

SGLT2i :
Farmaci cardio-
metabolici
ma non solo

Giuseppe Paolisso

*Università degli Studi della
Campania «Luigi Vanvitelli»*

Napoli

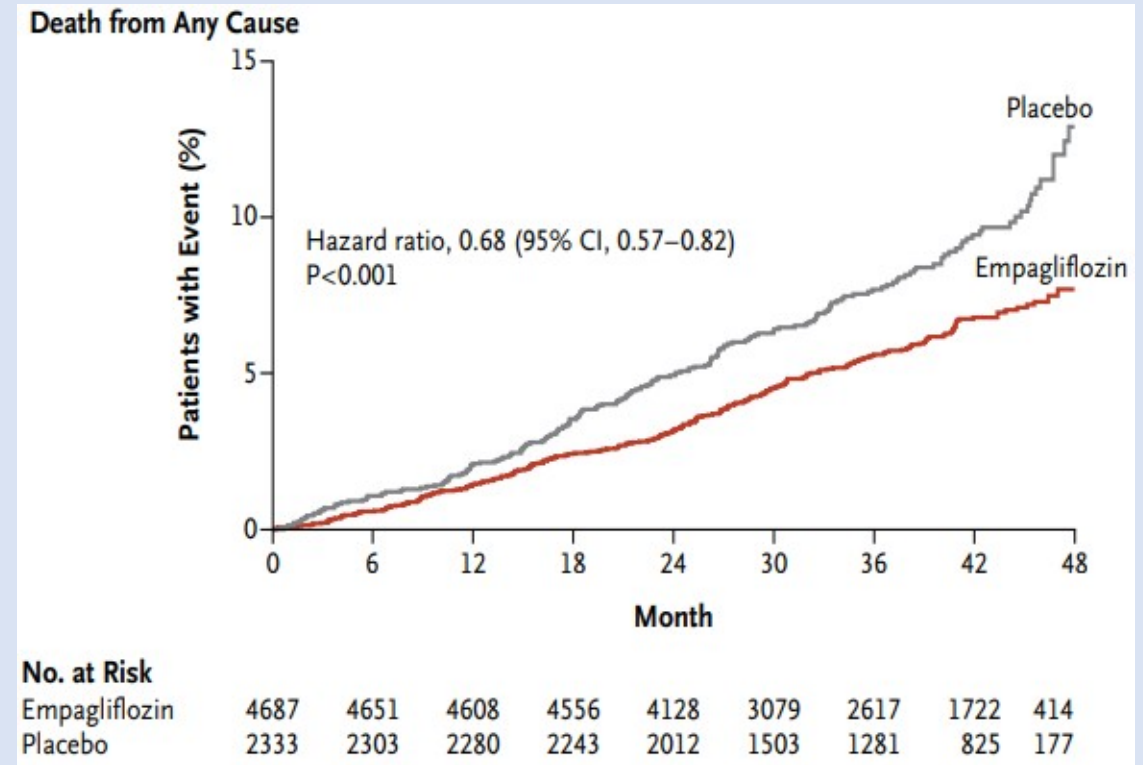
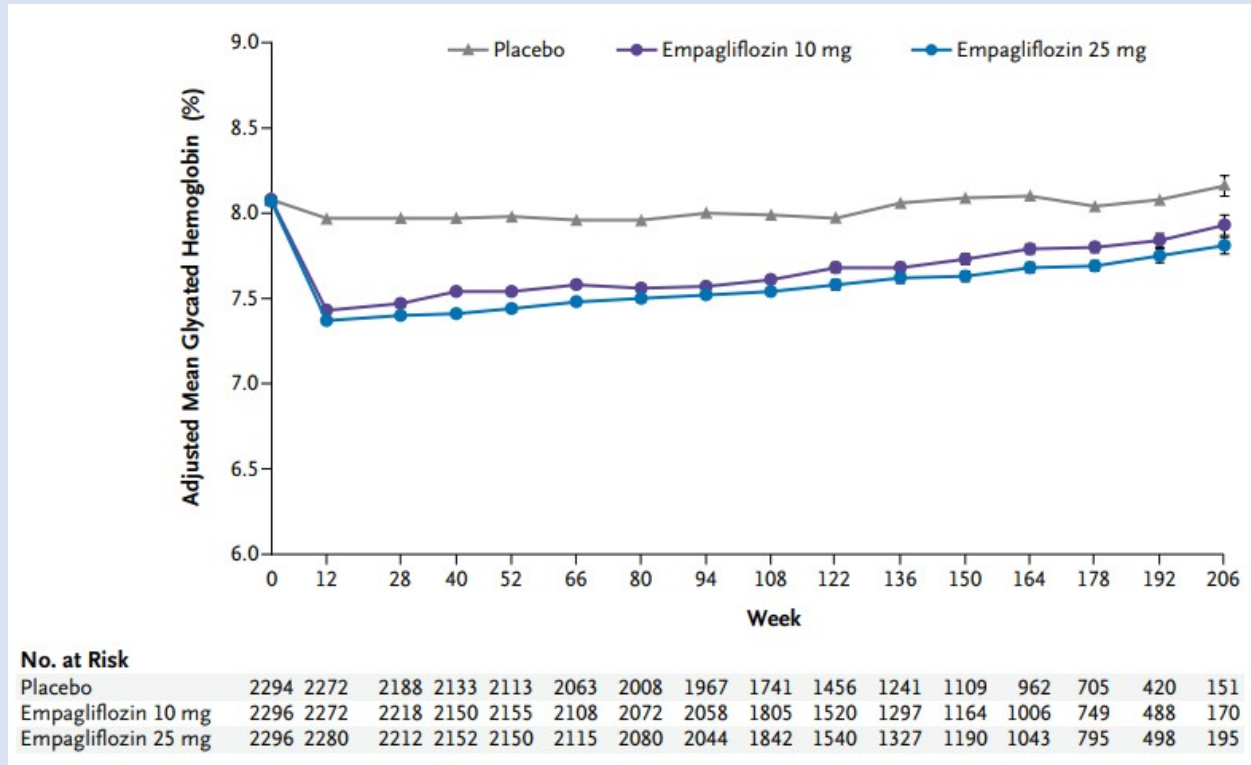


