PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
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9ª Edizione

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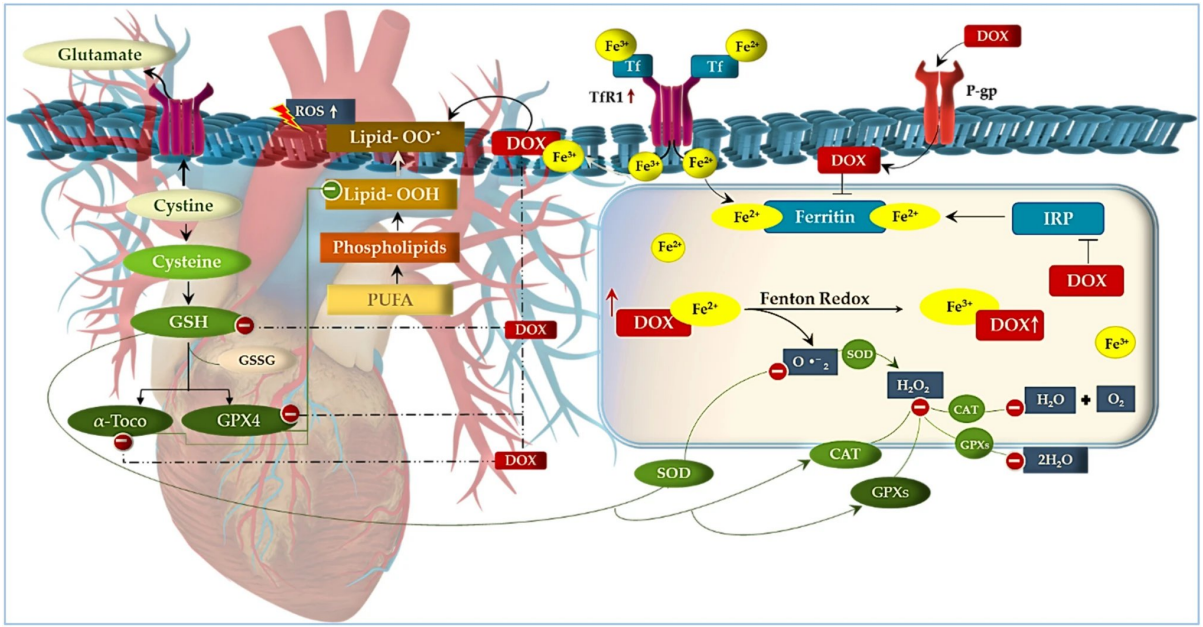
Cardioncologia: Update 2022: Parte 1

CARDIOTOSSICITÀ DA ANTRACICLINE E TRASTUZUMAB: RUOLO TERAPEUTICO DELLE GLIFLOZINE

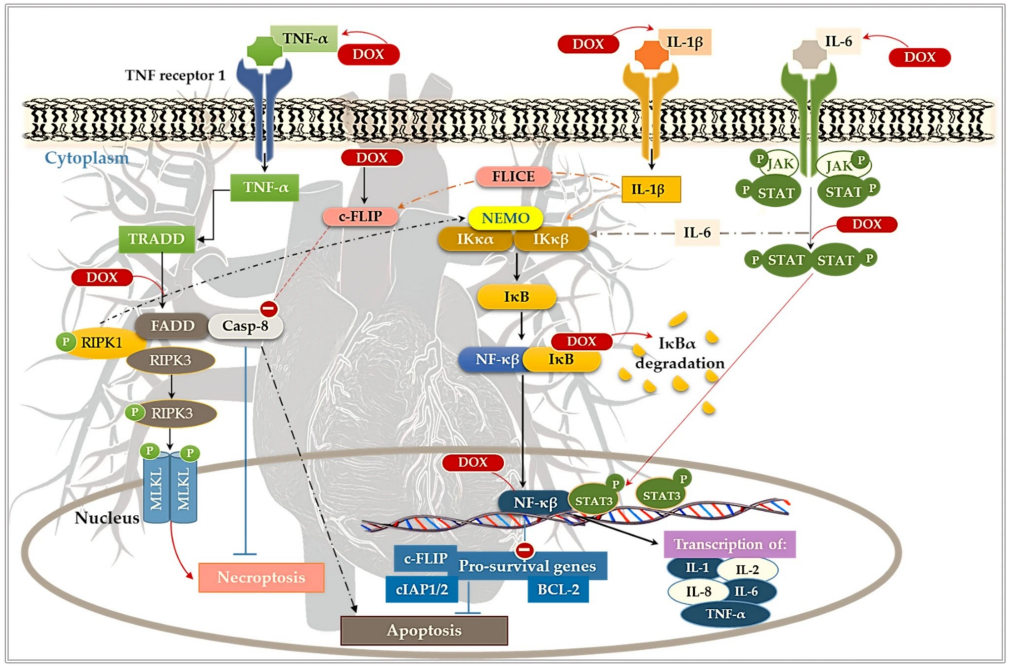
Vincenzo Quagliariello, PhD
Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale

