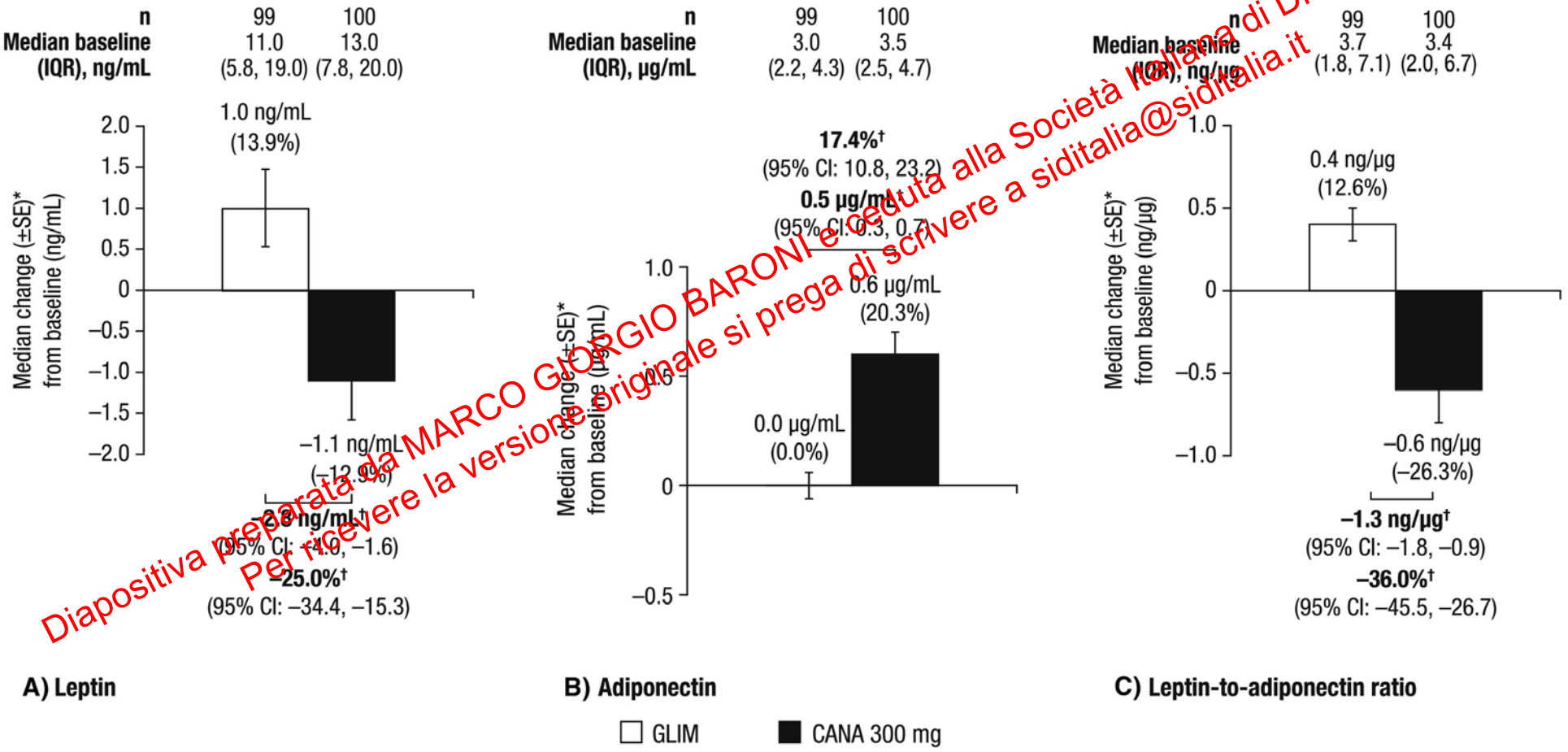
- EAT volume significantly decreased in the DG at the 6-month follow-up compared with the CTG ($-16.4 \pm 8.3$ vs. $4.7 \pm 8.8$ cm$^3$, $p = 0.01$).






*Sato T et al. Cardiovascular Diabetology 2018*

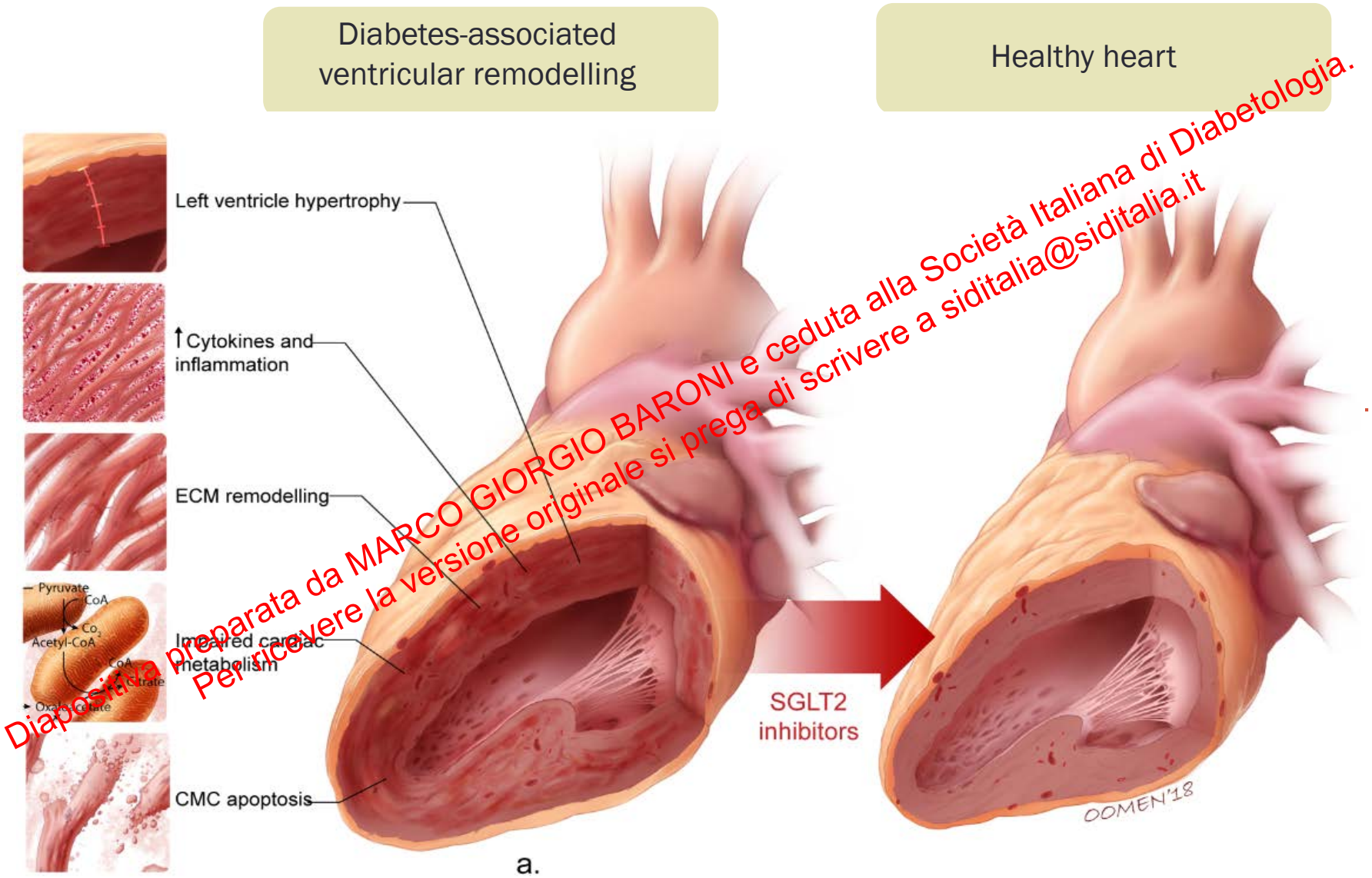
# Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes after 52 weeks