Financial Disclosure

- Il prof Giuseppe Paolisso dichiara di aver NON ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche interessate alla tematica oggetto della presentazione
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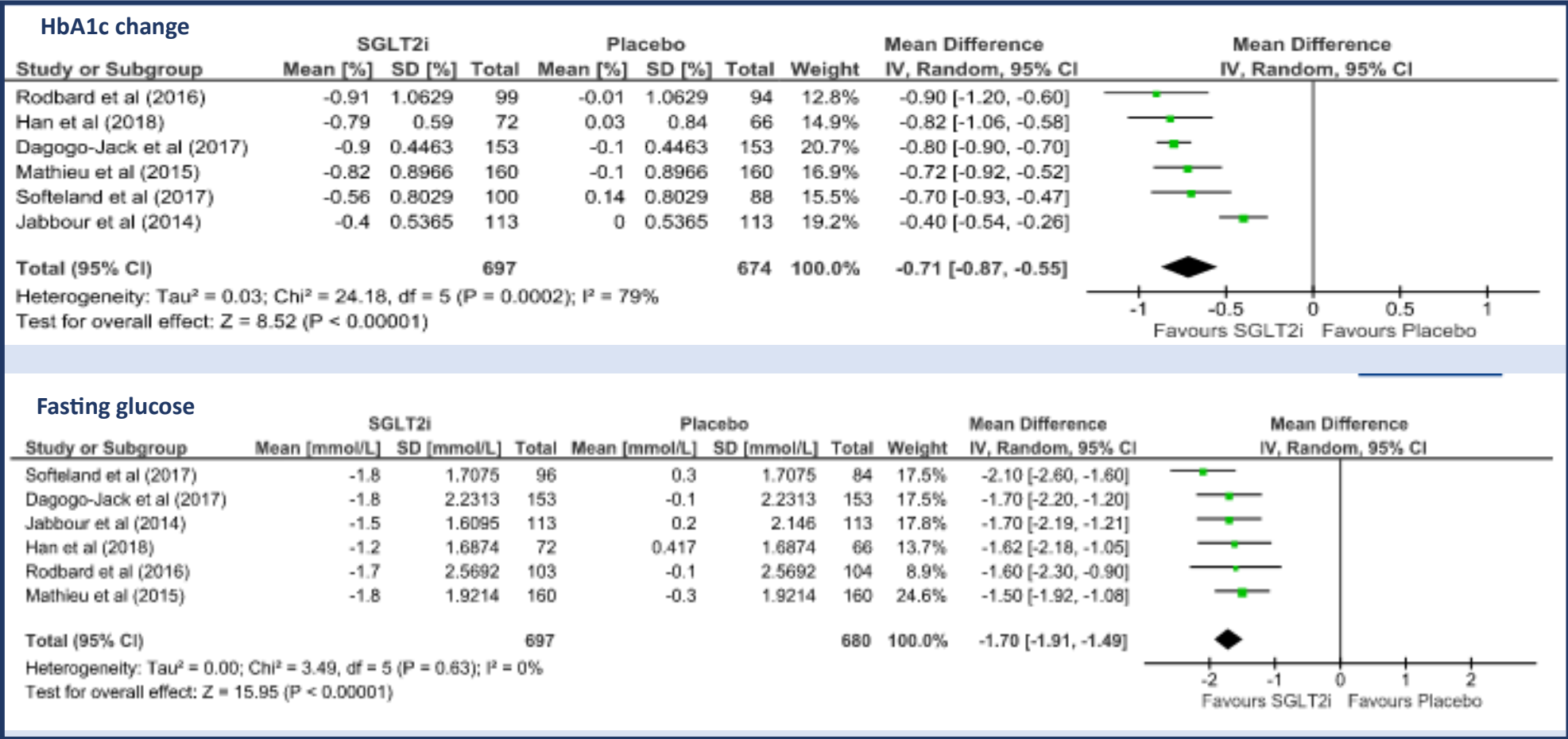


Empagliflozin, Metabolic Outcomes, and Mortality in Type 2 Diabetes: The EMPA-REG study



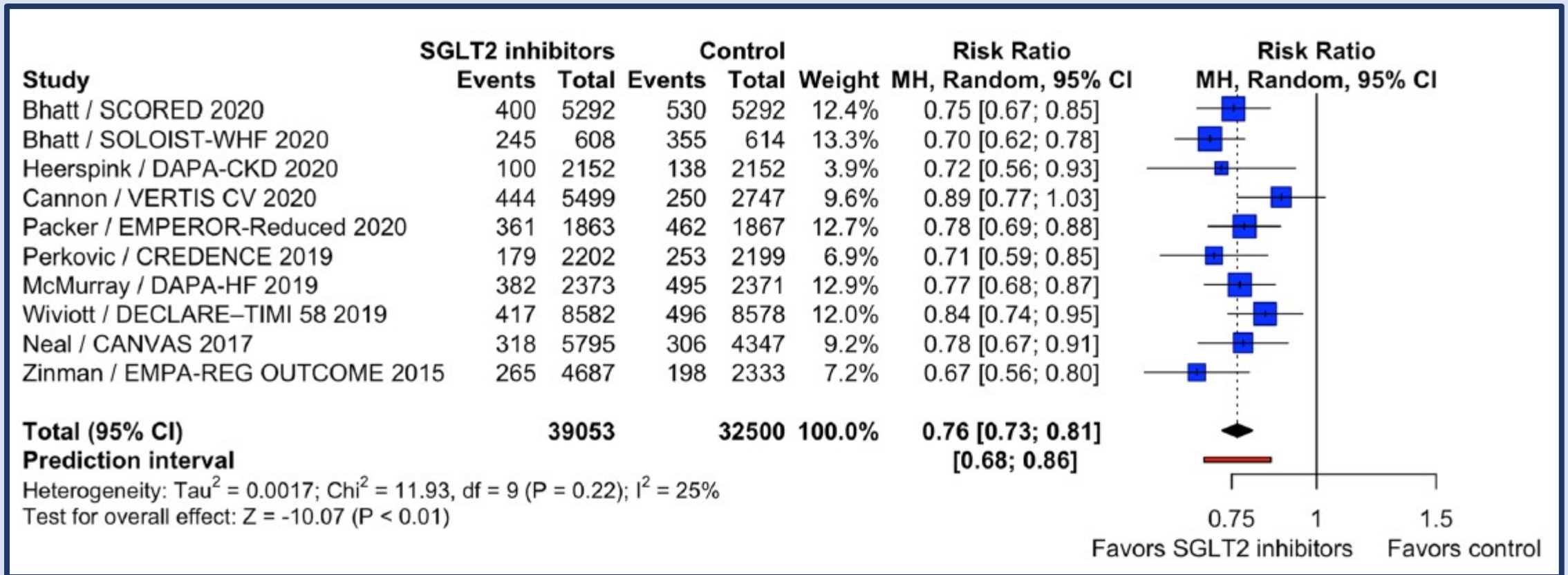
Bernard Zinman et al., N Engl J Med 373;22, November 26, 2015

Clinical trials on the effect of SGLT-2 inhibitors on metabolic compensation



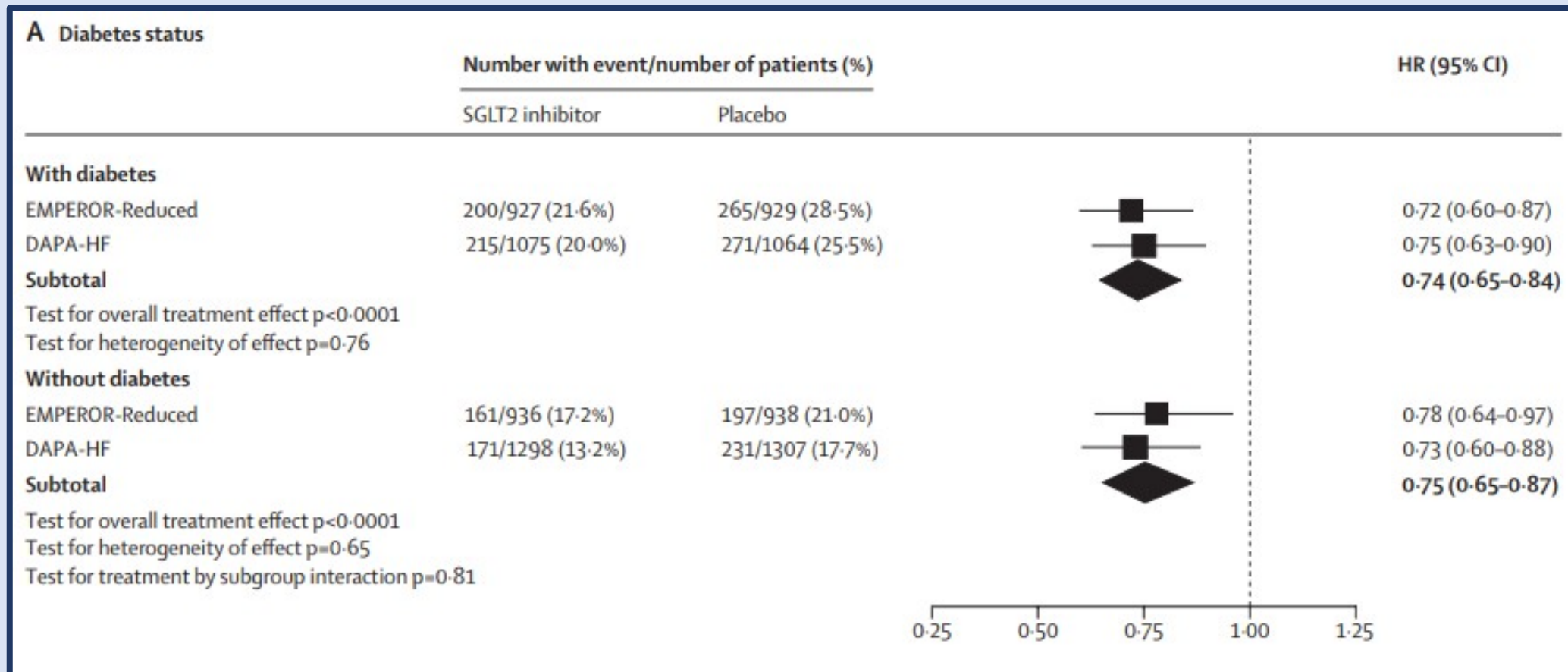
Forest plot showing the estimated HbA1c and fasting glucose change from baseline SGLT2 inhibitor vs placebo as add-on to metformin plus a dipeptidyl peptidase-4 (dpp-4) inhibitor.

