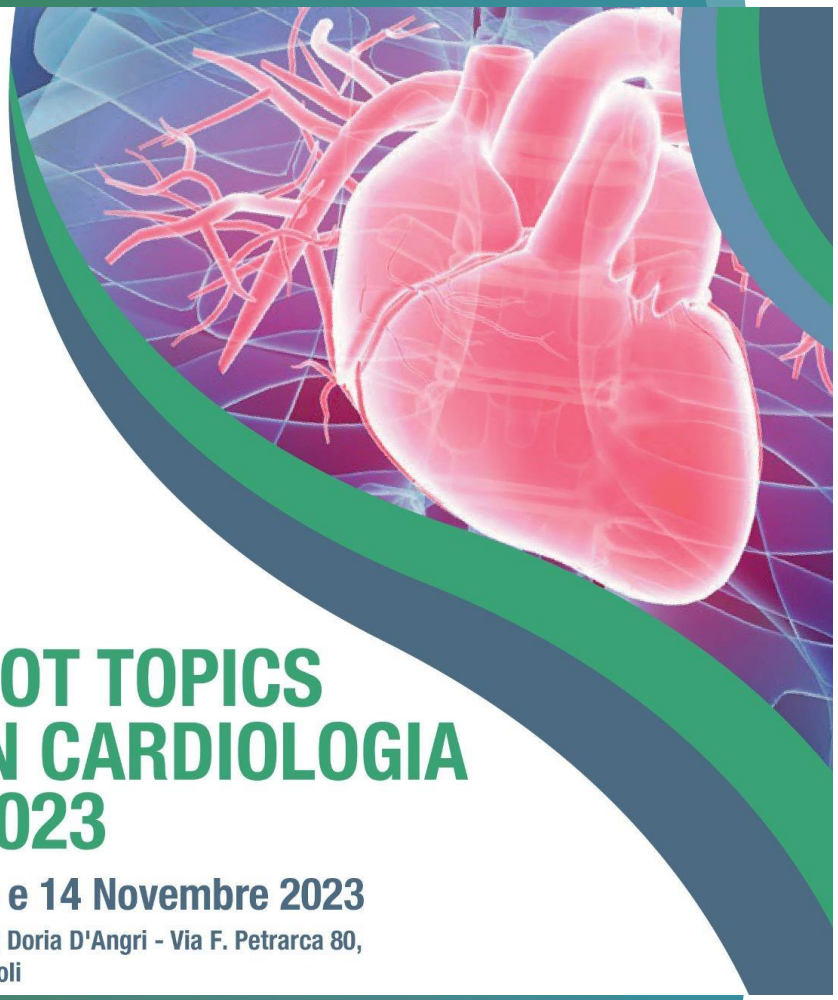


HOT TOPICS IN CARDIOLOGIA 2023

13 e 14 Novembre 2023

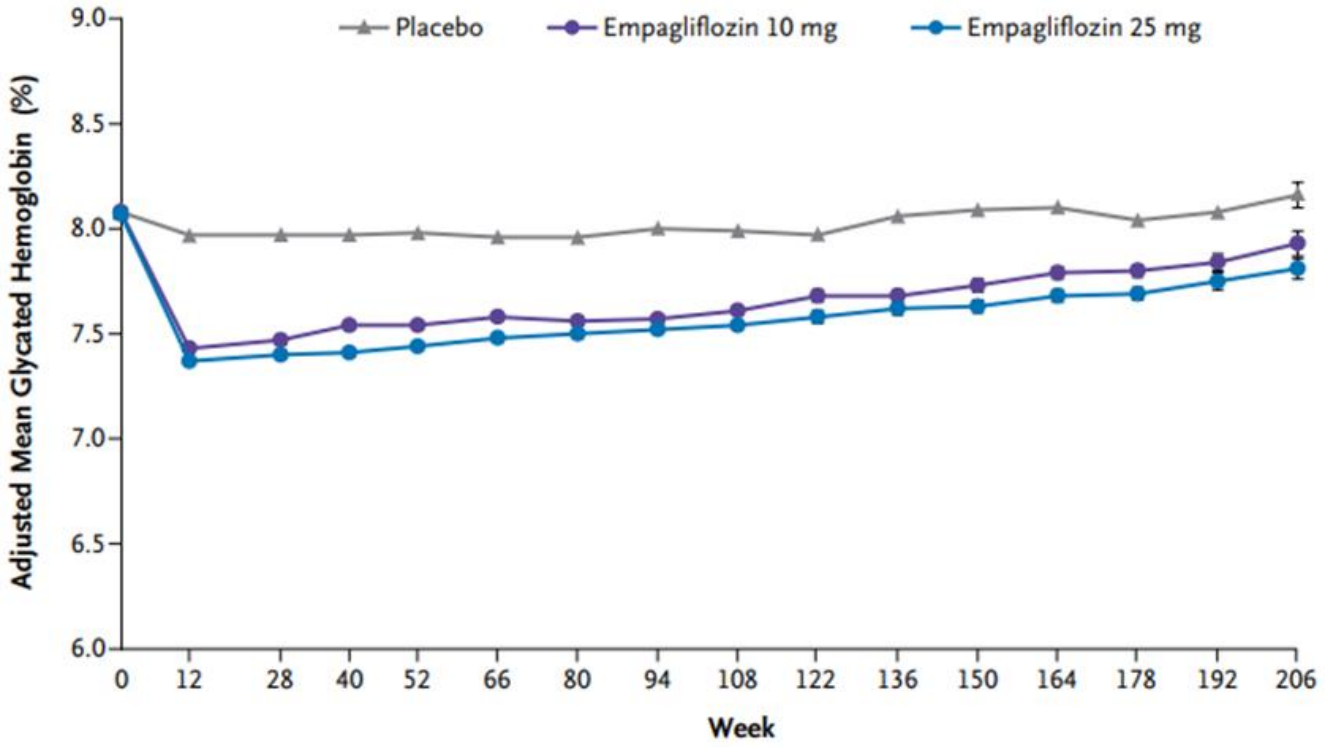
Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

Glifozine in prima linea contro lo scompenso

Raffaele Marfella

Link
profitable solutions

Clinical trials on the effect of SGLT2 on metabolic compensation



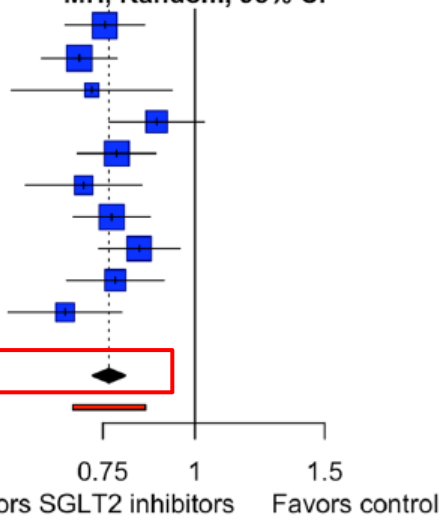
No. at Risk																
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Studi di efficacia sulle malattie cardiovascolari in pazienti diabetici