Garvey WT Metabolism 2018

# Cardiovascular protection by SGLT2 inhibitors






Verma and McMurray (2018) Diabetologia

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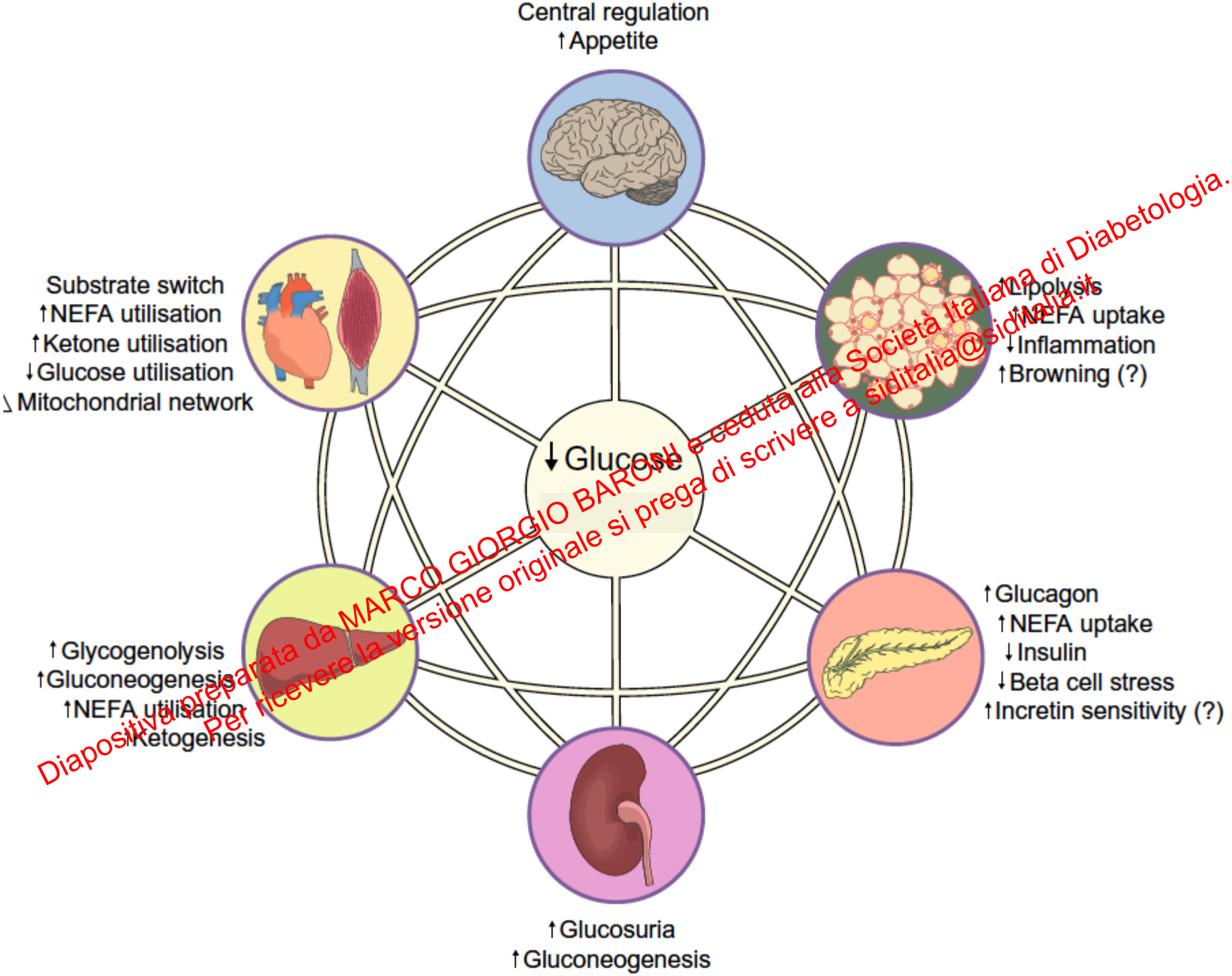
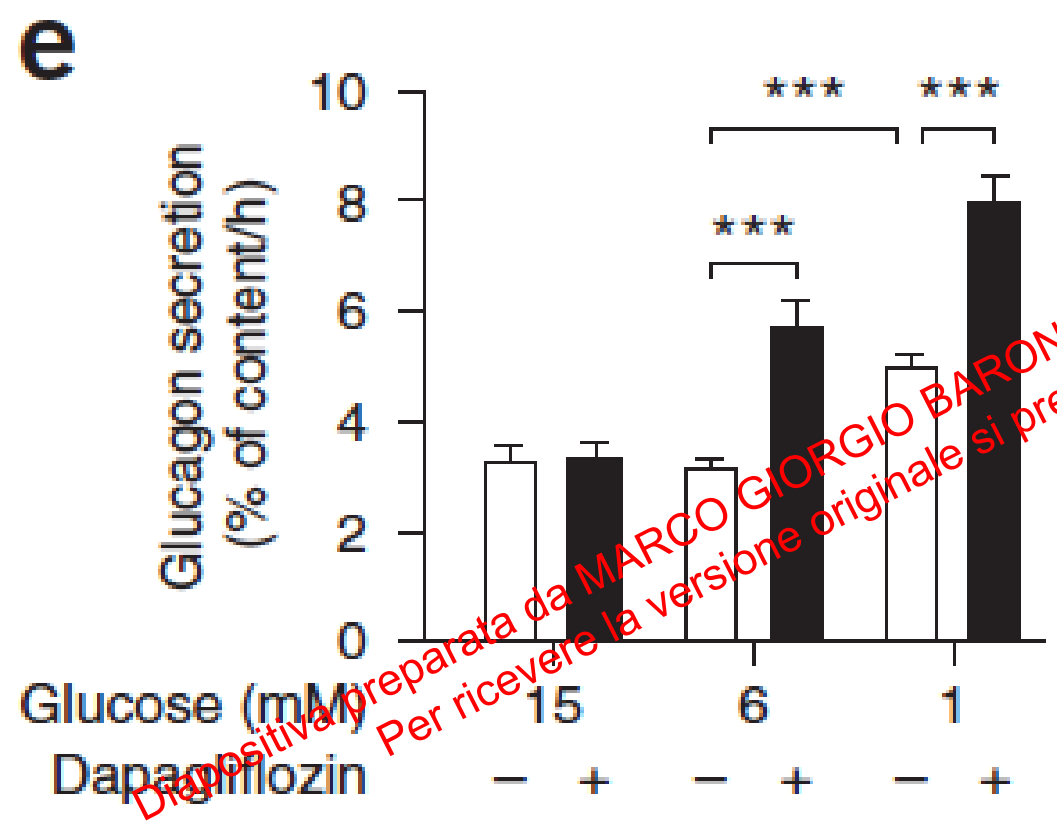
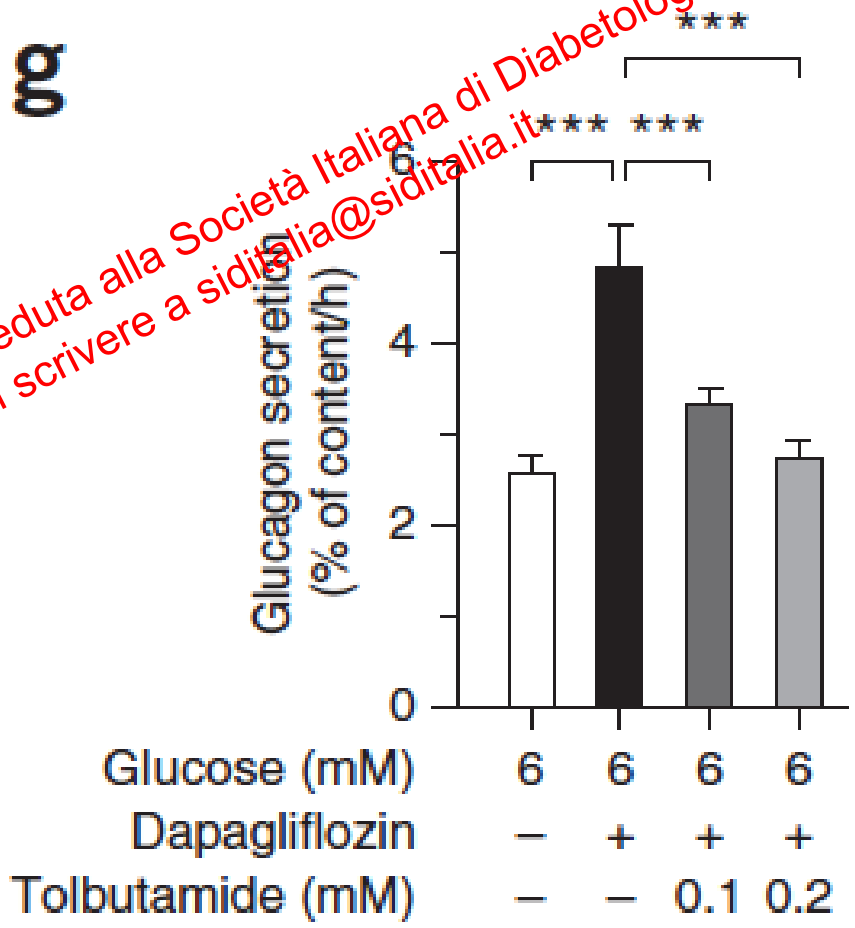


# Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion





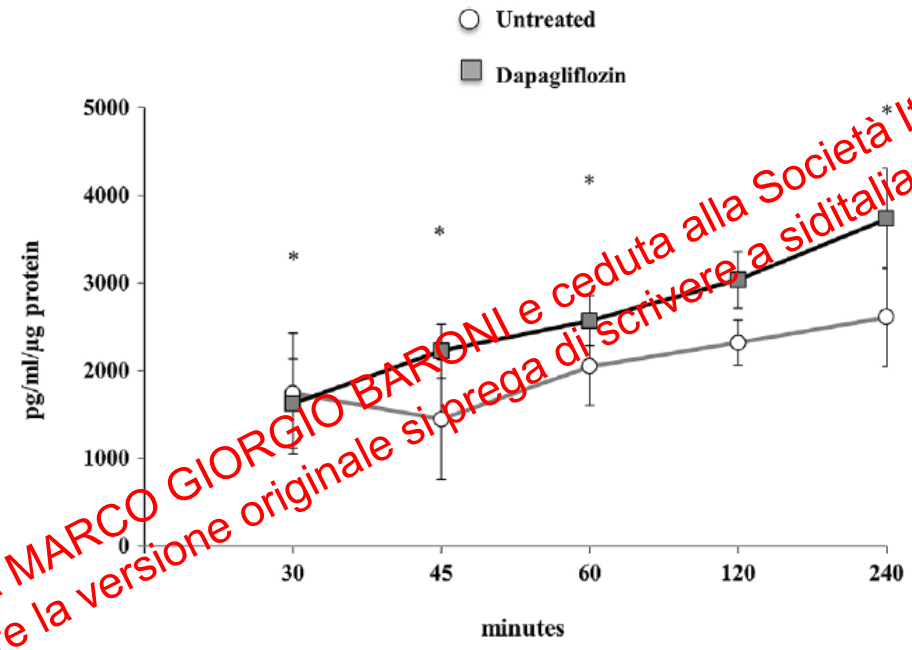

Bonner C et al Nat Med 2015

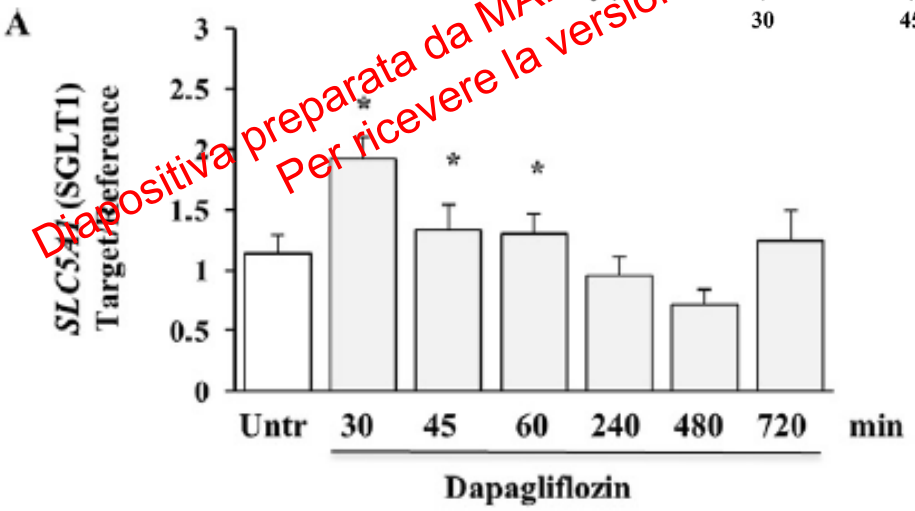
*Diabetes & Metabolism, 43(6), 512–520, 2017.*

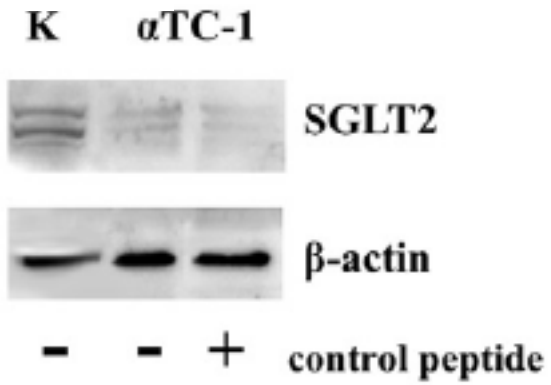
# Dapagliflozin modulates glucagon secretion in an SGLT2-independent manner in murine alpha cells