Clinical trials on the effect of SGLT2 inhibitors on cardiovascular outcome



Forest plot illustrating the results of the composite of HF hospitalization and cardiovascular mortality outcome

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

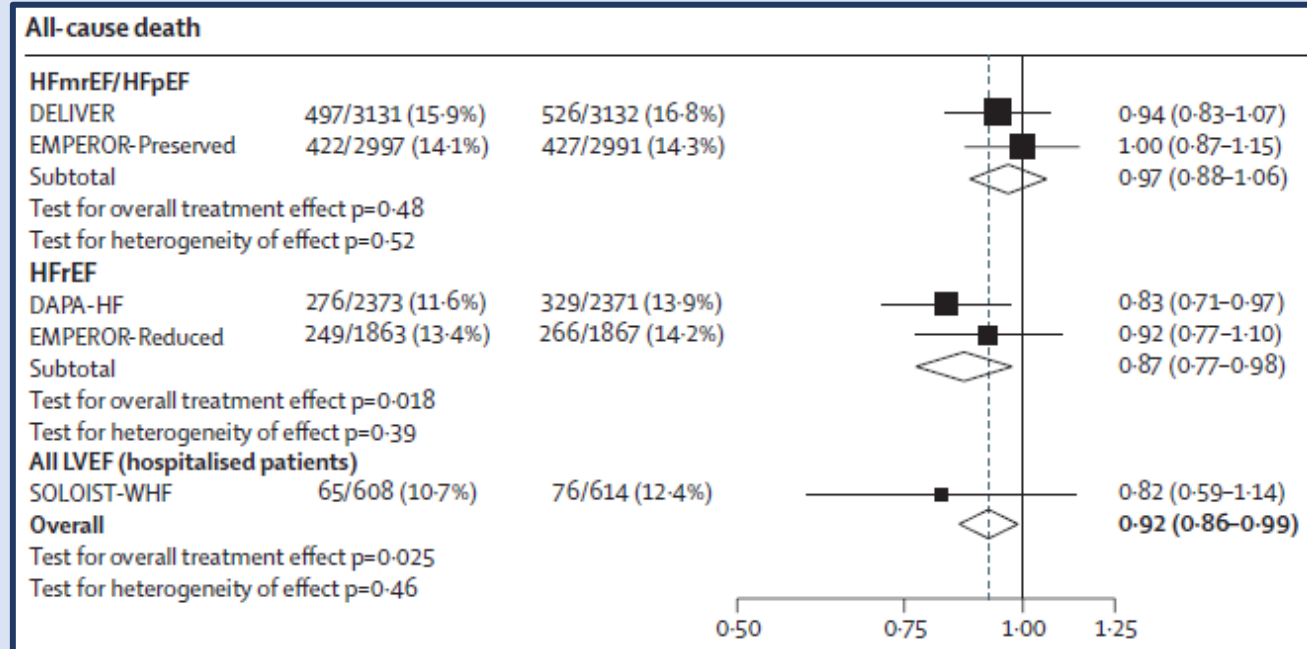
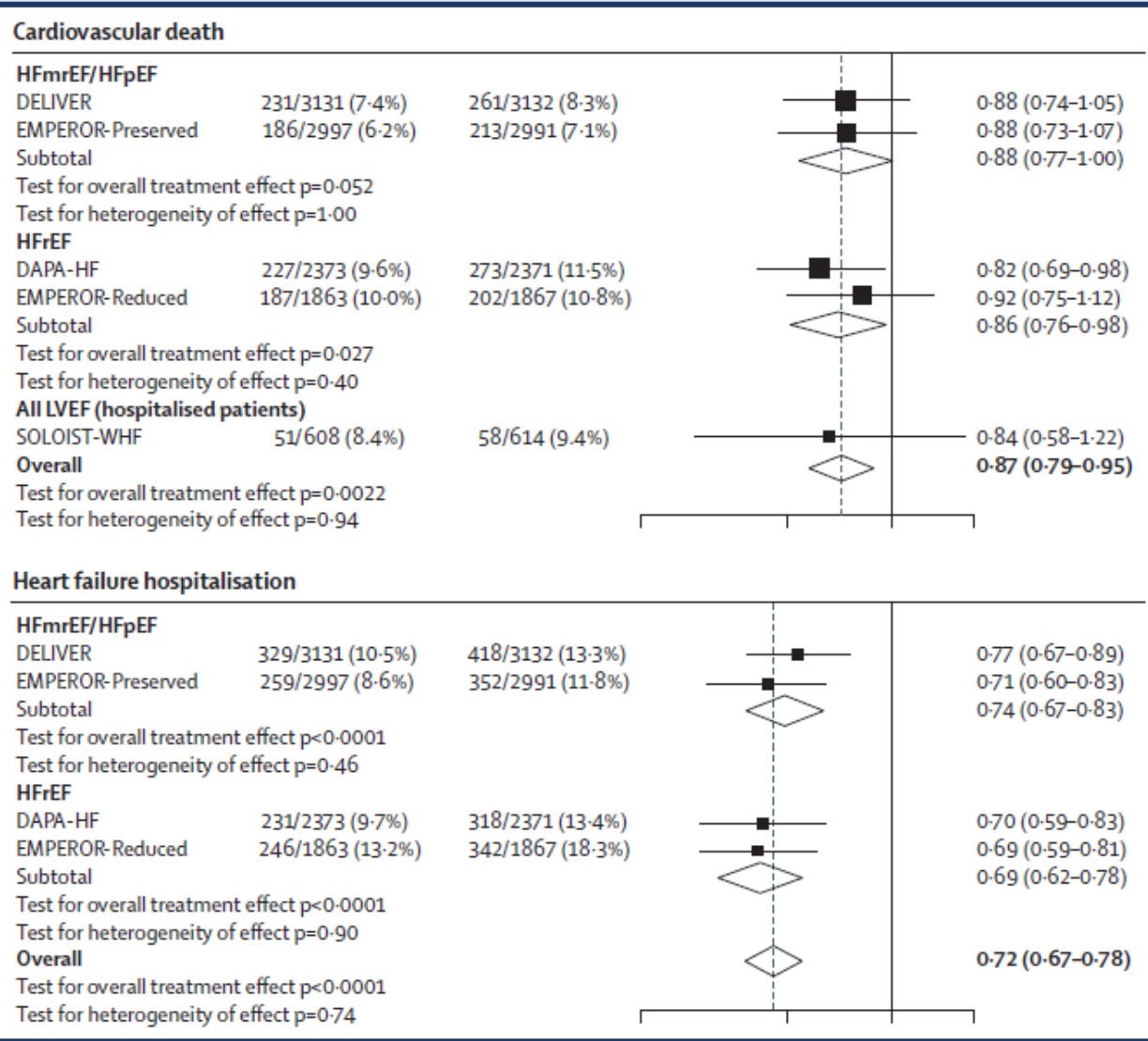


Empagliflozin in Heart Failure with a preserved Ejection Fraction

Subgroup	Empagliflozin <i>no. of patients with events/total no.</i>	Placebo <i>no. of patients with events/total no.</i>	Hazard Ratio (95% CI)
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