Pathophysiology of anthracycline-mediated cardiotoxicity



- Increased **transferrin receptor** (Tf)
- Increased cardiac **Fe^{2+}/Fe^{3+} - overload**
- Induction of **ferroptosis**
- Increased **MDA and 4-HNA levels**

Pathophysiology of anthracycline-mediated cardiotoxicity

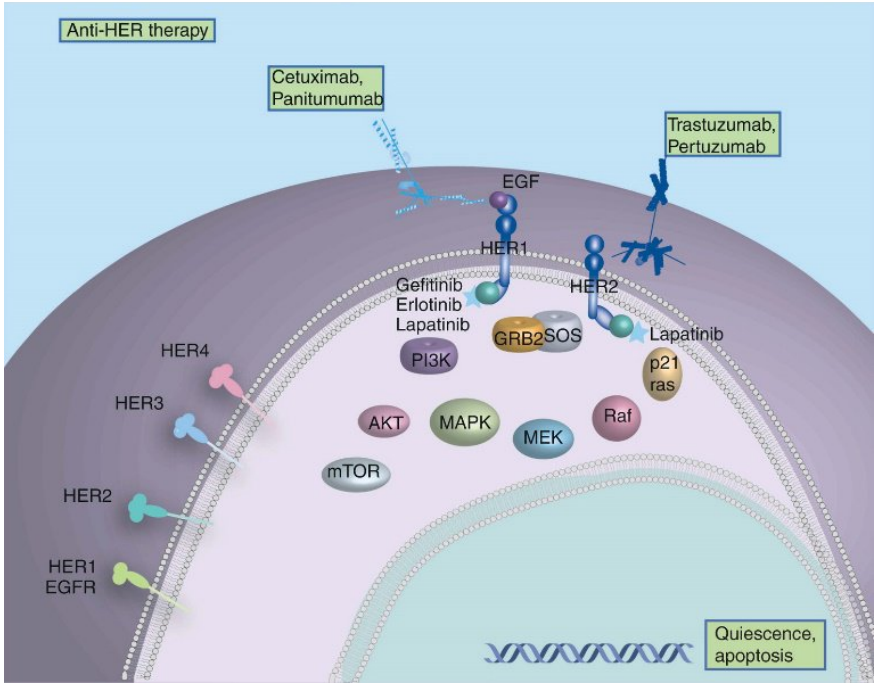


- Increased **nuclear factor kappa beta (NF-κβ) activity**
- Inhibition of **IkappaB (IκB)-kinase (IKK) complex** and **NEMO**
- Increased **IL-1β** and **IL-6** levels
- Inhibition of inhibition of the Janus kinase **(JAK)**-signal transducer and activator of transcription **(STAT3)** pathway
- Increased **apoptosis and necroptosis**

HER-2 blocking agents-mediated cardiotoxicity

Newer biologic therapies, such as the monoclonal antibody trastuzumab, also may cause cardiotoxicity.

Pooled data from randomized clinical trials estimate that trastuzumab is associated with an absolute increase in HF incidence by 1.6% and abnormalities in left ventricular systolic function by 7.2%.



La cardiotossicità da terapie di associazione

La cardiotossicità da terapie di associazione è un problema clinico di estrema importanza in oncologia, un esempio rilevante è la cardiotossicità additiva da associazione di antracicline e trastuzumab nella terapia del carcinoma mammario HER2+.L'incidenza cumulativa di eventi cardiaci nelle donne trattate con antracicline e trastuzumab a 1 anno dopo la diagnosi di carcinoma mammario è del ***16,4 %, a 2 anni il 23,8% e a 3 anni il 28,2%***

J Am Coll Cardiol. 2012 Dec 18;60(24):2504-12. doi: 10.1016/j.jacc.2012.07.068. Epub 2012 Nov 14.

Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer

Jersey Chen [1], Jessica B Long, Arti Hurria, Cynthia Owusu, Richard M Steingart, Cary P Gross

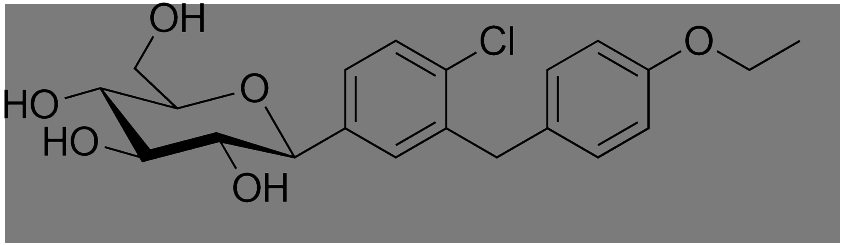
Cumulative Incidence of Heart Failure or Cardiomyopathy During First 3 Years After Diagnosis by Cancer Therapy

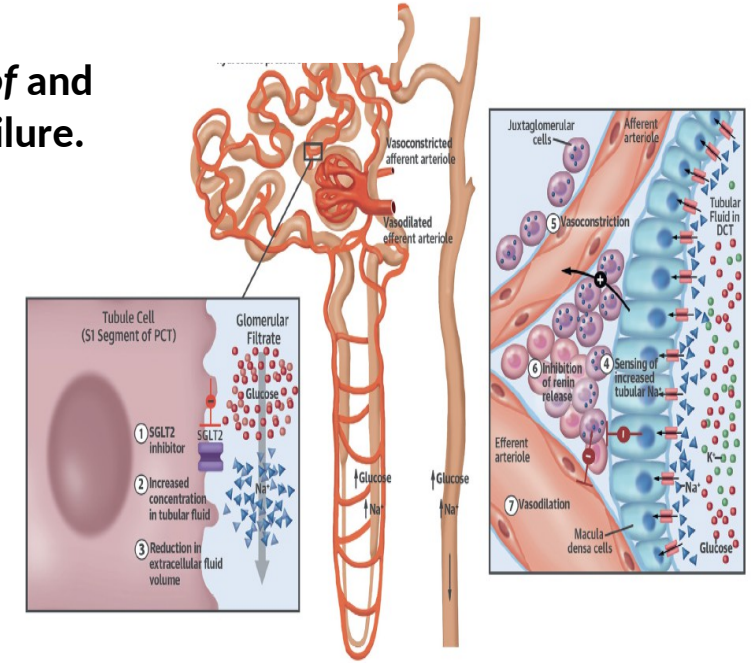
	All Cancer Patients	Anthracycline + Trastuzumab (n = 431)	Anthracycline (n = 5,257)	Trastuzumab (n = 437)	Other Chemotherapy (n = 2,712)	None (n = 36,700)
Observed cumulative incidence						
1 year	7.2	16.4*†	7.7‡	15.7*	7.8	6.8
2 years	12.3	23.8*†	11.9	20.7*	12.4	12.1
3 years	16.9	28.2*†	15.3‡	26.7*	17.0	16.9
Adjusted cumulative incidence						
1 year	7.5	22.0*†	9.8*	16.7*	8.4*	7.0
2 years	13.3	33.2*†	15.3*	23.2*	13.7*	12.8
3 years	18.7	41.9*†	20.2‡	32.1*	19.2	18.1

Values are %. Per 100 patients if surviving for the full time. Poisson model used to measure significance. *$p < 0.001$ versus no adjuvant therapy group. †$p < 0.001$ versus anthracycline group, only in the model containing anthracycline plus trastuzumab and anthracycline adjuvant therapy. ‡$p < 0.05$ versus no adjuvant therapy group.

Gliflozins: a new therapeutic weapon in cardioncology

- **Patients with type 2 DM are at high risk for *development of* and *complications from* atherosclerotic CV events and heart failure.**
- **Gliflozins are selective SGLT-2 inhibitors which blocks glucose and sodium resorption in the kidney, and thereby ↓ blood sugar, BP & weight.**