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

Study	SGLT2 inhibitors Events	Total	Control Events	Total	Weight	Risk Ratio MH, Random, 95% CI
Bhatt / SCORED 2020	400	5292	530	5292	12.4%	0.75 [0.67; 0.85]
Bhatt / SOLOIST-WHF 2020	245	608	355	614	13.3%	0.70 [0.62; 0.78]
Heerspink / DAPA-CKD 2020	100	2152	138	2152	3.9%	0.72 [0.56; 0.93]
Cannon / VERTIS CV 2020	444	5499	250	2747	9.6%	0.89 [0.77; 1.03]
Packer / EMPEROR-Reduced 2020	361	1863	462	1867	12.7%	0.78 [0.69; 0.88]
Perkovic / CREDENCE 2019	179	2202	253	2199	6.9%	0.71 [0.59; 0.85]
McMurray / DAPA-HF 2019	382	2373	495	2371	12.9%	0.77 [0.68; 0.87]
Wiviott / DECLARE–TIMI 58 2019	417	8582	496	8578	12.0%	0.84 [0.74; 0.95]
Neal / CANVAS 2017	318	5795	306	4347	9.2%	0.78 [0.67; 0.91]
Zinman / EMPA-REG OUTCOME 2015	265	4687	198	2333	7.2%	0.67 [0.56; 0.80]
Total (95% CI)		**39053**		**32500**	**100.0%**	**0.76 [0.73; 0.81]**
Prediction interval						**[0.68; 0.86]**

Heterogeneity: $Tau^2 = 0.0017$; $Chi^2 = 11.93$, df = 9 (P = 0.22); $I^2 = 25\%$
Test for overall effect: Z = -10.07 (P < 0.01)

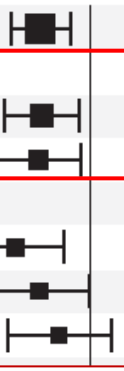


Heart Failure Reviews
https://doi.org/10.1007/s10741-021-10083-z

The NEW ENGLAND JOURNAL of MEDICINE

Empagliflozin in Heart Failure

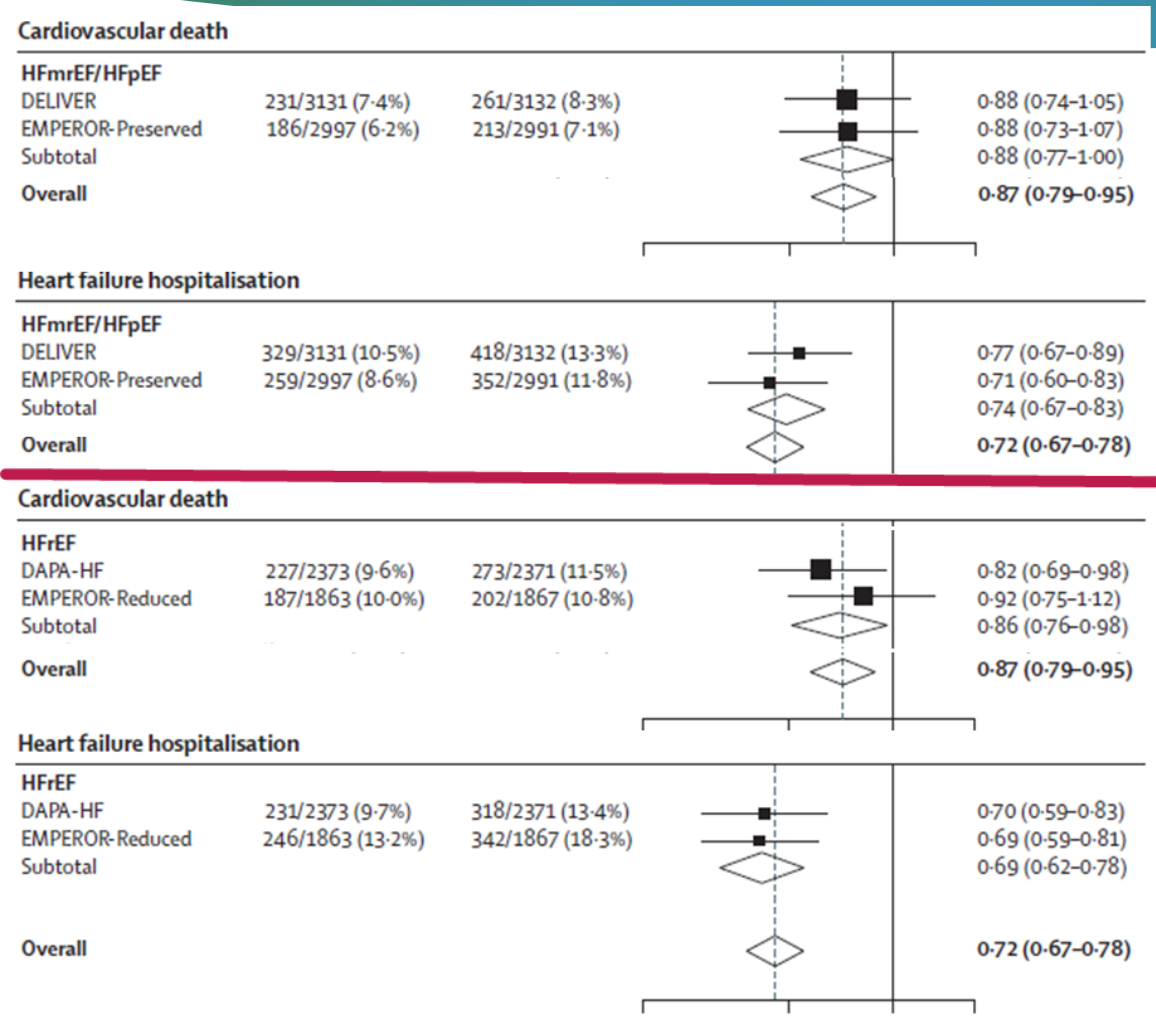
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50%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