Stefan D. Anker et al. N ENGL J MED 385;16 nejm.org October 14, 2021

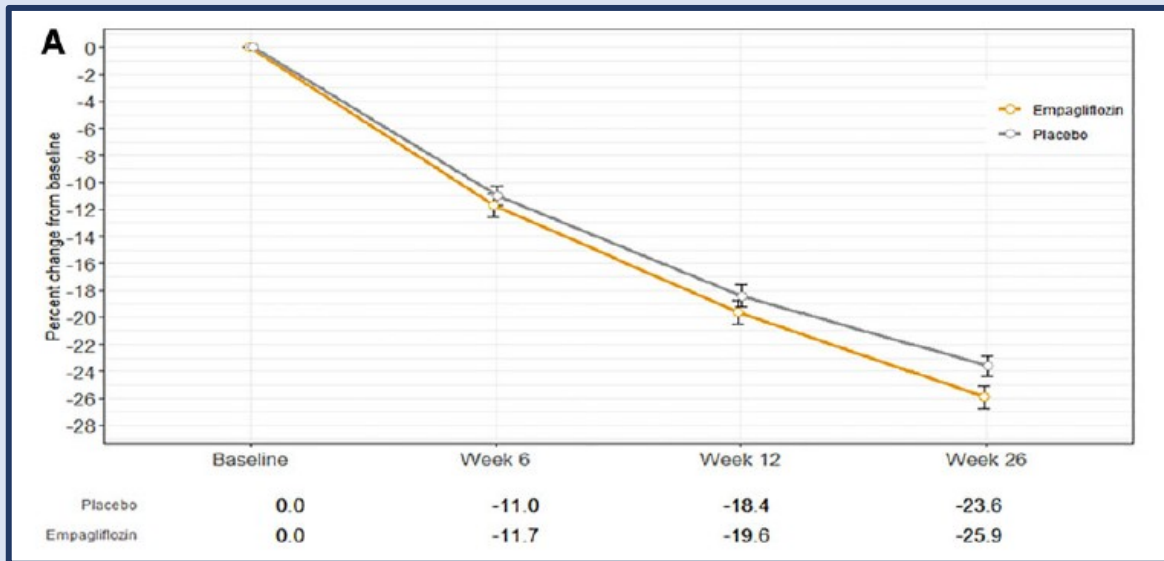
SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials



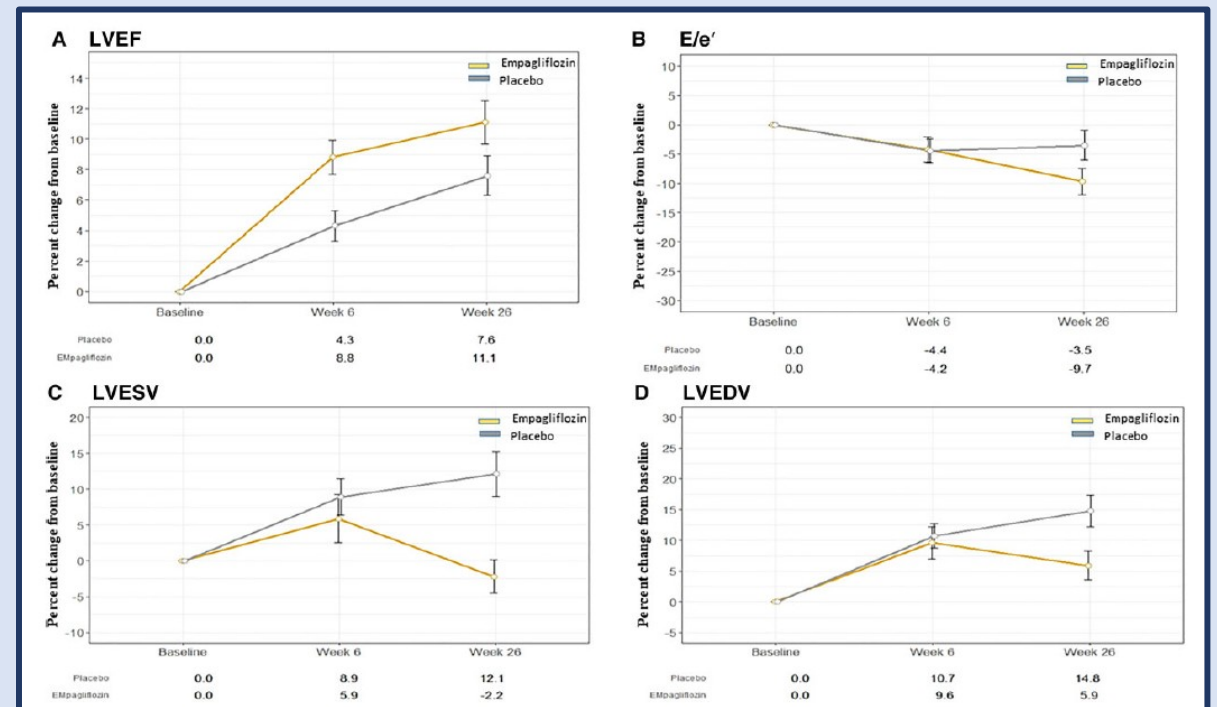
Muthiah Vaduganathan et al., Lancet 2022; 400: 757-67

Empagliflozin in acute Myocardial Infarction: the EMMY trial

Decline in NT-proBNP concentration



Changes in echocardiographic parameters



Infarct Size, Inflammatory Burden, And Admission Hyperglycemia In Diabetic Patients With Acute Myocardial Infarction Treated With SGLT2-inhibitors: Insights From A Multicenter International Registry

Table 3 Infarct size in patients with SGLT2-I versus patients with other OAD agents alone

	Total (N = 583)	SGLT2-I users (N = 98)	Non-SGLT-I users (N = 485)	p value
Hospital Admission				
Q wave, n (%)	131 (25.2)	18 (23.4)	113 (25.6)	0.615
Admission LVEDV, ml	108 ± 33	106 ± 35	108 ± 33	0.582
Admission LVEF, %	47 ± 11	48 ± 10	47 ± 11	0.161
RWMA, n (%)	491 (84.2)	81 (82.7)	410 (84.5)	0.641
I hs-Tnl, ng/L	210 [44–1431]	131 [33–773]	240 [50–1964]	0.003
II hs-Tnl, ng/L	1411 [338–10.032]	635 [165–2108]	1842 [370–13.447]	<0.001
III hs-Tnl, ng/L	1306 [390–11.028]	441 [160–1120]	2356 [566–18.056]	<0.001
hs-Tnl max, ng/L	2438 [591–16.227]	901 [307–2543]	3445 [710–9223]	<0.001
Hospital Discharge				
LVEDV, ml	108 ± 36	103 ± 29	110 ± 38	0.261
LVEF, %	49 ± 10	53 ± 19	48 ± 11	0.001
RWMA, n (%)	454 (78)	64 (65.3)	390 (80.6)	0.001
ST resolution, n (%)	187 (67)	42 (87.5)	146 (63.2)	0.001

Continuous variables are presented as median (IQR) while categorical ones as n (%). Hs-Tnl: High sensitivity Troponin; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; RWMA: Regional wall motion abnormalities

SGLT2-I, Hyperglycemia, Inflammation, Infarct size, Acute myocardial infarction: Data from the observational registry: SGLT2-I AMI PROTECT