A. Solini [a,*], G. Sebastiani [b], L. Nigi [b], E. Santini [c], C. Rossi [c], F. Dotta [b,*]

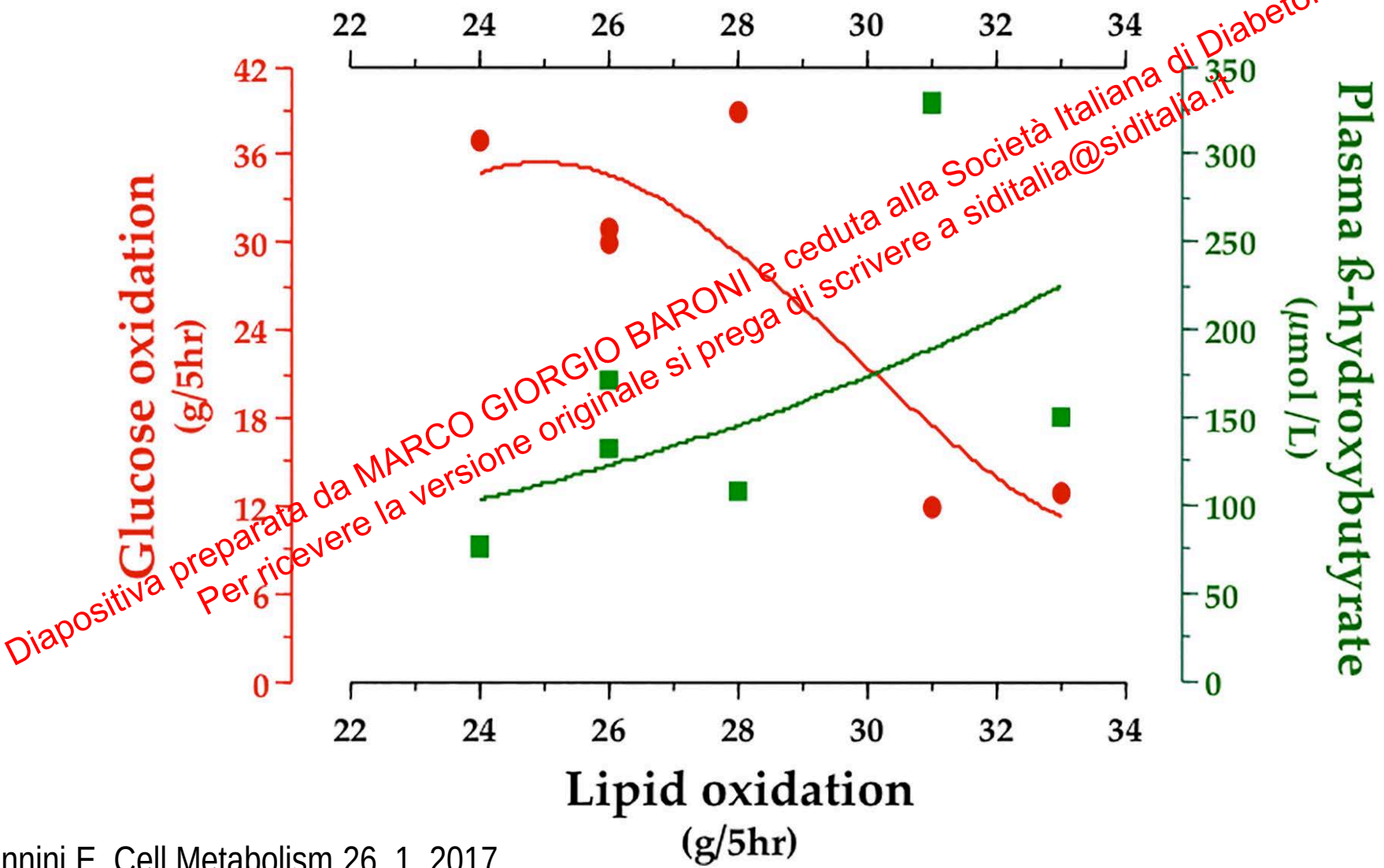




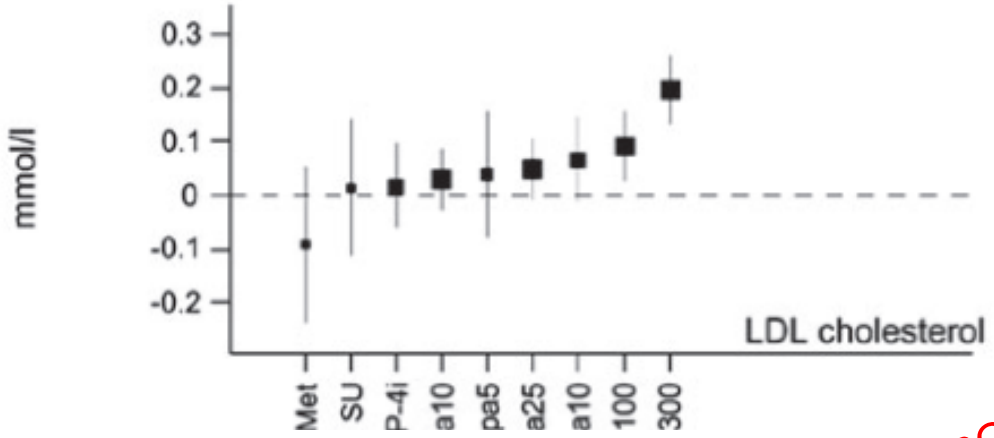
# Chronic shifts in metabolic substrate utilisation and ketogenesis after 4 weeks Empagliflozin