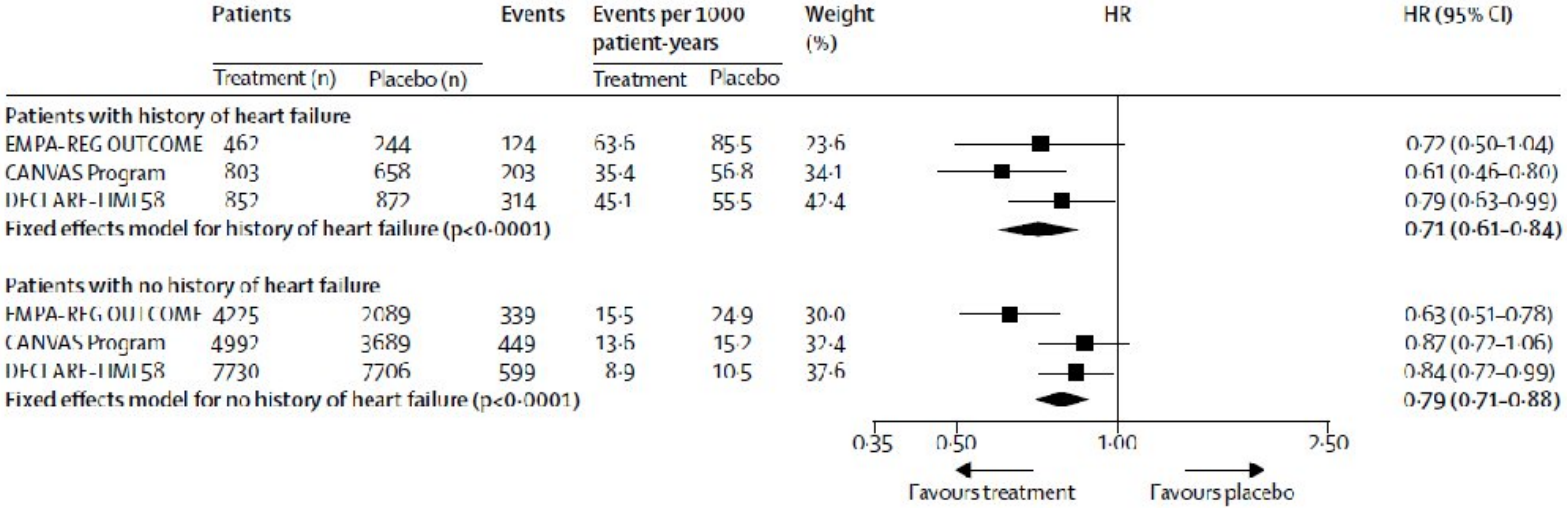




SGLT2 inhibitors

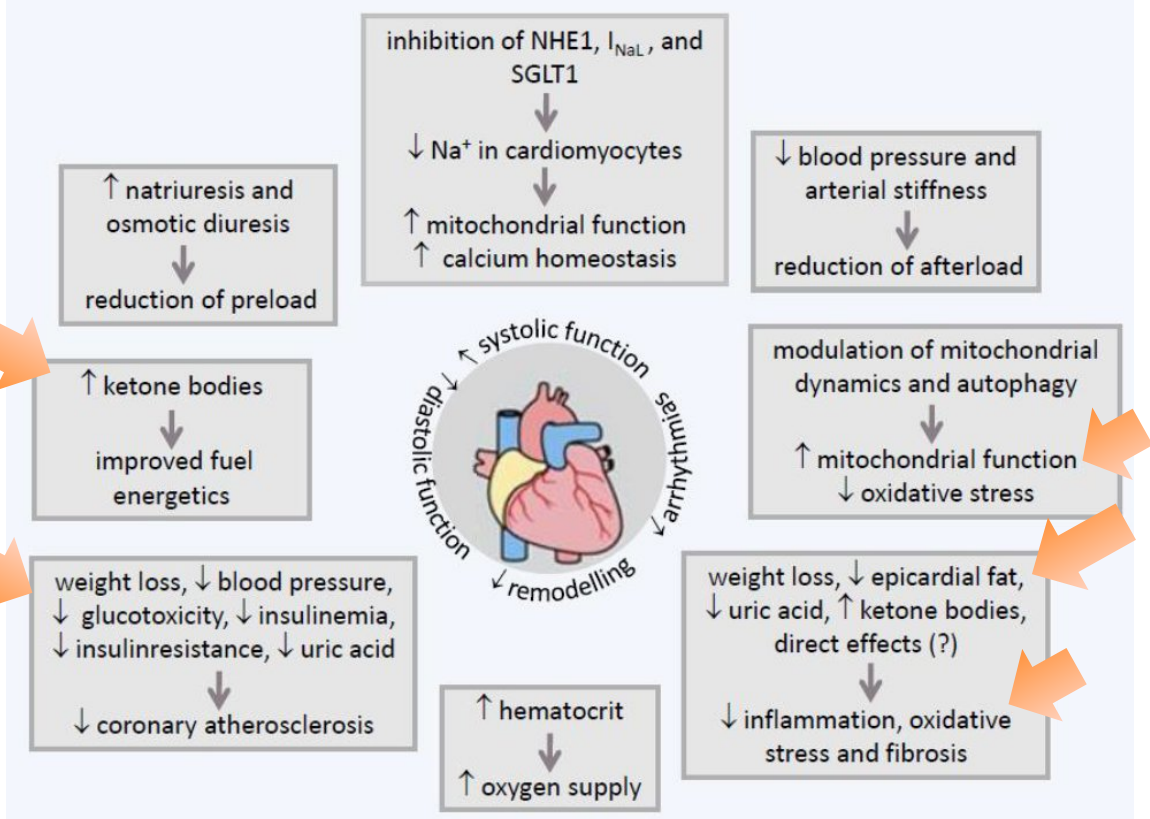
THE LANCET

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials



Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure

Overview of the main systemic and cardiac effects of SGLT2-inhibitors



Int. J. Mol. Sci. 2022, 23, 3651. https://doi.org/10.3390/ijms23073651

SGLT-2 inhibitors : Overview of the main pleiotropic effects of SGLT2-inhibitors on the heart.

Drug	Trial (Ref.)	Patients	Follow-Up (Median)	Outcomes	Hazard Ratio (95% CI)
Empagliflozin	EMPAREG OUTCOME study [47]	7020 T2DM patients at high risk for CV events and an eGFR $\geq$ 30 mL/min/1.73 m^2 empagliflozin 10 mg vs. empagliflozin 25 mg vs. matching placebo	3.1 years (2.6 years of treatment)	composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	**0.86** (0.74–0.99)
				death from cardiovascular causes	**0.62** (0.49–0.77)
				nonfatal myocardial infarction	0.87 (0.70–1.09)
				nonfatal stroke	1.24 (0.92–1.56)
				hospitalization for heart failure	**0.65** (0.50–0.85)
				death from any cause	**0.68** (0.57–0.82)
	EMPEROR-Reduced [101]	3730 diabetic or not diabetic patients with class II, III, or IV HF and EF $\leq$ 40% empagliflozin 10 mg vs. placebo (in addition to recommended therapy)	16 months	cardiovascular death or hospitalization for worsening heart failure	**0.75** (0.65–0.86)
				hospitalization for heart failure	**0.70** (0.58–0.85)
	EMPEROR-Preserved [114]	5988 diabetic or not diabetic patients with class II-IV HF and EF > 40% empagliflozin 10 mg vs. placebo (in addition to usual therapy)	26.2 months	cardiovascular death or hospitalization for worsening heart failure	**0.79** (0.69–0.90)
				hospitalization for heart failure	**0.73** (0.61–0.88)
	EMPERIAL [104]	patients with HFrE (EF $\leq$ 40%, n = 312) or with HFpEF (EF > 40%, n = 315) empagliflozin 10 mg vs. placebo	12 weeks	change in 6-minute walk test distance	*ns*
				KCCQ-TSS (Kansas City Cardiomyopathy Questionnaire Total Symptom Score)	*ns*
				CHQ-SAS (Chronic Heart Failure Questionnaire Self-Administered Standardized format) dyspnoea score	*ns*