N ENGL J MED 385;16 nejm.org October 14, 2021

Lancet 2022; 400: 757–67

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

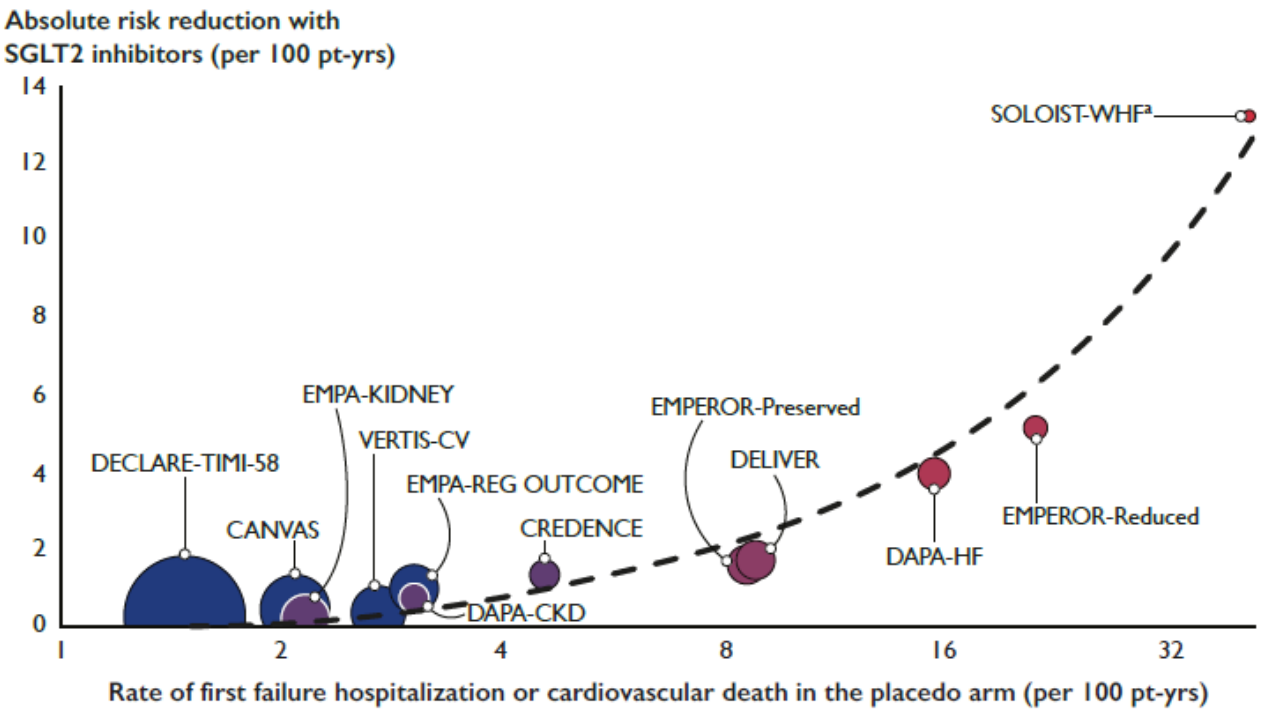


HFmrEF/HFpEF: **-23%**

HFrEF:**-28%**

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

High risk T2DM	CKD	Chronic HFpEF	Chronic HFrEF	Worsening HF
ARR: 0.25–1.04 per 100 pt-yrs	ARR: 0.80–1.39 per 100 pt-yrs	ARR: 1.8 per 100 pt-yrs	ARR: 3.9–5.2 per 100 pt-yrs	ARR: 10.4 per 100 pt-yrs
NNT: 96–400 RRR: 12%–34%	NNT: 72–125 RRR: 29%–31%	NNT: 59 RRR: 21%	NNT: 21–36 RRR: 25%	NNT: 10 RRR: 129%



ESC

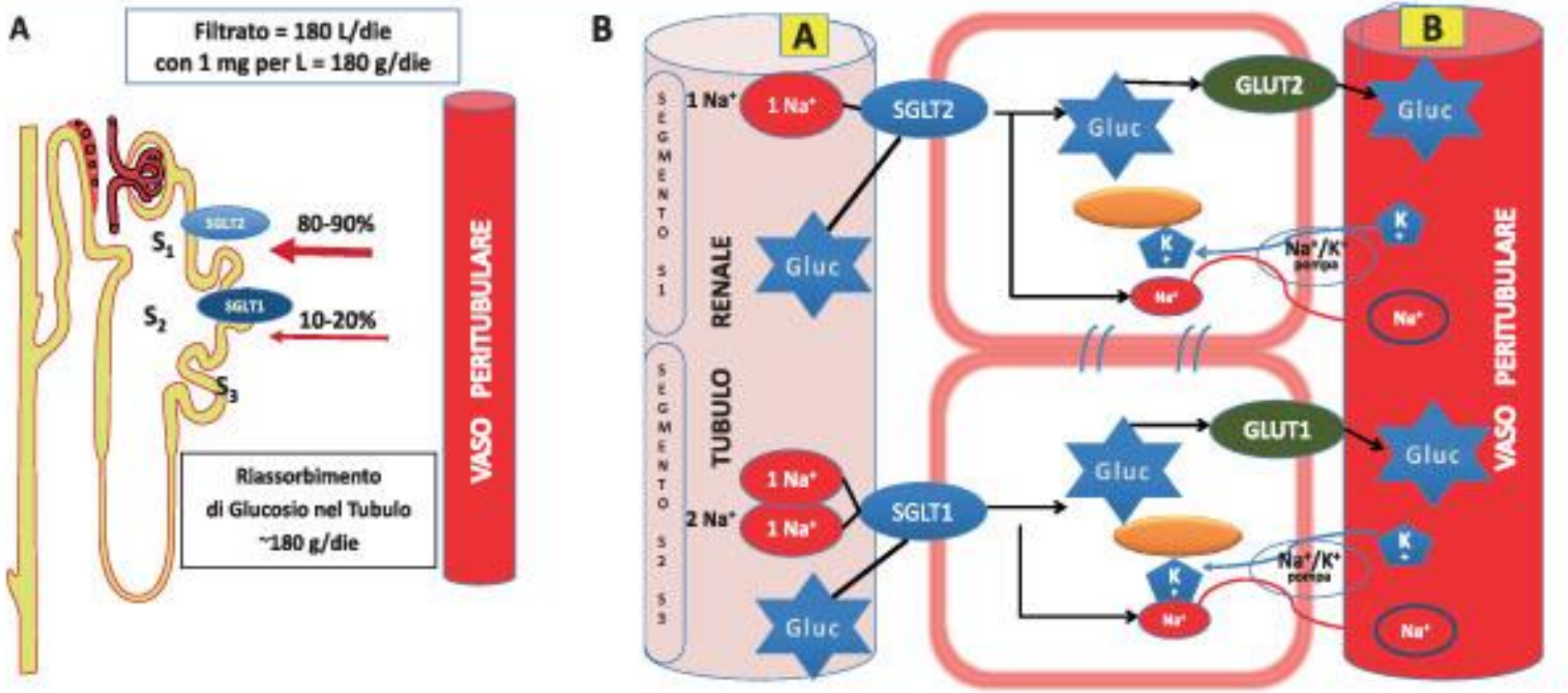
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

Le glifozine provocano ipoglicemia nei pazienti normo-glicemici?