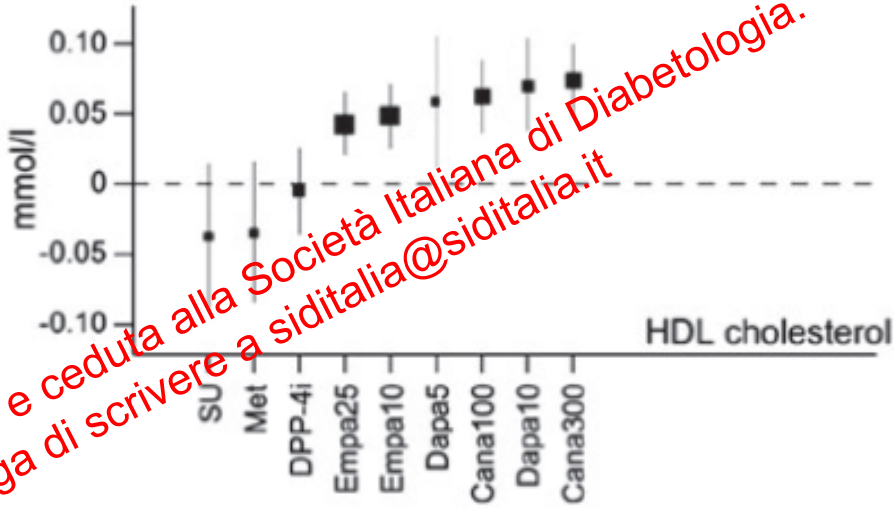


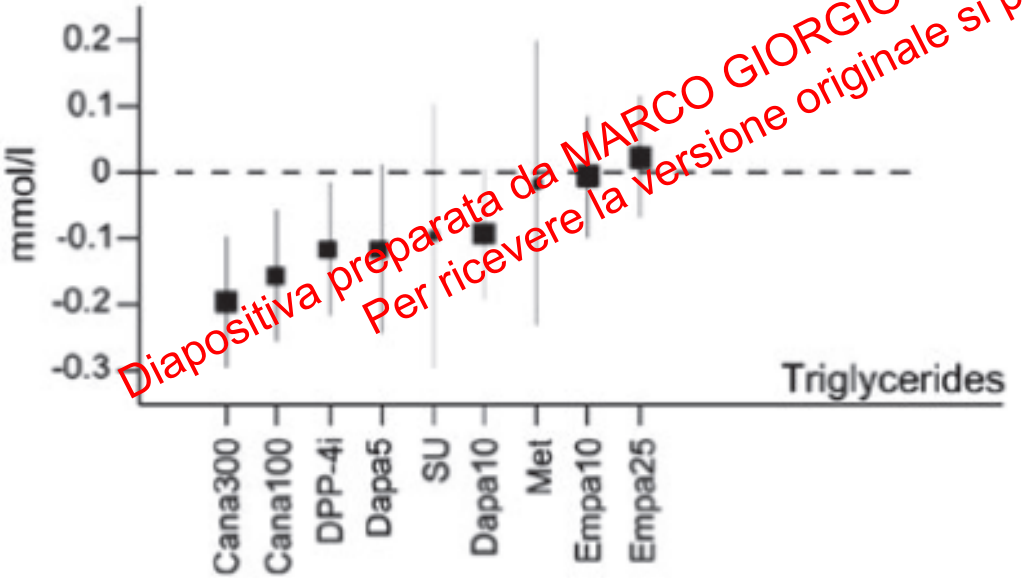


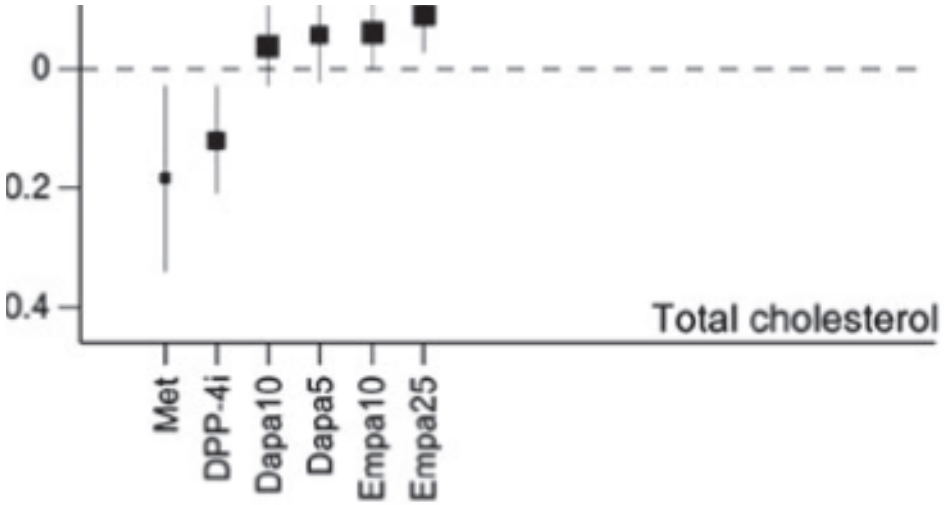

Ferrannini E. Cell Metabolism 26, 1, 2017

# Lipid Changes with SGLT2i



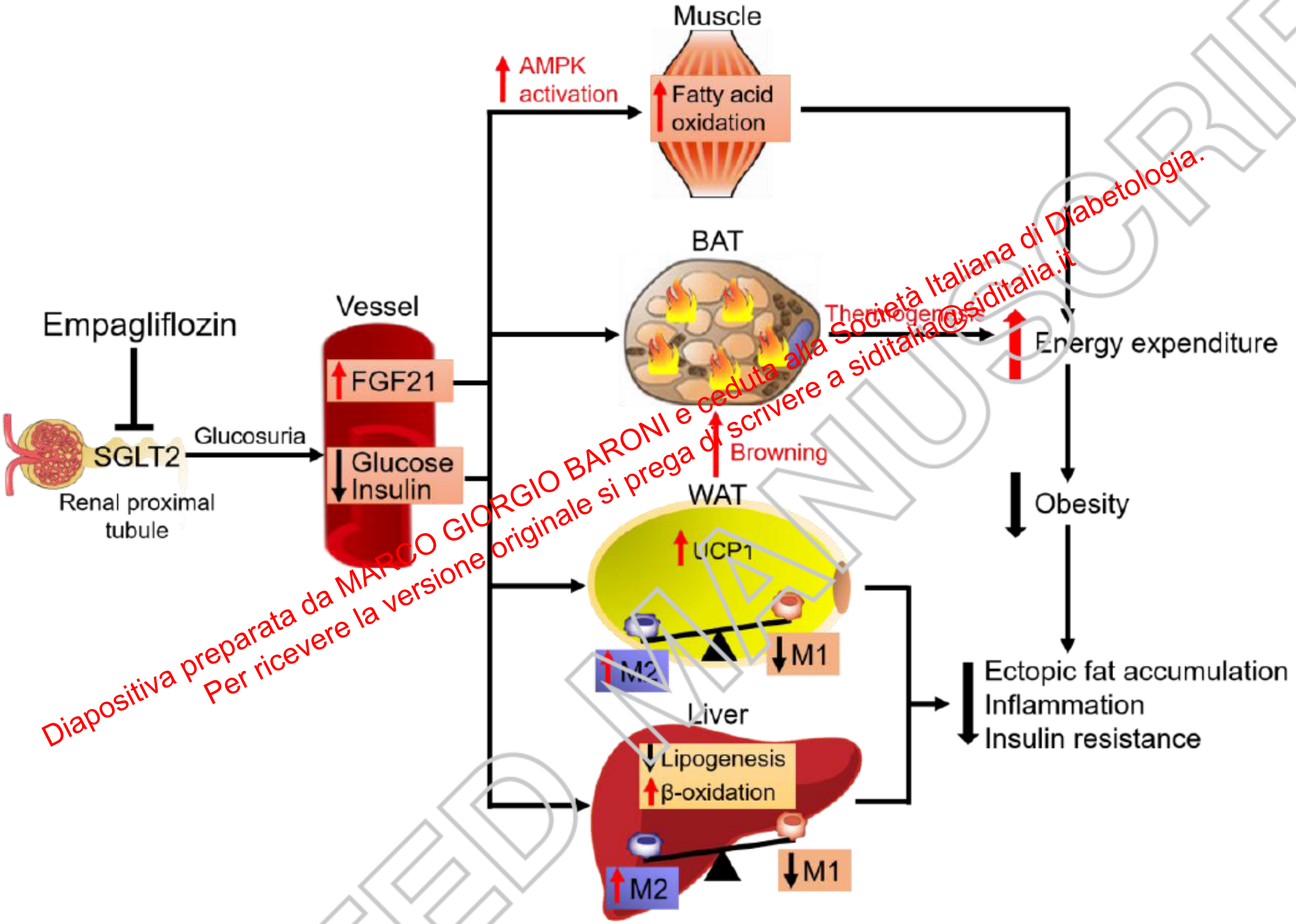



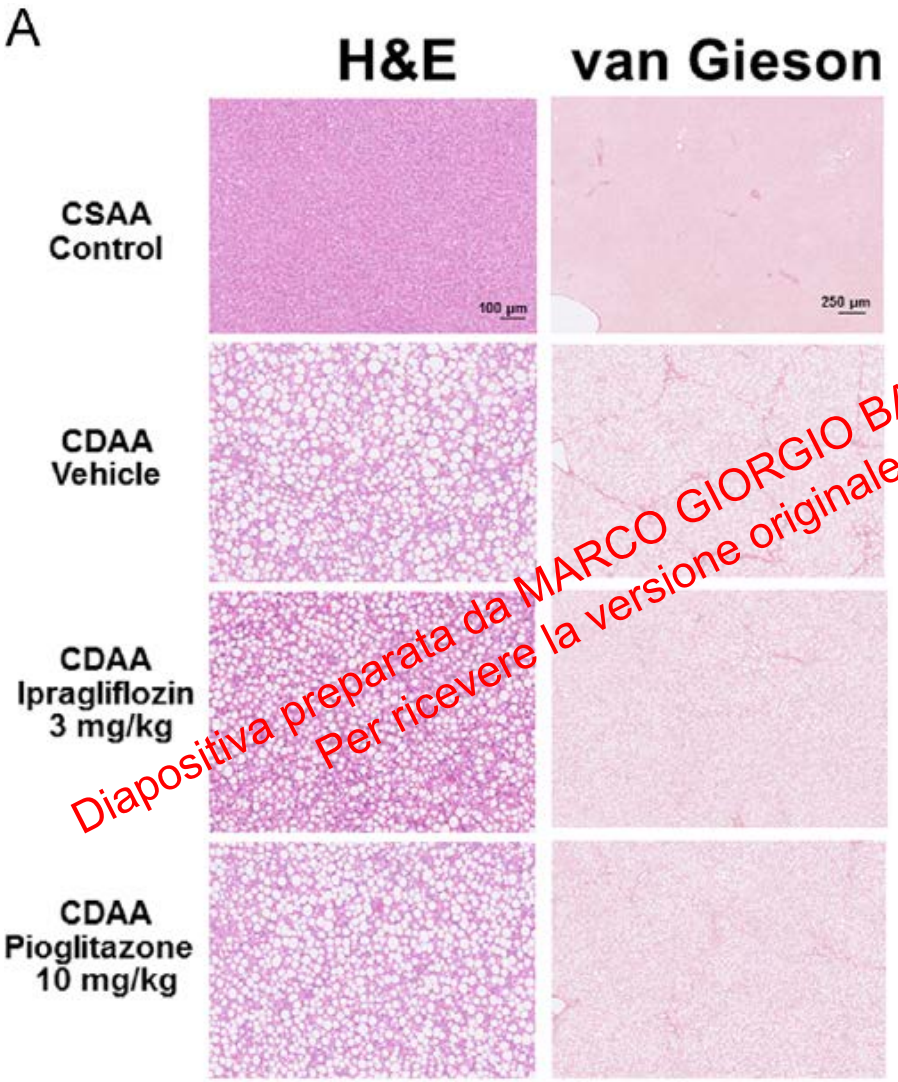



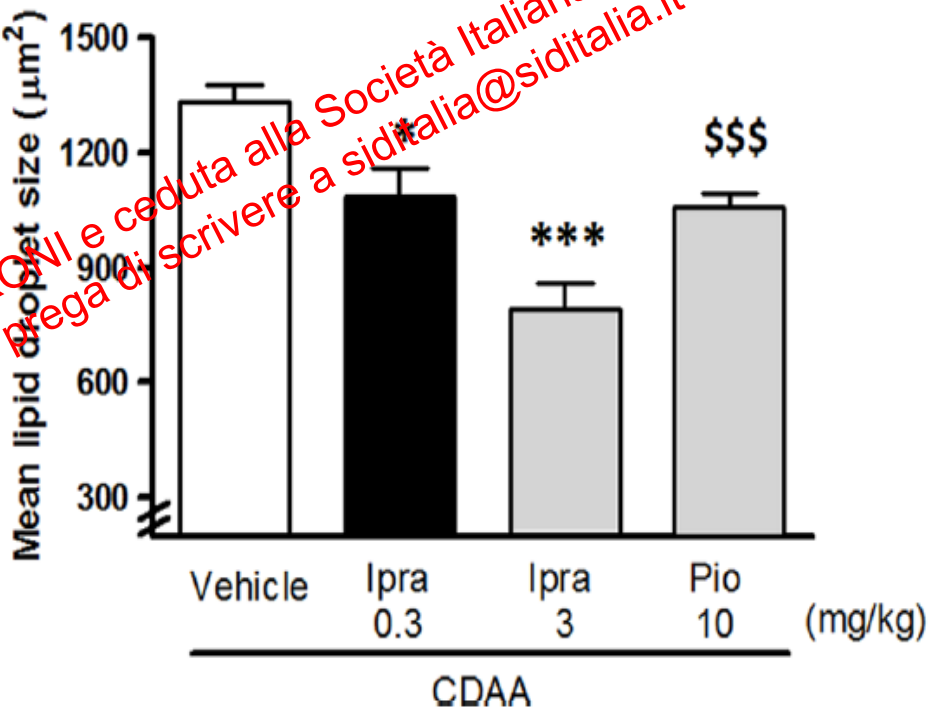



Zaccardo F. et al DOM 2016

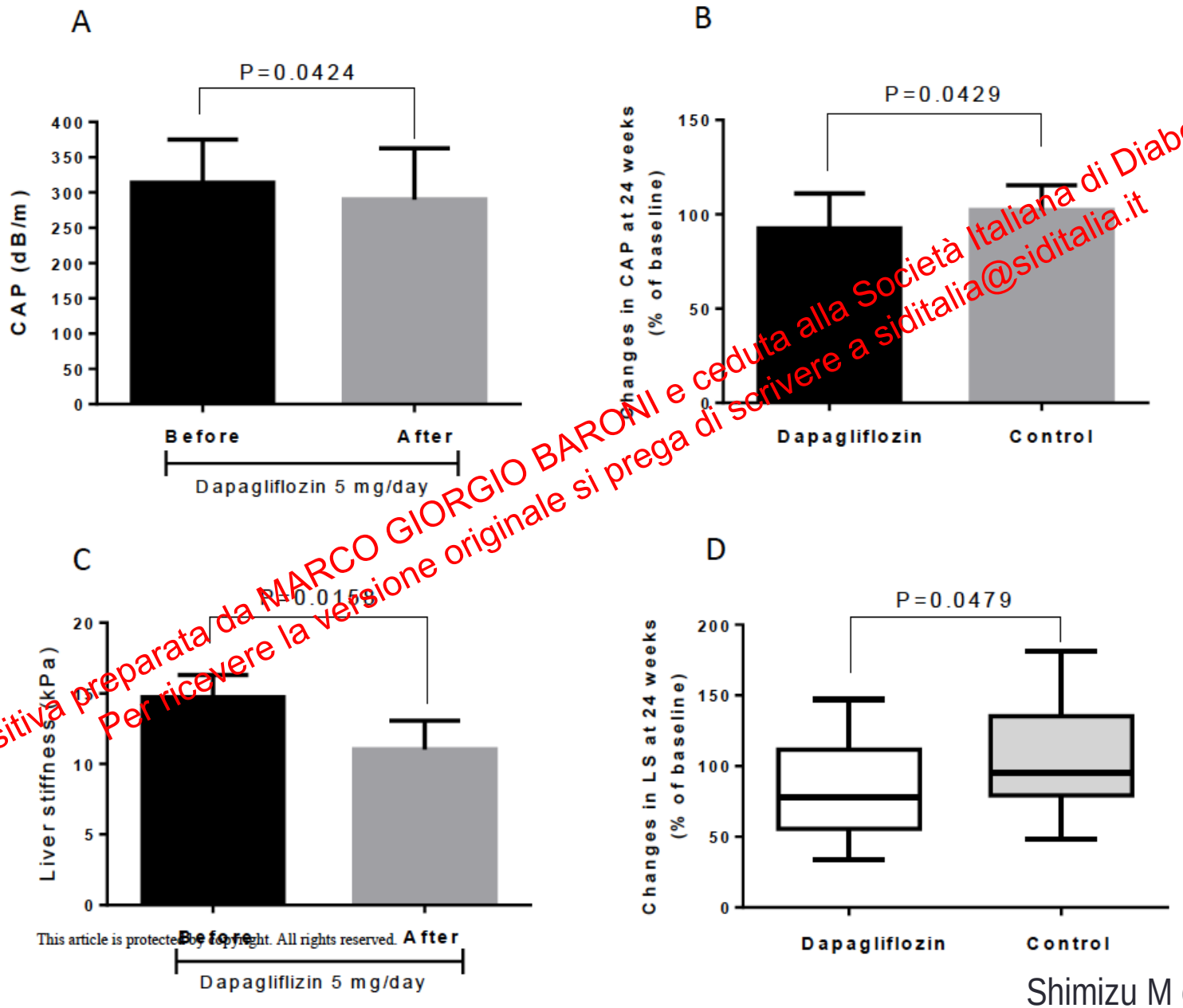


# Effect of ipragliflozin and pioglitazone on liver histopathological changes



# Liver parameters after 24 weeks dapagliflozin







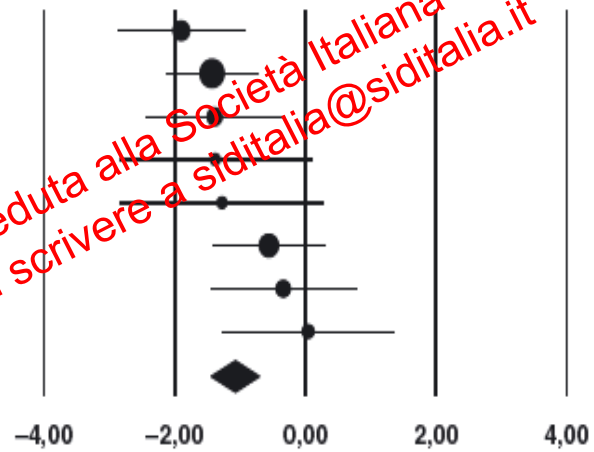