Canagliflozin	CANVAS study [46]	10,142 participants with T2DM and high CV risk 100 mg (with an optional increase to 300 mg) vs. placebo	188.2 weeks	composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	**0.86** (0.75–0.97)

Int. J. Mol. Sci. 2022, 23, 3651. https://doi.org/10.3390/ijms23073651

SGLT-2 inhibitors : Overview of the main pleiotropic effects of SGLT2-inhibitors on the heart.

Drug	Trial (Ref.)	Patients	Follow-Up (Median)	Outcomes	Hazard Ratio (95% CI)
Dapagliflozin	DECLARE-TIMI 58 [48]	17,160 T2DM patients at high risk for CV events (only 7% of patients had an eGFR < 60 mL/min/1.73 m^2) dapagliflozin 10 mg vs. placebo	4.2 years	composite of CV death, myocardial infarction, or ischemic stroke	0.93 (0.84–1.03)
				CV death or hospitalization for HF	**0.83** (0.73–0.95)
				hospitalization for HF	**0.73** (0.61–0.88)
	DAPA-HF Trial [100]	4304 diabetic (68%) or not diabetic patients with class II-IV HF dapagliflozin 10 mg vs. placebo (in addition to recommended therapy)	18.2 months	worsening HF (hospitalization or urgent visit resulting in IV therapy for HF) or CV death	**0.74** (0.65–0.85)
				first worsening HF event	**0.70** (0.59–0.83)
				CV death	**0.83** (0.71–0.97)
	DEFINE HF [103]	263 diabetic or not diabetic patient with class II-III HF dapagliflozin 10 mg vs. placebo	12 weeks	mean NT-proBNP	*ns*
				% of patients with ameliorated functional status	**1.8** (1.03–3.06)
Sotagliflozin	SCORED [93]	10,584 T2DM patients with CKD and CV risk sotagliflozin 200–400 mg vs. placebo	16 months	composite of CV death, hospitalization fo HF, and urgent visit for HF	**0.74** (0.63–0.88)
	SOLOIST-WHF [102]	1222 T2DM patients recently hospitalized for worsening HF sotagliflozin 200–400 mg vs. placebo	9 months	CV deaths and hospitalization or urgent visits for HF	**0.67** (0.52–0.85)
				CV death	0.84 (0.58–1.22)
				death from any cause	0.82 (0.59–1.14)
Ertugliflozin	VERTIS CV study [92]	8246 T2DM patients with established CV disease and an eGFR $\geq$ 30 mL/min/ 1.73 m^2 ertugliflozin 5 or 15 mg vs. placebo	3 years	composite of CV death, myocardial infarction, or ischemic stroke	**0.97** (0.85–1.11)
				death from CV causes or hospitalization for HF	**0.88** (0.75–1.03)
				death from CV causes	**0.92** (0.77–1.11)