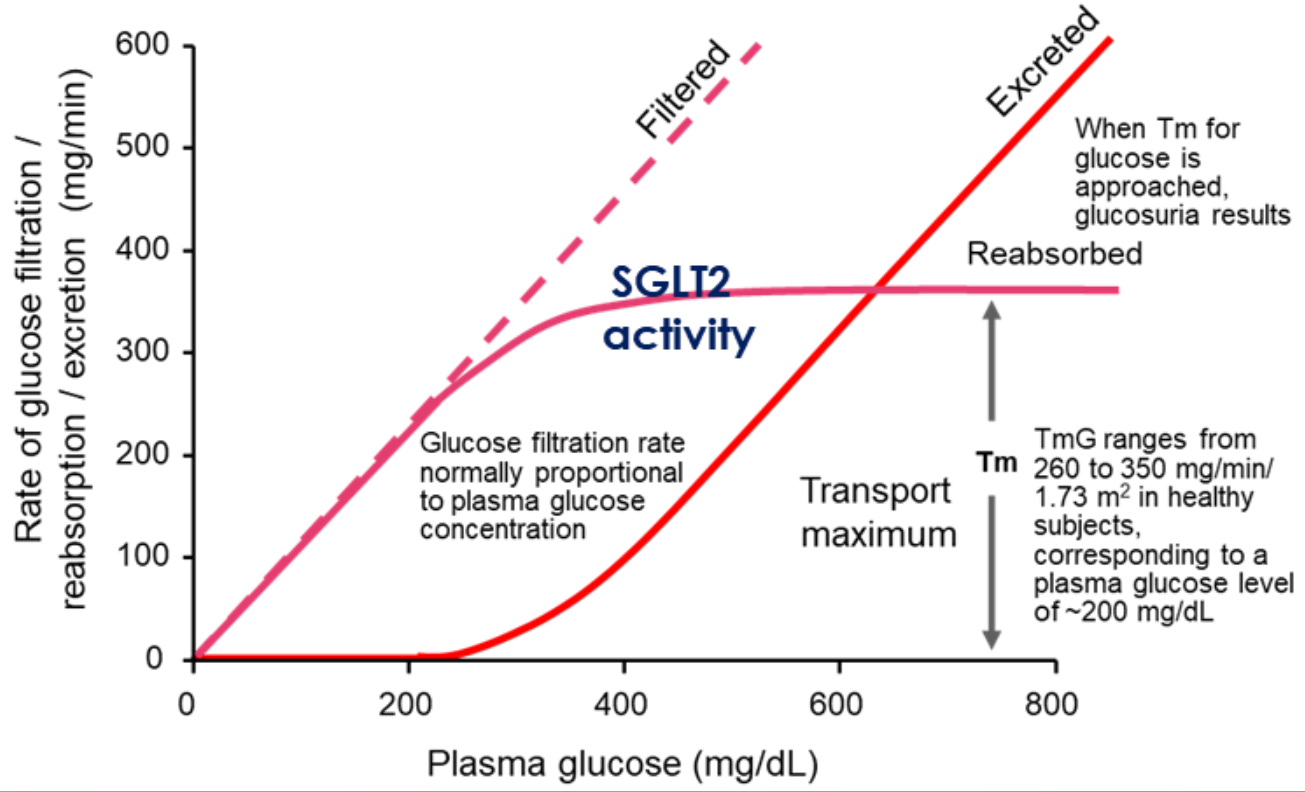
il rene è in grado di riassorbire tutto il glucosio filtrato, attraverso SGLT2 nel tubulo prossimale (90%) e SGLT1 (10%) nel suo tratto più distale.



Diabetes & Metabolism
Volume 40, Issue 6, Supplement 1, December 2014, Pages S4-S11

L'attività ipoglicemizzante delle glifozine è glucosio dipendente.

L'attività di SGLT2 è massima quando la glicemia supera la soglia renale 180mg/dl, mentre è trascurabile per livelli di glicemia inferiori.

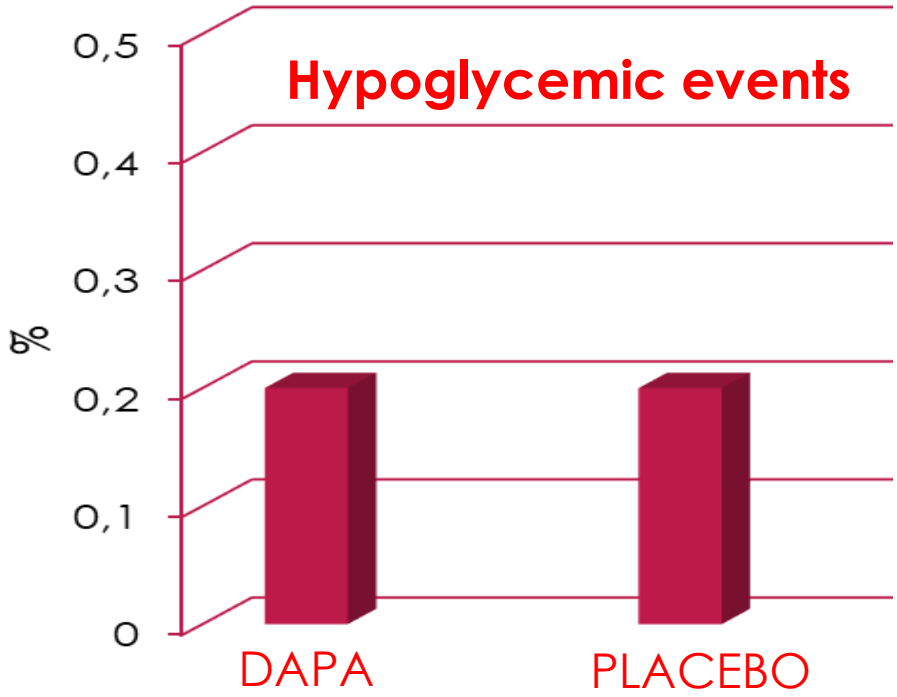


The NEW ENGLAND JOURNAL of MEDICINE

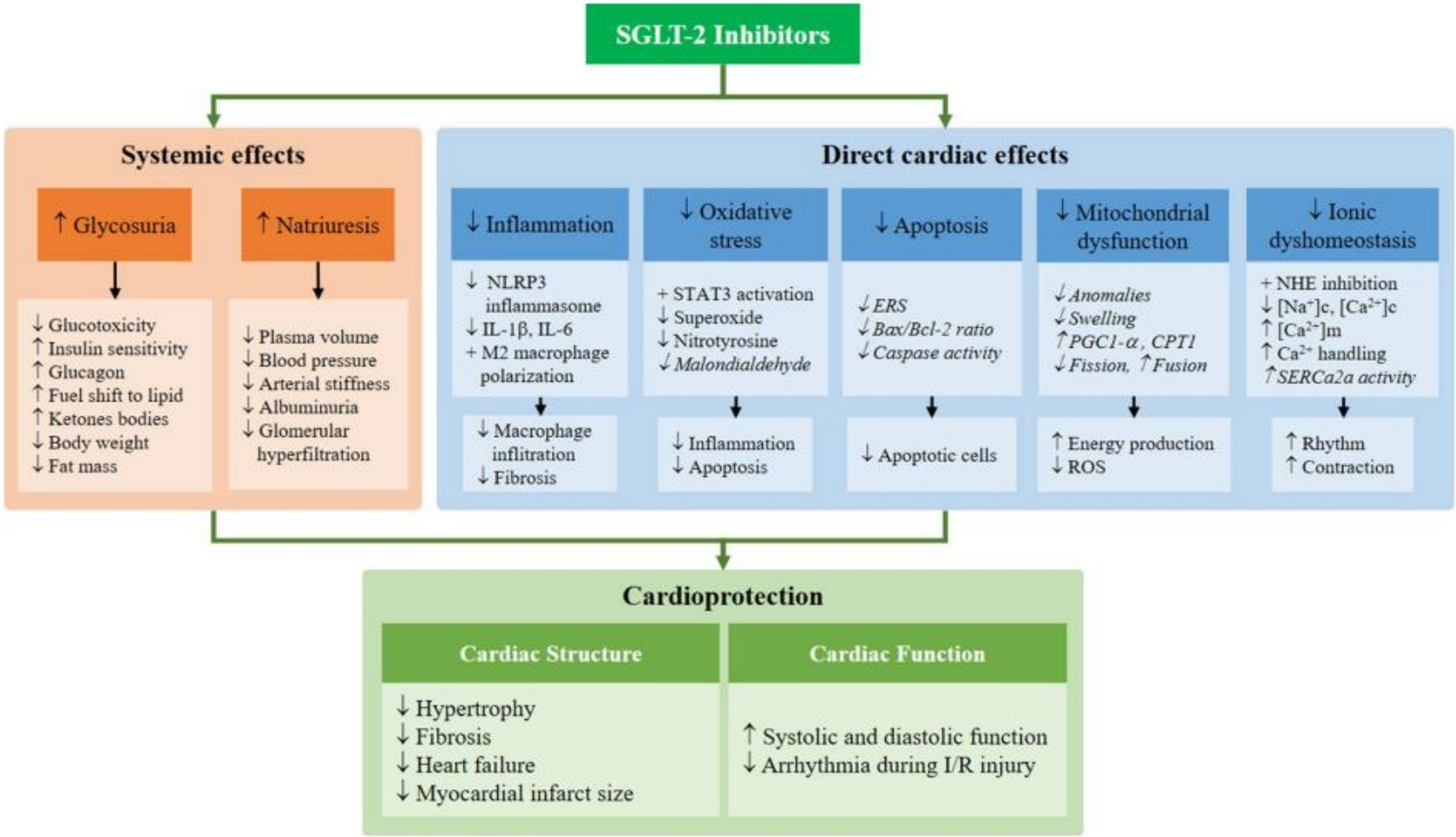
ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Le glifozine non provocano ipoglicemia nei pazienti normo-glicemici