Shimizu M et al. DOM 2018

# SGLT2 inhibitors and weight loss

| Study name | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Bailey (26) | –1,900 | 0,508 | 0,259 | –2,897 | –0,903 | –3,737 | 0,000 |
| Bode (21) | –1,430 | 0,366 | 0,134 | –2,147 | –0,713 | –3,910 | 0,000 |
| Stenlof (22) | –1,390 | 0,552 | 0,305 | –2,472 | –0,308 | –2,519 | 0,012 |
| Bailey (25) | –1,380 | 0,757 | 0,574 | –2,864 | 0,104 | –1,822 | 0,068 |
| Yale (23) | –1,280 | 0,797 | 0,636 | –2,843 | 0,283 | –1,605 | 0,108 |
| Wilding (34) | –0,560 | 0,447 | 0,200 | –1,436 | 0,316 | –1,253 | 0,210 |
| Bolinder (27) | –0,340 | 0,578 | 0,334 | –1,473 | 0,793 | –0,588 | 0,556 |
| Ferrannini (28) | 0,040 | 0,680 | 0,463 | –1,293 | 1,373 | 0,059 | 0,953 |
| OVERALL | –1,094 | 0,189 | 0,036 | –1,464 | –0,725 | –5,802 | 0,000 |

Statistics for each study

Difference in means and 95% CI




BMI at 24–26 weeks

| Study name | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Bailey (26) | –1,300 | 0,508 | 0,259 | –2,297 | –0,303 | –2,557 | 0,011 |
| Wilding (34) | –0,740 | 0,447 | 0,200 | –1,616 | 0,136 | –1,656 | 0,098 |
| OVERALL | –0,984 | 0,336 | 0,113 | –1,642 | –0,326 | –2,932 | 0,003 |