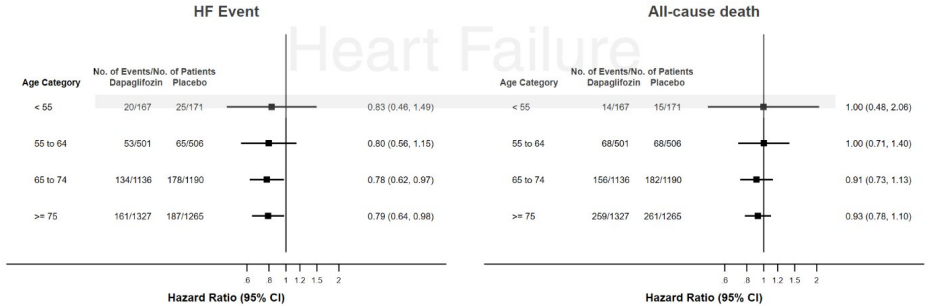
Int. J. Mol. Sci. 2022, 23, 3651.
https://doi.org/10.3390/ijms23073651

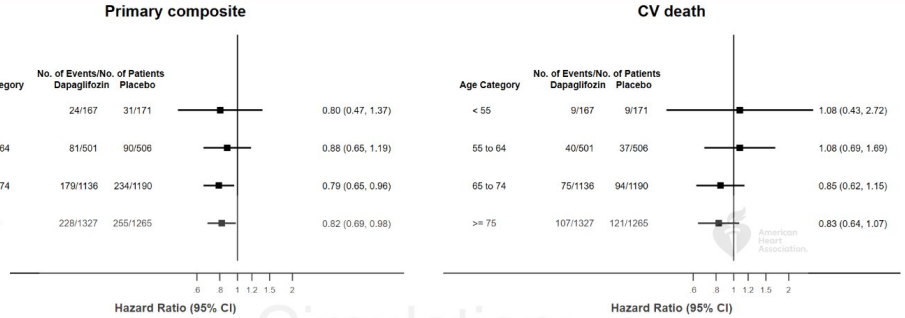
The DELIVER trial (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure)

Circ Heart Fail. 2022 Aug 27. doi: 10.1161/CIRCHEARTFAILURE.122.010080. Online ahead of print.

Efficacy and Safety of Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial

Alexander Peikert, Felipe A Martinez, Muthiah Vaduganathan, Brian L Claggett, Ian J Kulac, Akshay S Desai, Pardeep S Jhund [1], Rudolf A de Boer, David DeMets, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Sanjiv J Shah, Tzvetana Katova, Béla Merkely, Orly Vardeny, Ulrica Wilderäng, Daniel Lindholm, Magnus Petersson, Anna-Maria Langkilde, John J V McMurray, Scott D Solomon





- ❑ - Primary composite outcome (first occurrence CV death, HF hospitalization or urgent HF visit) ;
- ❑ - Heart failure events (HF hospitalization and urgent HF visit)

Conclusions: In patients with HF and mildly reduced or preserved EF enrolled in DELIVER, Dapagliflozin reduced cardiovascular death or HF events across the spectrum of age, with a consistent safety profile, including among the traditionally under-treated older segment of patients ≥75 years.