SGLT2-inhibitors: more than just glycosuria and diuresis



Lahnwong et al. Cardiovasc Diabetol (2018) 17:101

JAMA®
The Journal of the American Medical Association
JAMA, August 20, 2008—Vol 300, No. 7

Raffaele Marfella, MD, PhD
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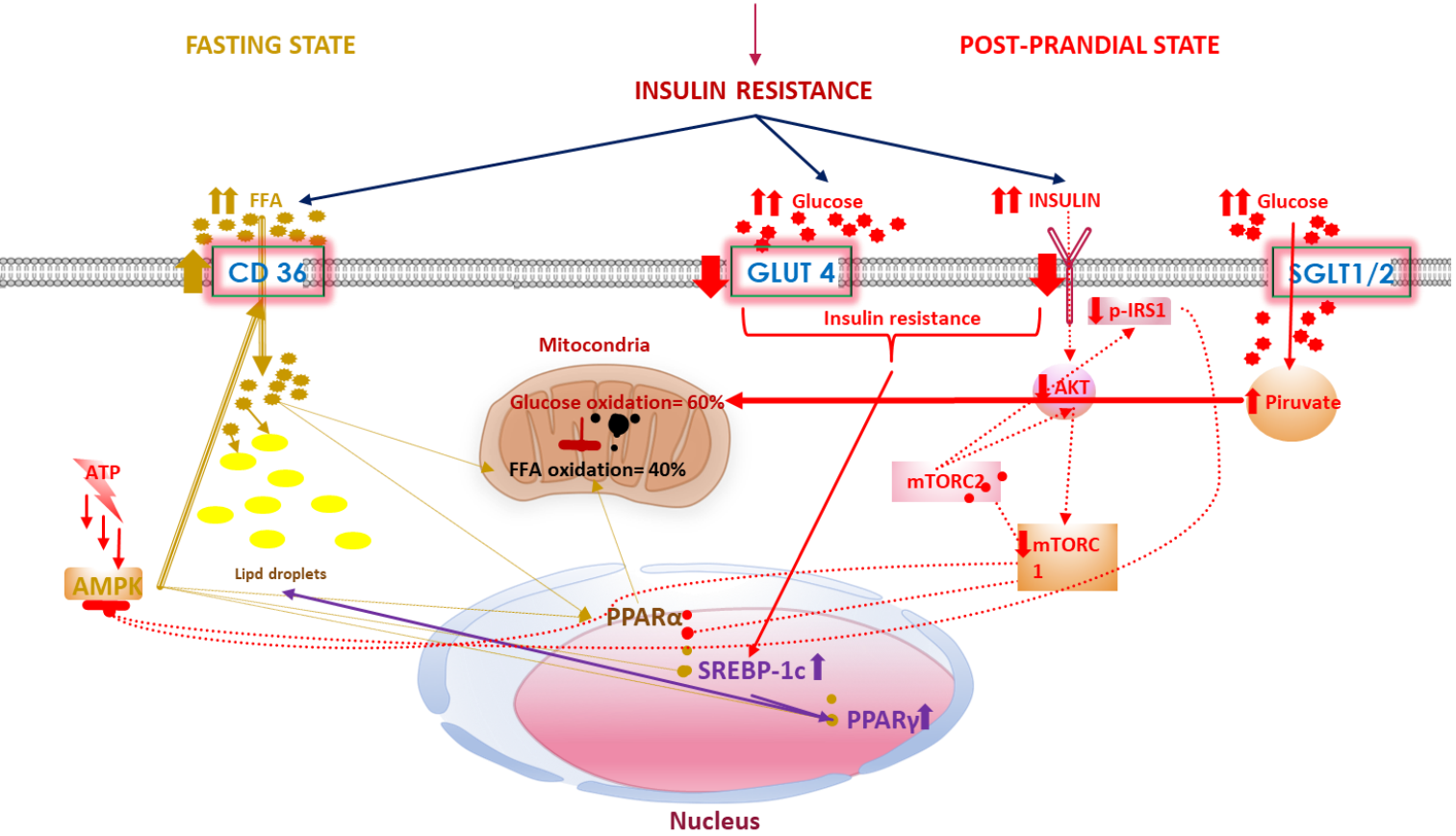
Michelangela Barbieri, MD, PhD
Giuseppe Paolisso, MD