Statistics for each study

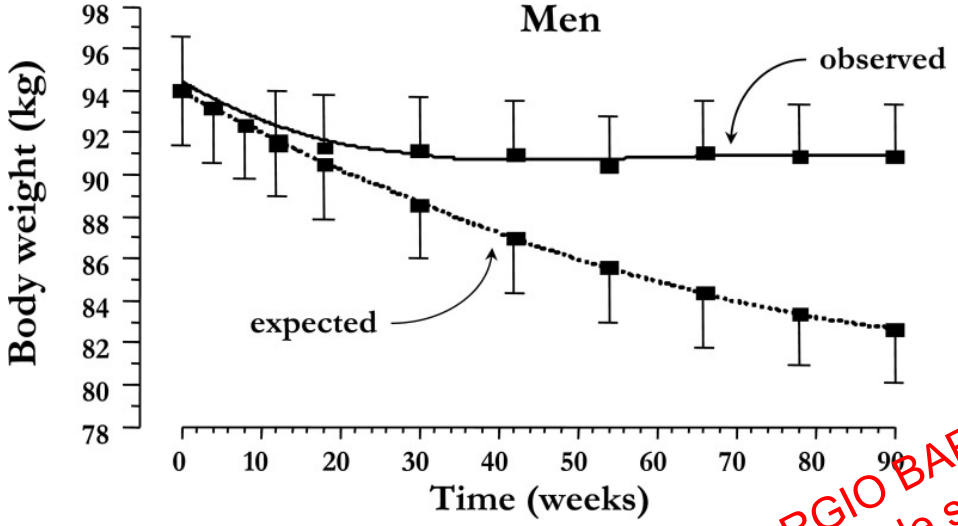
Difference in means and 95% CI

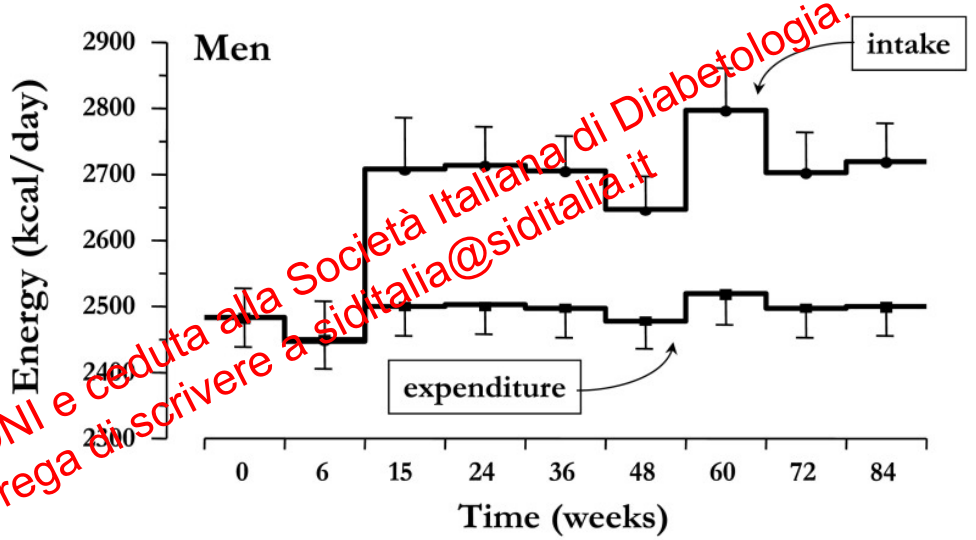

BMI at 48–52 weeks

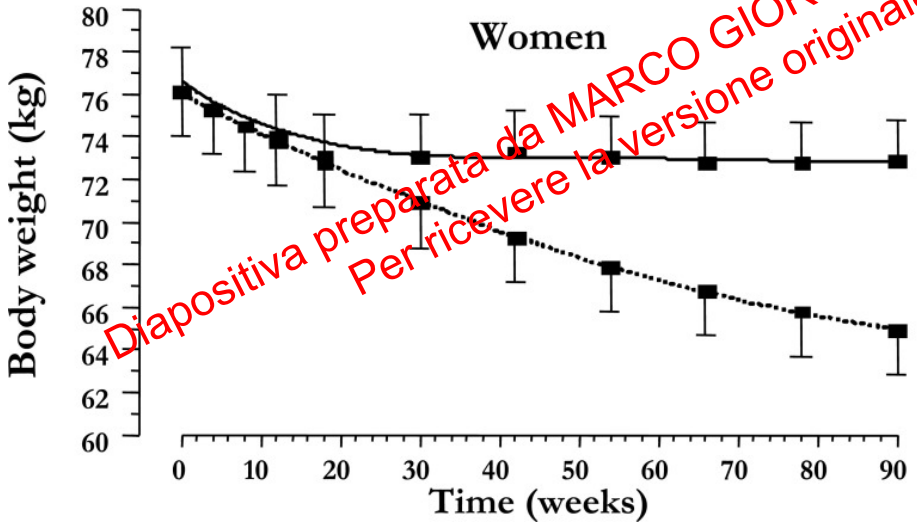


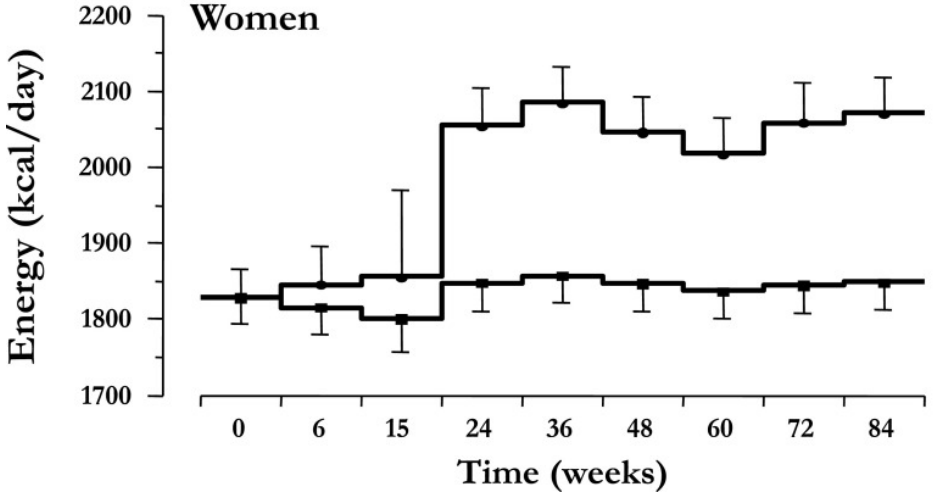
Monami M et al. DOM 2014

# Weight loss and energy expenditure in men and women with T2DM treated with empagliflozin (25 mg/day) for 90 weeks



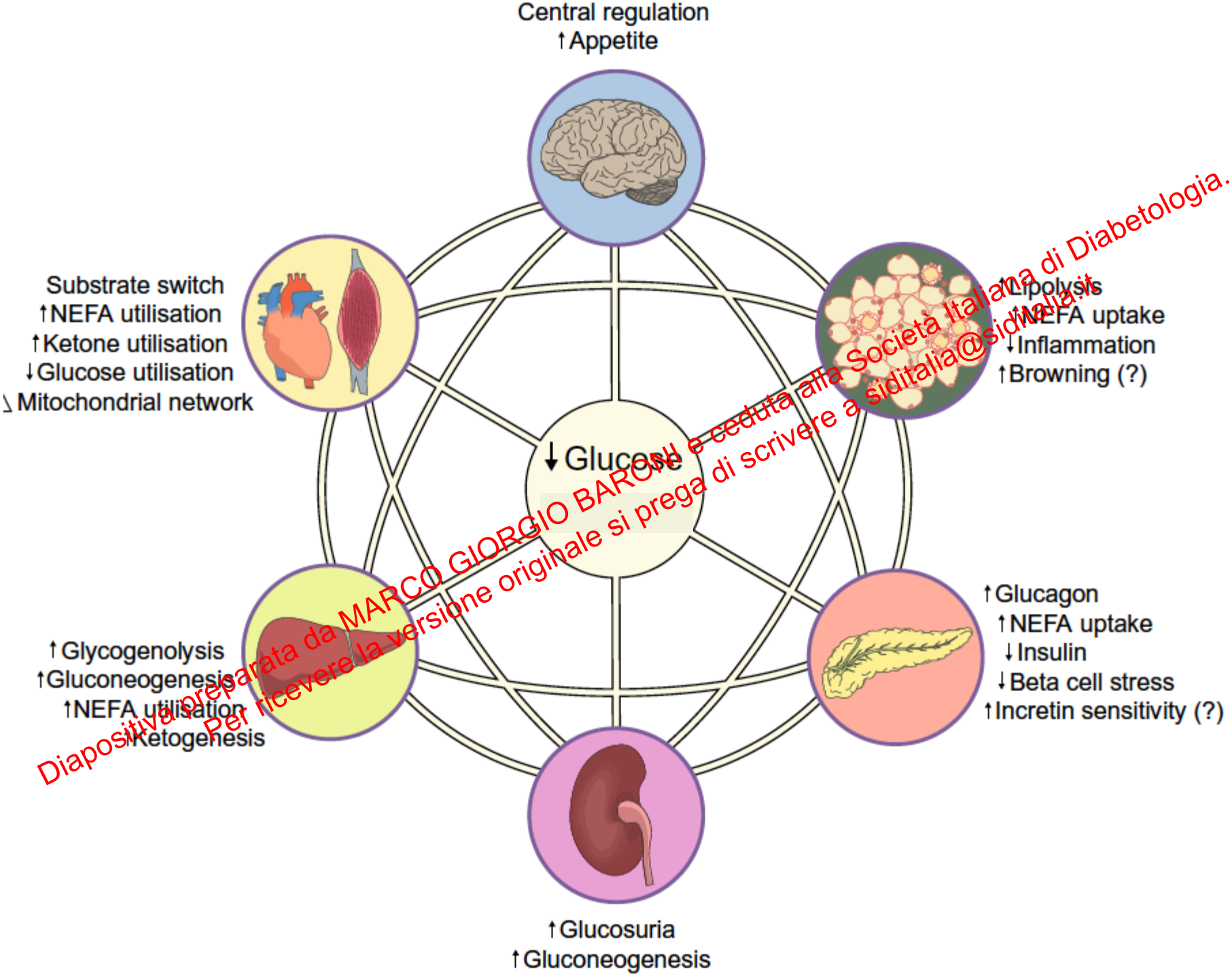






Ferrannini G et al. Diabetes Care 2015



# Future directions

- SGLT2i show renal and cardiovascular glucose-independent beneficial effects
- The rationale for undertaking trials with SGLT2 inhibition in patients who do not have T2D is to take advantage of glucose-independent cardiorenal protective pathways in response to SGLT2 inhibition
- Smaller mechanistic studies in patients with or without T2D are warranted to better define SGLT2 inhibition–mediated mechanisms resulting in clinical cardio-renal benefits:
  - sympathetic nervous system and neurohumoral activation.
  - peripheral arterial disease,
  - obesity,
  - NAFLD,
  - Hypertension,

# Potential medical repurposing for SGLT2i

| Large randomized controlled clinical trials in patients with HF | | | | |
|---|---|---|---|---|
| DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Diabetes Patients With Heart Failure) | Double-blind, placebo-controlled RCT (phase 4) | Dapagliflozin 10 mg daily vs placebo | 12 wk | 250 patients with HF (≥19 y) |
| PRESERVED HF (Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and Preserved Ejection Fraction Heart Failure) | Double-blind, placebo-controlled RCT (phase 4) | Dapagliflozin 10 mg daily vs placebo | 12 wk | 320 patients with HF (≥19 y) |
| DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on Incidence of Worsening Heart failure or Cardiovascular Death in Patients with CHF) | Double-blind, placebo-controlled RCT (phase 3) | Dapagliflozin 10 mg daily vs placebo | 36 mo | 4500 patients with HFrEF (≥18 y) |
| EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) | Double-blind, placebo-controlled RCT (phase 3) | Empagliflozin 10 mg daily vs placebo | 38 mo | 4126 patients with HFpEF (≥18 y) |
| EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) | Double-blind, placebo-controlled RCT (phase 3) | Empagliflozin 10 mg daily vs placebo | 38 mo | 2850 patients with HFrEF (≥18 y) |



*Circulation.* 2017;136:1643–1658.