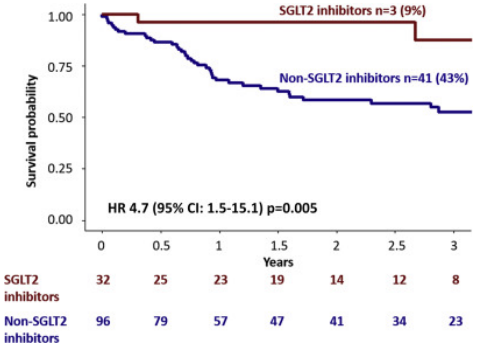
SGLT-2 inhibitors : Cardiac Outcomes Among Patients Treated With Anthracyclines

JACC: Heart Failure
Volume 10, Issue 8, August 2022, Pages 559-567

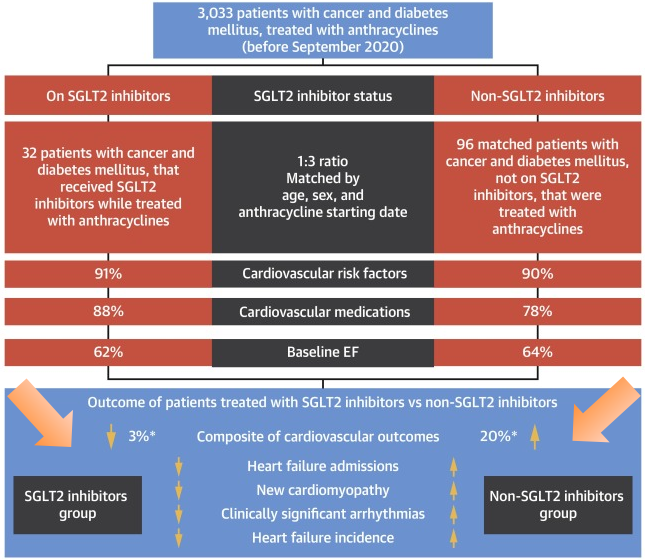
Clinical Research

Sodium-Glucose Co-Transporter-2 Inhibitors and Cardiac Outcomes Among Patients Treated With Anthracyclines

Conclusions: SGLT2 inhibitors were associated with lower rate of cardiac events among patients with cancer and DM who were treated with anthracyclines. Additionally, SGLT2 inhibitors appeared to be safe. These data support the conducting of a randomized clinical trial testing SGLT2 inhibitors in patients at high cardiac risk treated with anthracyclines.



CENTRAL ILLUSTRATION: Cardiovascular Outcomes of Cancer Patients With Diabetes Mellitus, Treated With Anthracyclines, Divided in Groups by Sodium-Glucose Co-Transporter-2 Inhibitors Status



Gongora CA, et al. J Am Coll Cardiol HF. 2022;10(8):559-567.

Preclinical studies on short-term DOXO-induced cardiotoxicity

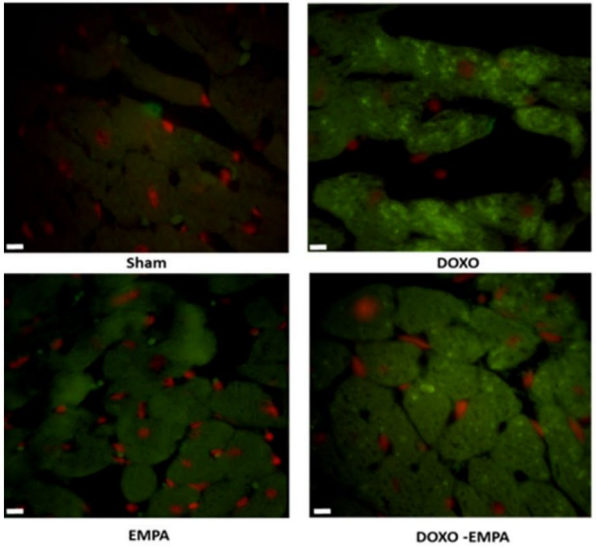
Quagliariello et al. Cardiovasc Diabetol (2021) 20:150
https://doi.org/10.1186/s12933-021-01346-y

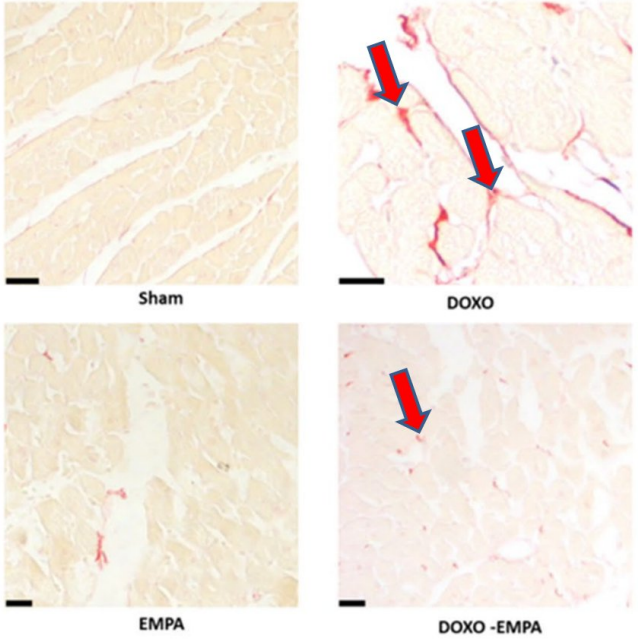
Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