FAILING HEART METABOLIC FLEXIBILITY LOSS

INFLAMMATION



SGLT2 inhibitors

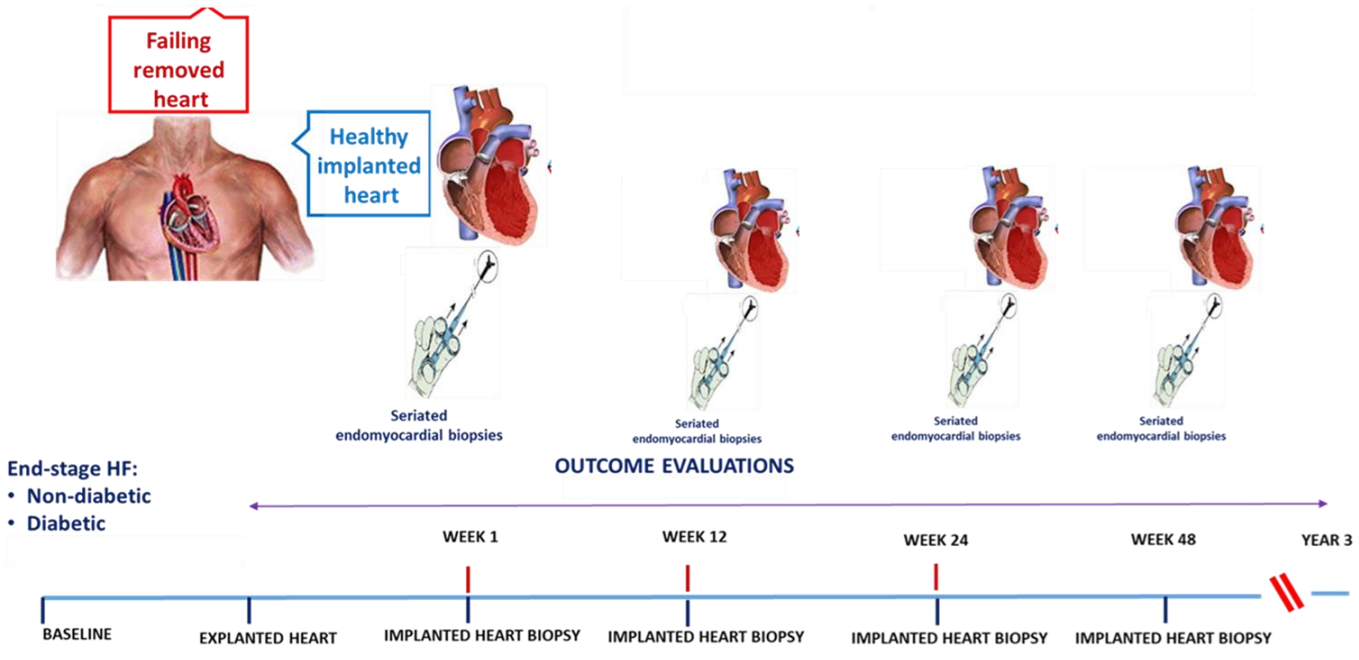
- ↑ SGLT2
- ↓ PPARα
- ↑ PPARγ
- ↑ Red-Oil-O
- ↑ Ceramide
- ↑ Fibrosis

Journal of the American College of Cardiology
Volume 75, Issue 11, 24 March 2020, Pages 1249-1262

Lipid Accumulation in Hearts Transplanted From Nondiabetic Donors to Diabetic Recipients

Raffaele Marfella, MD, PhD,[a,*] Cristiano Amarelli, MD,[b,*] Francesco Cacciatore, MD, PhD,[c] Maria Luisa Balestrieri, PhD,[d] Gelsomina Mansueto, MD, PhD,[e] Nunzia D'Onofrio, PhD,[d] Salvatore Esposito, MD,[f] Irene Mattucci, MD,[g] Gemma Salerno, MD,[g] Marisa De Feo, MD,[h] Michele D'Amico, PhD,[i] Paolo Golino, MD, PhD,[g] Ciro Maiello, MD,[b] Giuseppe Paolisso, MD,[a,†] Claudio Napoli, MD, PhD[a,j,†]

- SGLT2 inhibitor-treated patients
- NO-SGLT2 inhibitor-treated patients



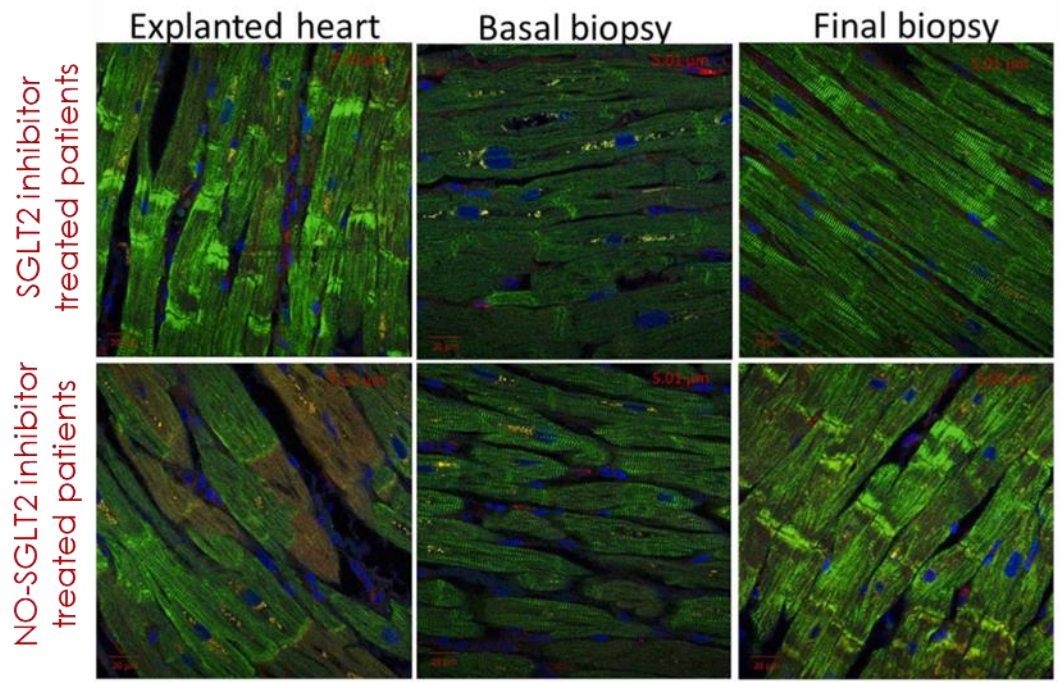
Sodium-glucose cotransporter-2 (SGLT2) expression in diabetic and non-diabetic failing human cardiomyocytes

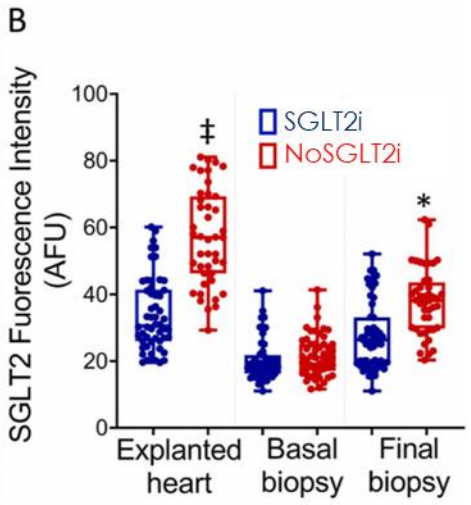
Raffaele Marfella [a,b,1], Lucia Scisciola [a,1], Nunzia D'Onofrio [c,1], Ciro Maiello [d], Maria Consiglia Trotta [e], Celestino Sardu [a], Iacopo Panarese [f], Franca Ferraraccio [f], Annalisa Capuano [e], Michelangela Barbieri [a], Maria Luisa Balestrieri [c], Claudio Napoli [a,2], Giuseppe Paolisso [a,b,*,2]

Pharmacological Research 184 (2022) 106448

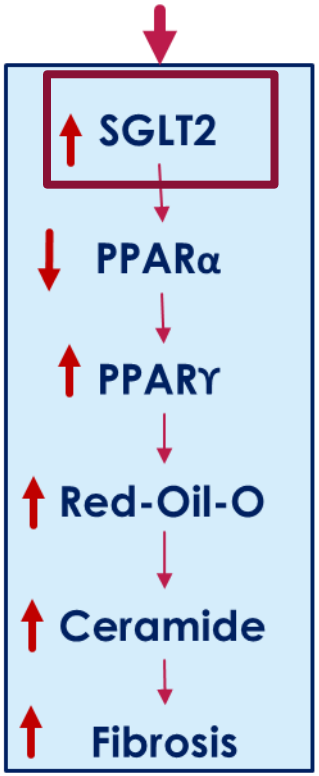
SGLT2 is expressed in human cardiomyocytes