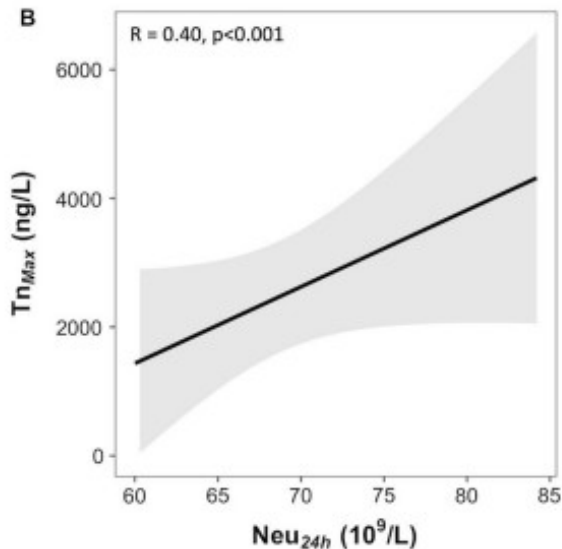
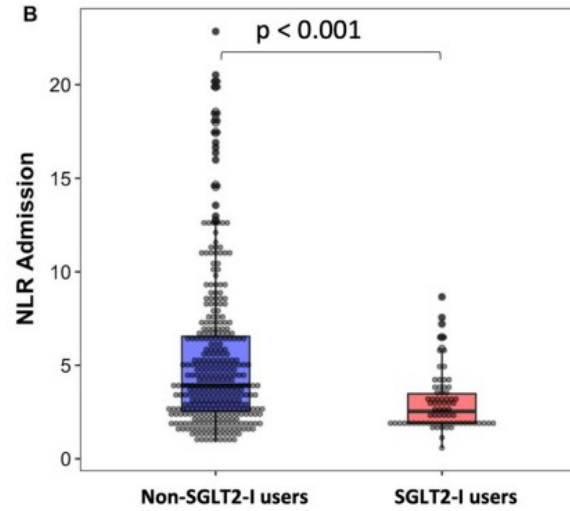
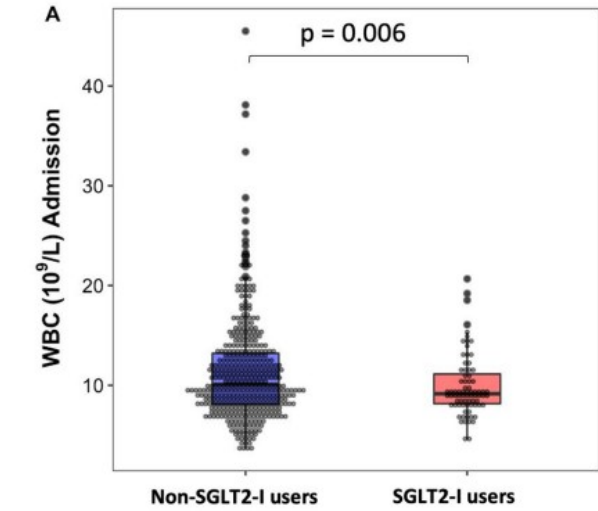
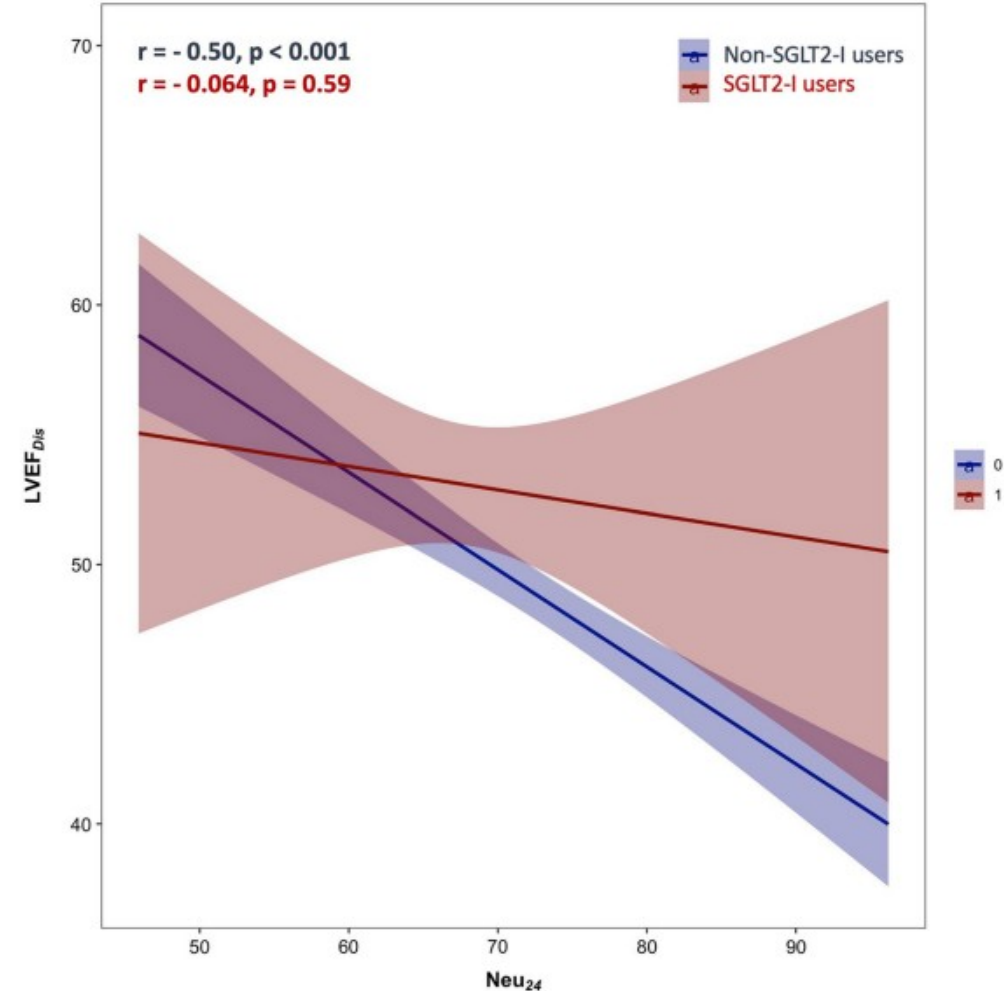
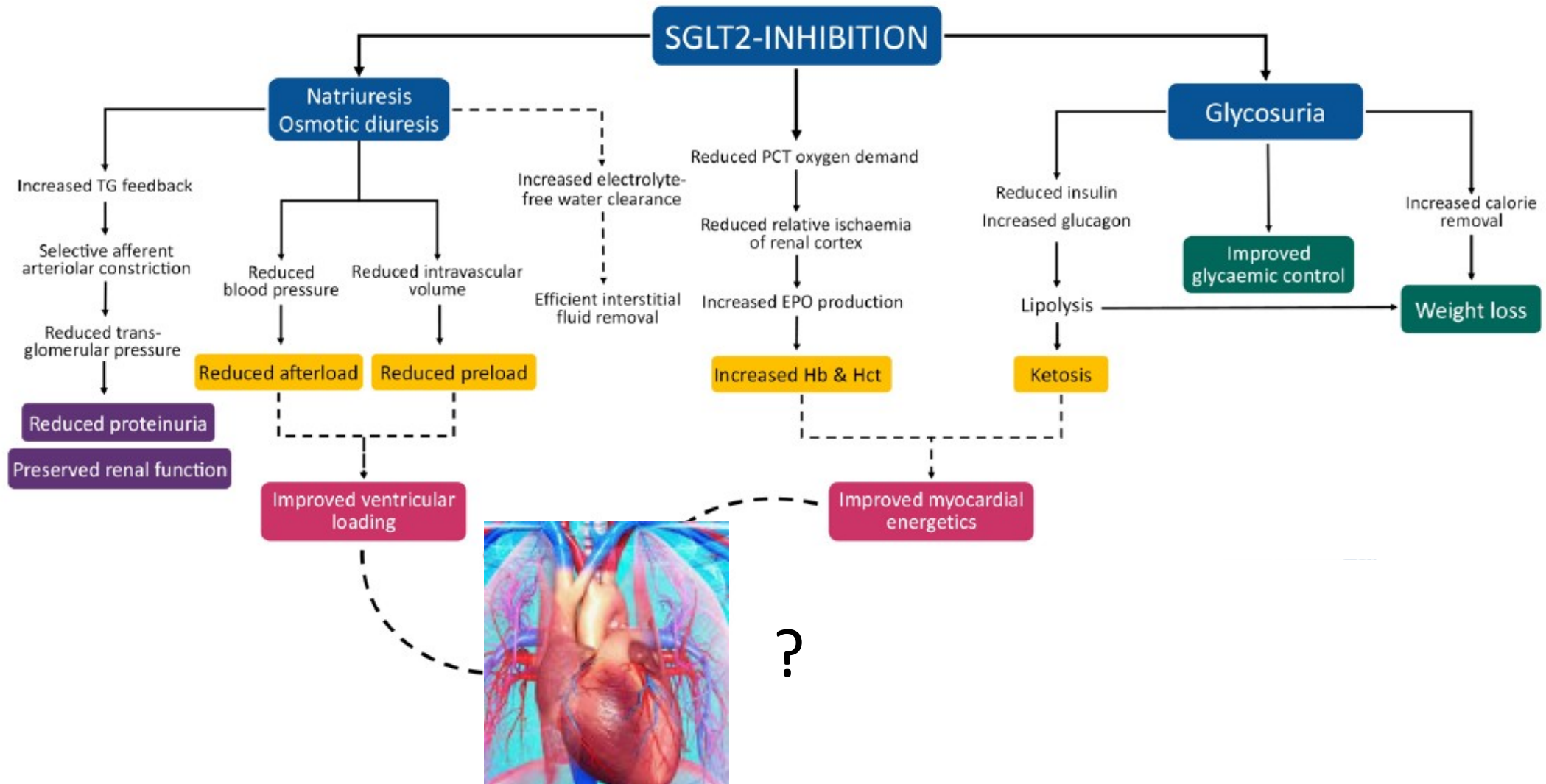