SGLT2 inhibitors reduce SGLT2 expression in cardiomyocytes





SGLT2 inhibitors

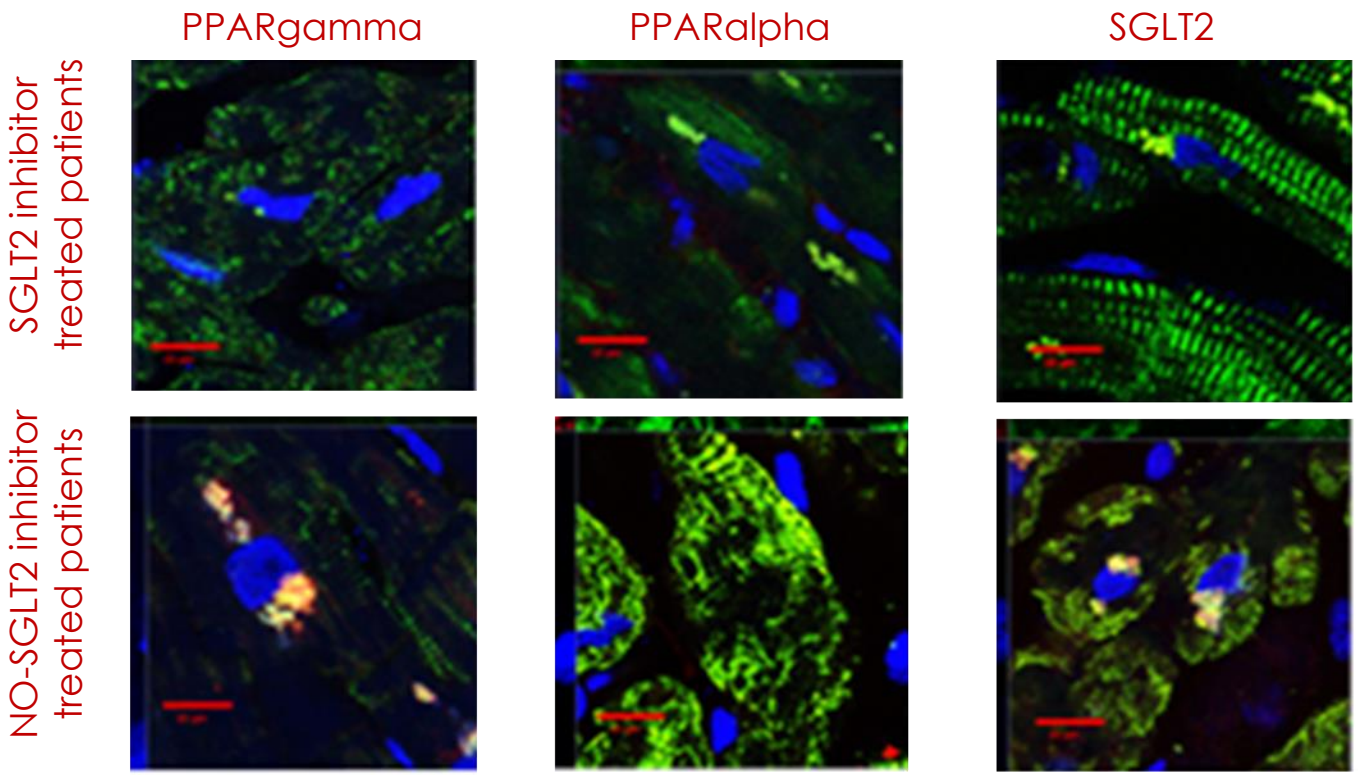


Basic Science

Sodium/glucose cotransporter 2 (SGLT2) inhibitors improve cardiac function

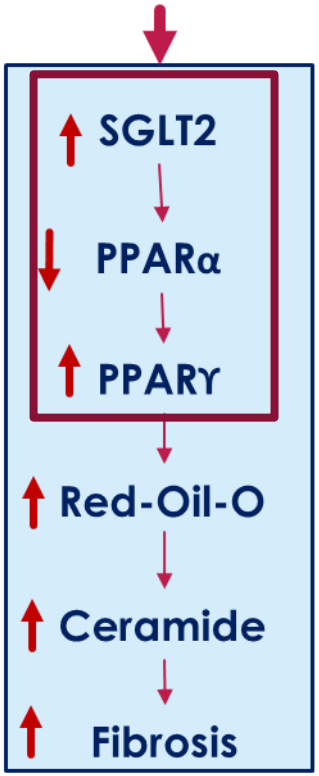
Raffaele Marfella [a,b,*], Nunzia D'Onofrio [c], Maria Consiglia Trotta [d], Celestino Sardu [a], Lucia Scisciola [a], Cristiano Amarelli [e], Maria Luisa Balestrieri [d], Vincenzo Grimaldi [a], Gelsomina Mansueto [a], Salvatore Esposito [f], Michele D'Amico [d], Paolo Golino [g], Giuseppe Signoriello [h], Marisa De Feo [i], Ciro Maiello [e], Claudio Napoli [a,l], Giuseppe Paolisso [a,b,l]

- Il cuore scompensato perde la flessibilità metabolica
- Il cuore scompensato è costantemente in fase post-prandiale
- L'inibizione di SGLT2 ripristina la flessibilità metabolica