Table 5 Multivariable analysis – Predictors of inflammatory response

Variables	Std. Err.	OR	95% CI	p-value
Age, years	0.009	1.011	0.994–1.028	0.197
Adm. Creatinine, mg/dL	0.152	1.333	0.990–1.796	0.060
Admission glycemia, mg/dL	0.001	1.002	1.000–1.004	0.100
NSTEMI	0.209	1.702	1.129–2.566	0.011
hs-TnI max, ng/L	0.001	1.008	1.001–1.015	0.025
SGLT2-I	0.259	0.457	0.275–0.758	0.002



Mechanims of cardiovascular benefits:



Improved CV Outcomes

SGLT2-inhibitors: more than just extracardiac effects

Optimizing myocardial oxygen supply/demand

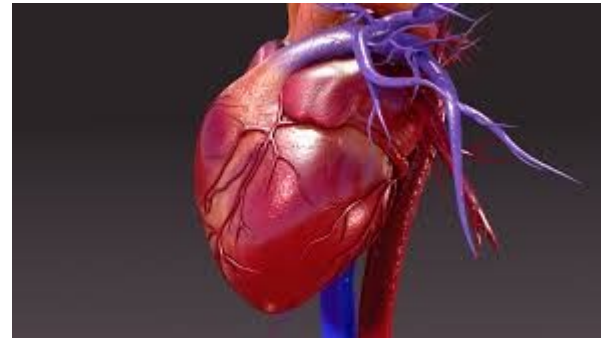
- Enhance myocardial energy metabolism
- Improve coronary microcirculation
- Increase hematocrit level
- Decrease inflammation and oxidative stress

Myocardial cellular hemostasis

- **Inducing autophagy**
Activate AMPK, SIRT1, and HIF-1 α , all of which are integral to autophagy
- **Reducing oxidative stress**
Increase the level of antioxidant enzymes (e.g., SOD) and decreases oxidation products (e.g., lipid hydroperoxide, NOX4)

Electrophysiological effects

- Decrease SNS activity and increase PSN activity
- Improve sodium and calcium homeostasis by inhibiting late- I_{Na} and NHE1 activity



Optimizing mitochondrial energy metabolism

- Increase ketone body levels upregulate fatty acid β -oxidation
- Inhibit the switch from fatty acid oxidation to glycolysis
- Decrease myocardial glucose uptake
- Counteract age-related disruption in mitochondrial/sarcoplasmic reticulum Ca^{2+} homeostasis

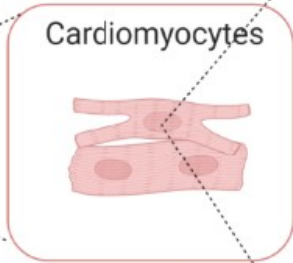
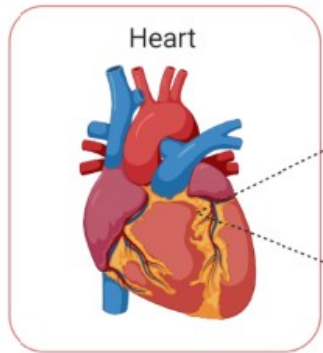
Attenuating inflammation

- Decrease the plasma levels of TNFR1, MMP7, IL-6, and FN1
- Decrease the activity of NLRP3 inflammasome
- Decrease the upregulation of Tnfrsf12a

Improving microvascular circulation

- Increase serum L-arginine /asymmetric dimethyl arginine ratio
- Increase nitric oxide bioavailability