Metabolism Clinical and Experimental 127 (2022) 154936

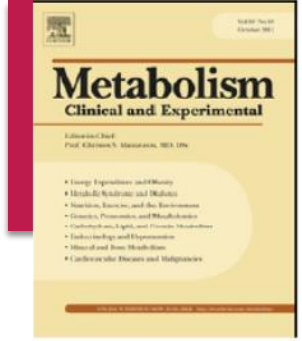
SGLT2 inhibitors

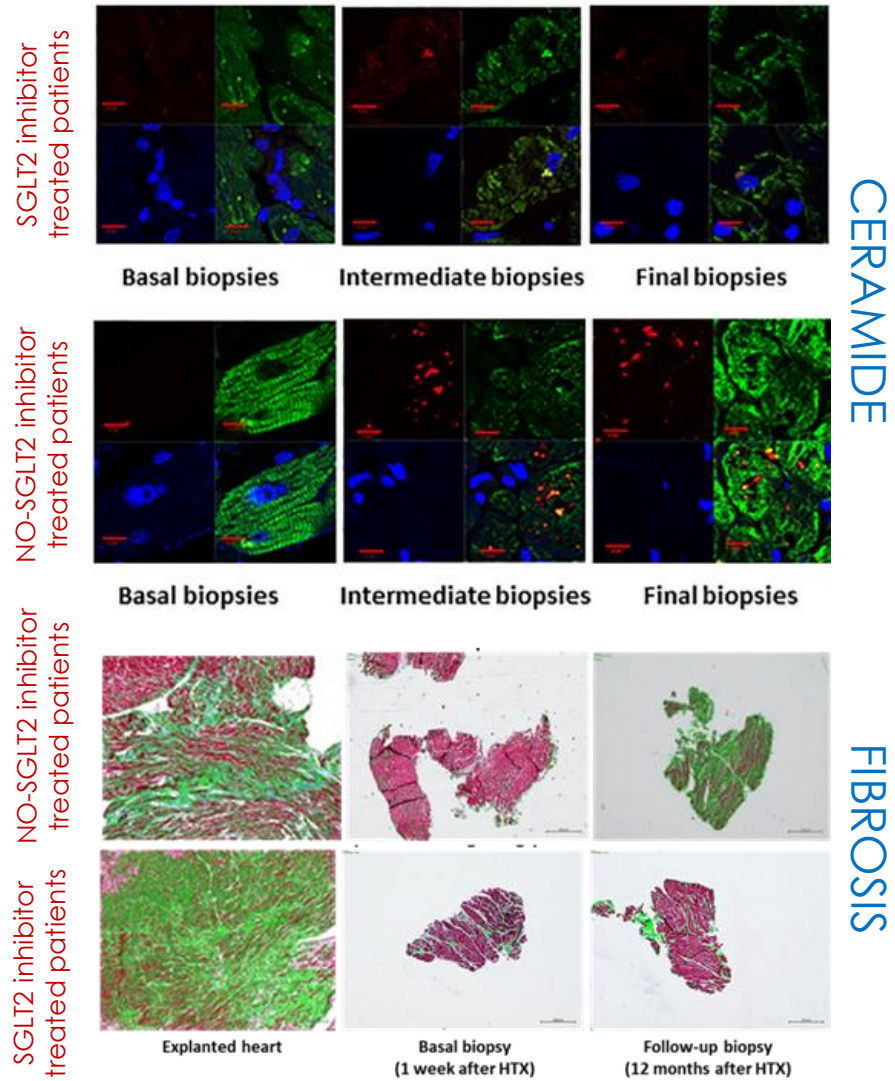


Basic Science

Sodium/glucose cotransporter 2 (SGLT2) inhibitors improve cardiac function

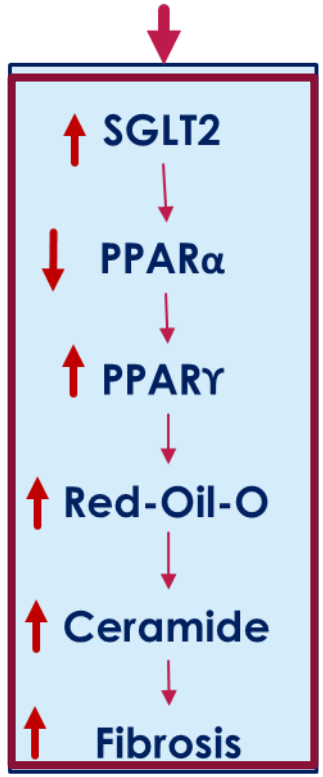
Raffaele Marfella [a,b,*], Nunzia D'Onofrio [c], Maria Consiglia Trotta [d], Celestino Sardu [a], Lucia Scisciola [a], Cristiano Amarelli [e], Maria Luisa Balestrieri [d], Vincenzo Grimaldi [a], Gelsomina Mansueto [a], Salvatore Esposito [f], Michele D'Amico [d], Paolo Golino [g], Giuseppe Signoriello [h], Marisa De Feo [i], Ciro Maiello [e], Claudio Napoli [a,1], Giuseppe Paolisso [a,b,1]





- L'inibizione di SGLT2 riduce la morte cellulare
- L'inibizione di SGLT2 riduce la fibrosi

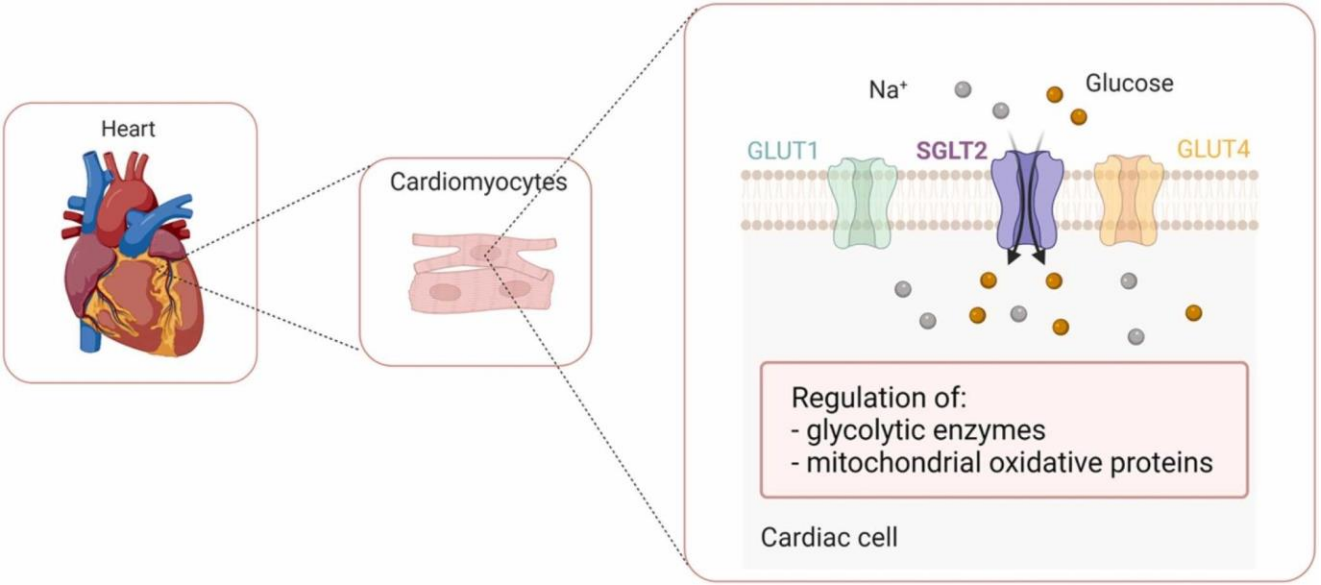
SGLT2 inhibitors



Metabolism Clinical and Experimental 127 (2022) 154936

Take Home Message

- SGLT2 inhibitors do not cause hypoglycemia in normoglycemic patients
- Failing Cardiomyocytes express SGLT2 protein
- SGLT2 inhibition acts directly on cardiomyocytes



Arteriosclerosis, Thrombosis, and Vascular Biology

BRIEF REVIEW

How Do SGLT2 (Sodium-Glucose Cotransporter 2) Inhibitors and GLP-1 (Glucagon-Like Peptide-1) Receptor Agonists Reduce Cardiovascular Outcomes?

Completed and Ongoing Mechanistic Trials

Matthew M.Y. Lee, Mark C. Petrie, John J.V. McMurray, Naveed Sattar

Volume: 40, Issue: 3, Pages: 506-522, DOI: (10.1161/ATVBAHA.119.311904)

Reverse translation

Benefits in Outcome Trials

SGLT2 Inhibitors → Renal > HF/CV Death > MACE *(independent of glycemia)*

GLP-1 RA → MACE/CV Death > HF > Renal (?) *(independent of glycemia)*

A Review of Ongoing Mechanistic Trials Across Different Systems

- Cardiac
- Vascular
- Renal
- Respiratory
- Metabolic
- Musculoskeletal
- Neurological