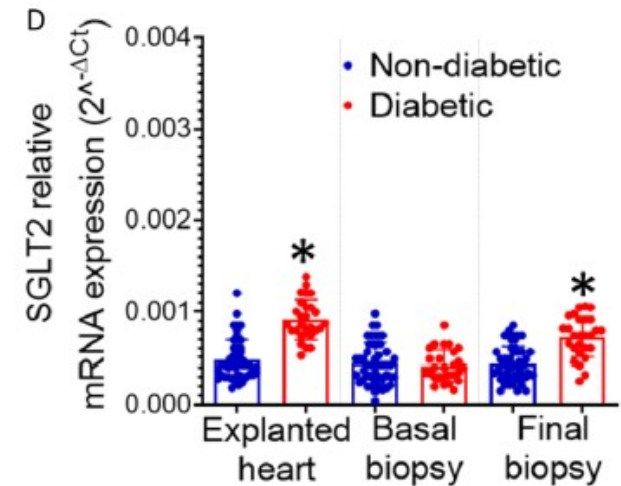
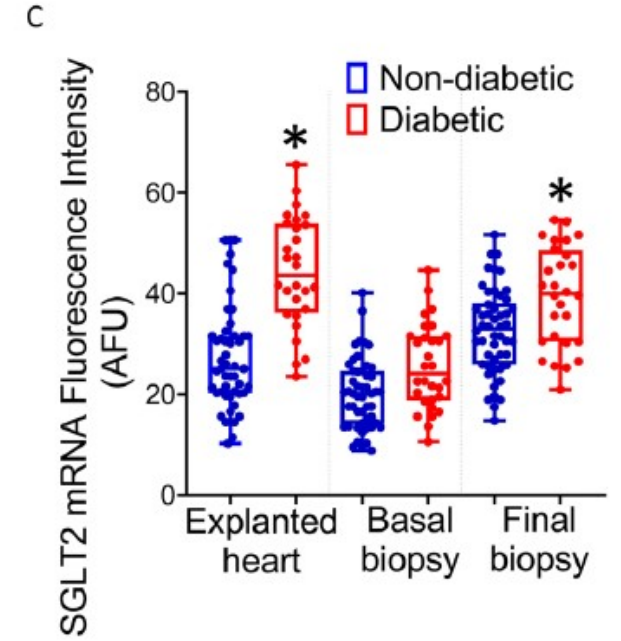
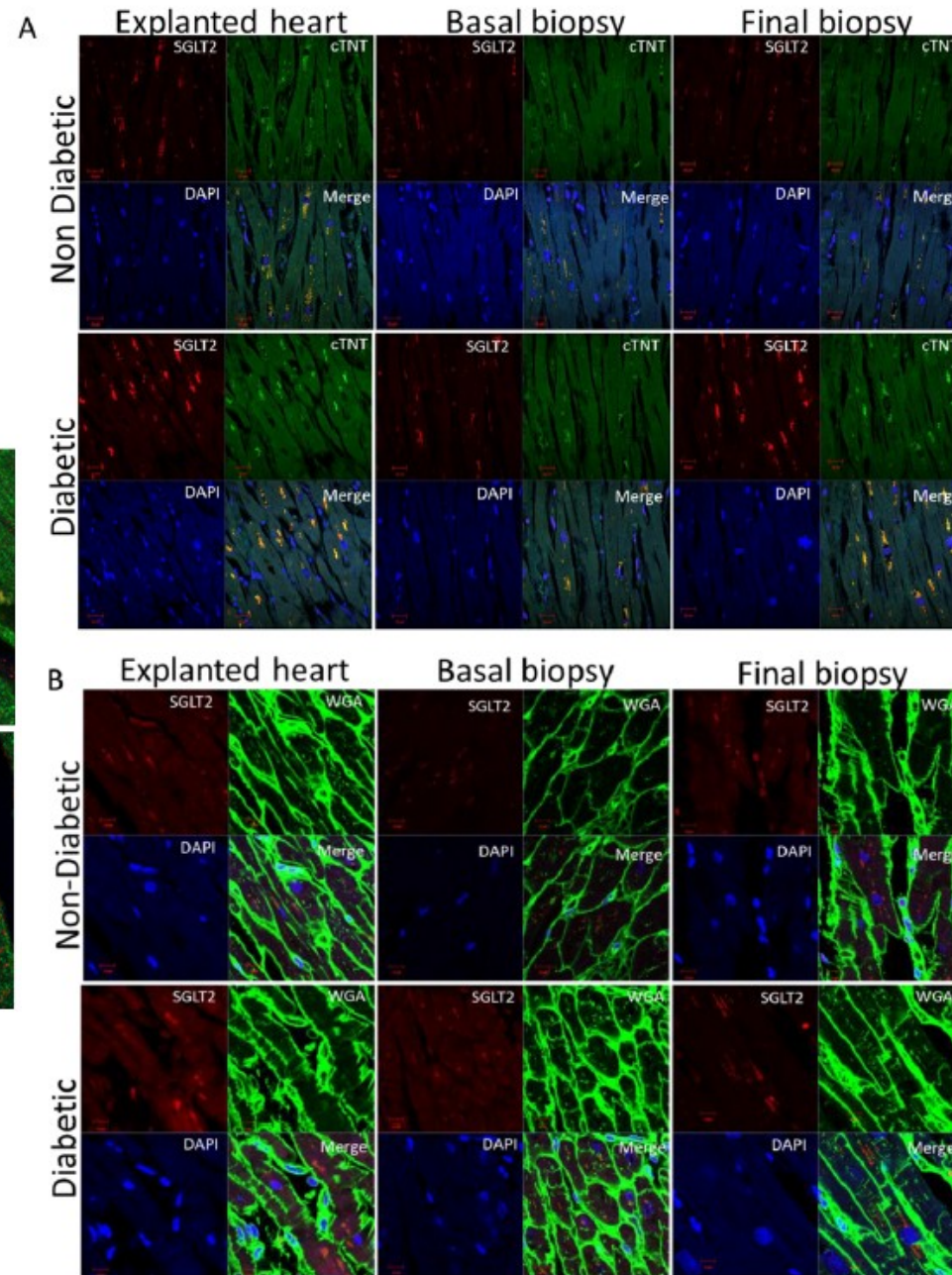
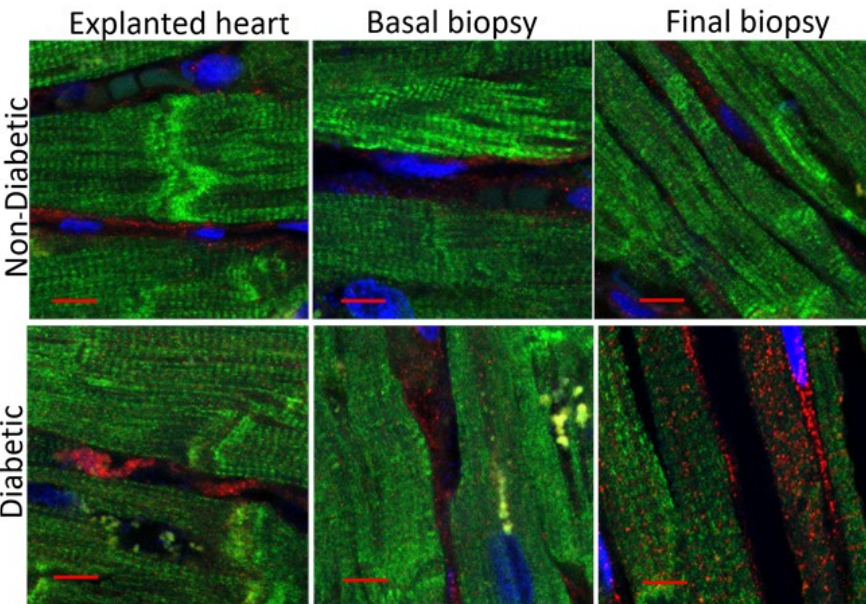
Controversial results on SGLT2 expression in cardiomyocytes



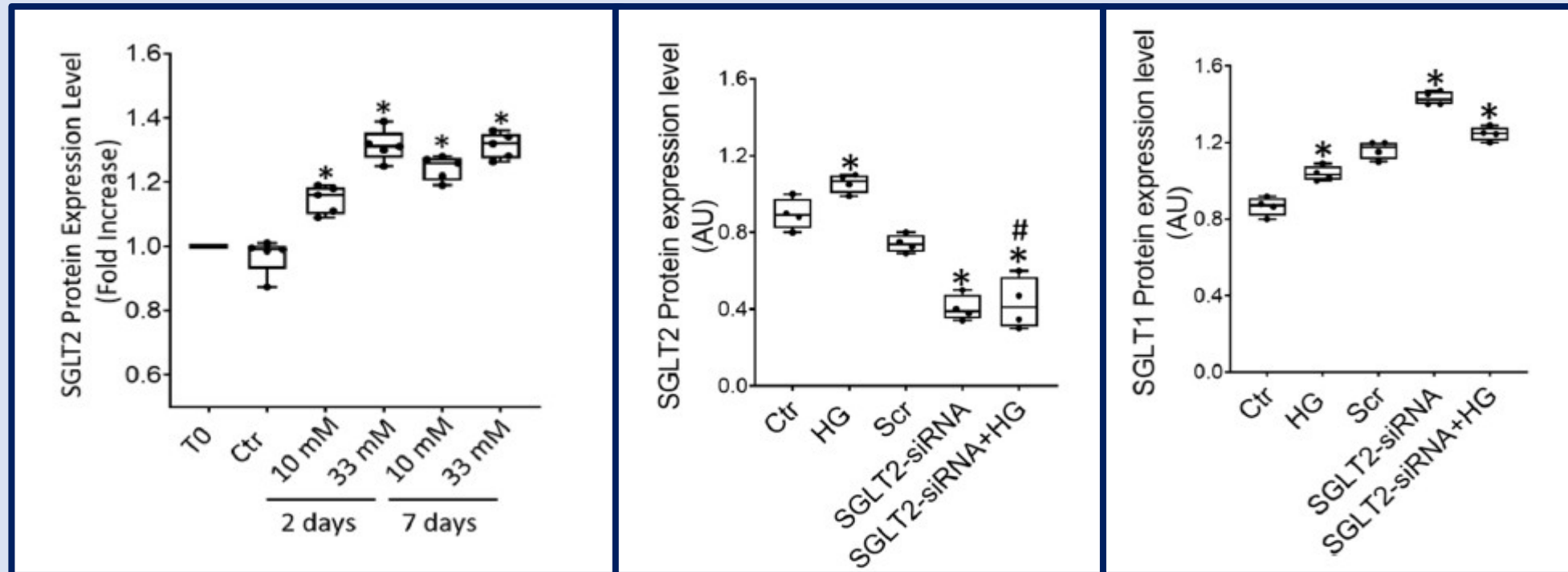
**SGLT-2 IS
NOT EXPRESSED OR
UNDETECTED**



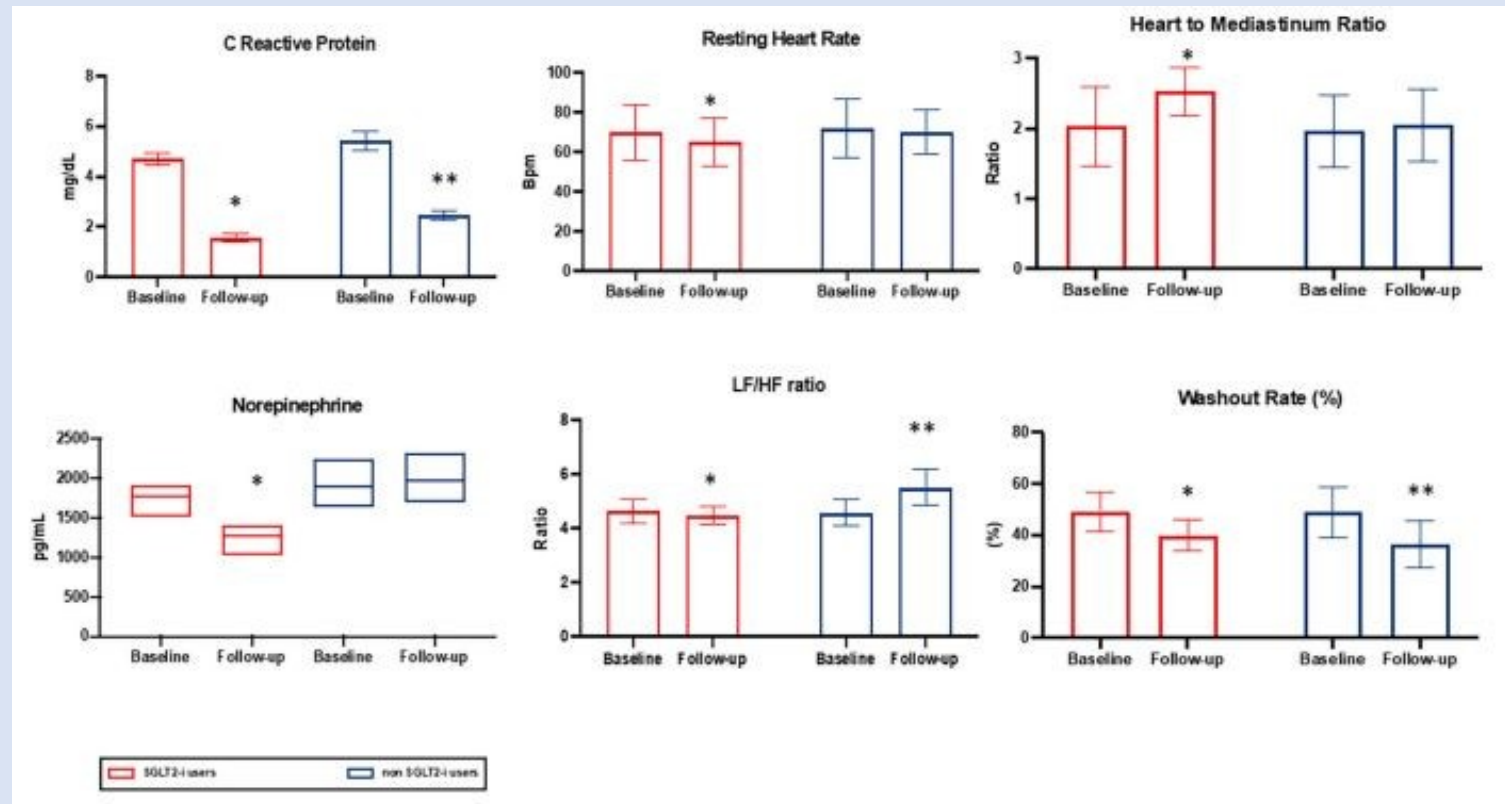
SGLT2 protein localization in human cardiomyocyte



SGLT2 protein expression in human cardiomyocyte cell line exposed to high glucose concentration

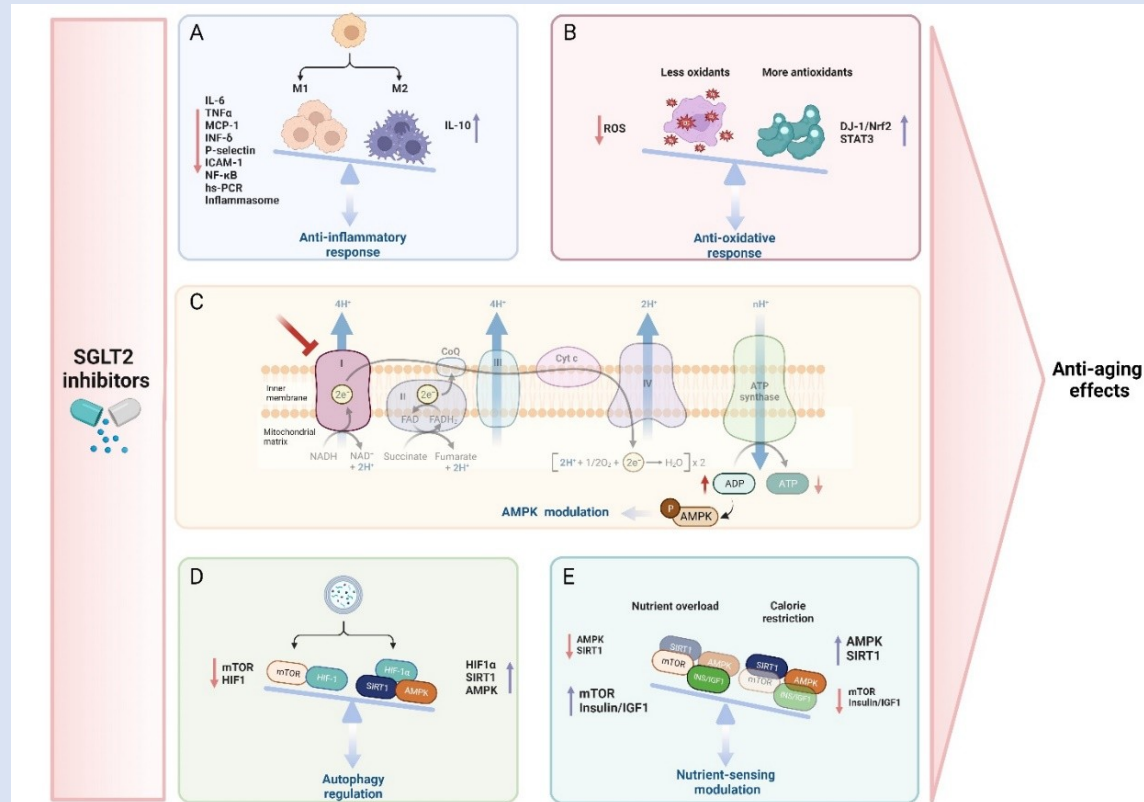


SGLT2-inhibitors reduce the cardiac autonomic neuropathy dysfunction and vaso-vagal syncope recurrence in patients with type 2 diabetes mellitus: the SCAN study



SGLT2-I users at 1 year follow-up showed a significant reduction of CRP, serum norepinephrine, HR, LF/HFratio, WHR and a significant increase of Heart to Mediastinum Ratio; the Non-SGLT2-I users exhibited a significant reduction of CRP and WHR, with a significant increase of LF/ HF ratio.

Anti-aging cellular effects of SGLT2 inhibitors



Take Home Messages

1. SGLT-2 inhibitors were born as drugs for diabetes but we can now consider them «ALSO drugs for diabetes»
2. Their protective effects at the cardiovascular level are well proven.
3. Extracardiac molecular mechanisms seem to be very well defined (mainly the anti-inflammatory action)
4. Cardiomyocyte SGLT2 expression is mainly detectable in presence of myocardial structural and functional impairment.
5. There are several evidences for a more HUGE effect of SGLT2 inhibitors than ones reported at cardiovascular level