The SGLT-2 inhibitor empagliflozin improves myocardial strain, reduces cardiac fibrosis and pro-inflammatory cytokines in non-diabetic mice treated with doxorubicin

Vincenzo Quagliariello[1*], Michelino De Laurentiis[2], Domenica Rea[3], Antonio Barbieri[3], Maria Gaia Monti[4], Andreina Carbone[1], Andrea Paccone[1], Lucia Altucci[5], Mariarosaria Conte[5], Maria Laura Canale[6], Gerardo Botti[7] and Nicola Maurea[1*]

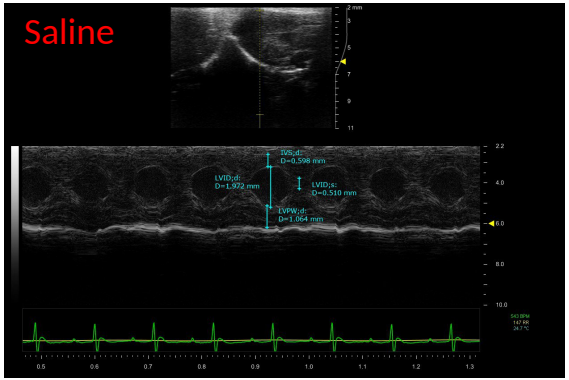


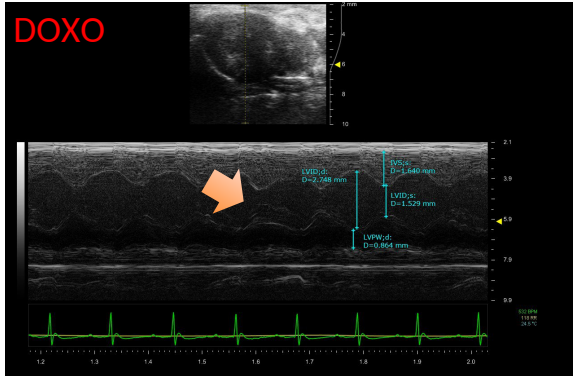


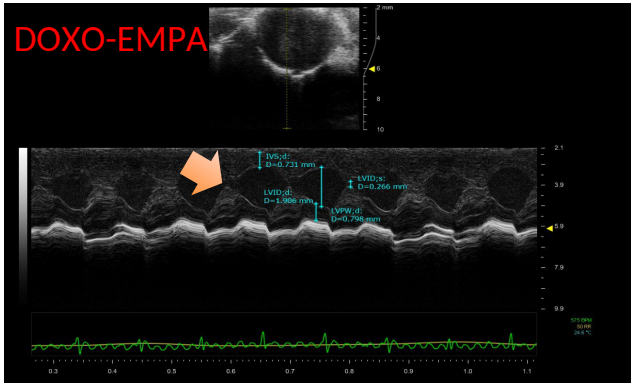
Conclusion: EMPA reduced ferroptosis, fibrosis, apoptosis and inflammation in doxorubicin-treated mice through the involvement of NLRP3 and MyD88-related pathways, resulting in significant improvements in cardiac functions. These findings provides the proof of concept for translational studies designed to reduce adverse cardiovascular outcomes in non-diabetic cancer patients treated with doxorubicin.

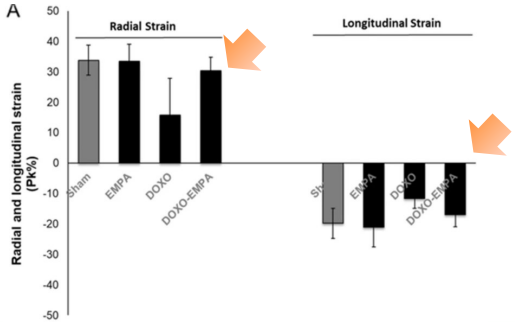
Quagliariello V et al., Cardiovasc Diabetol . 2021 Jul 23;20(1):150.

Preclinical studies on short-term DOXO-induced cardiotoxicity









Quagliariello V et al., Cardiovasc Diabetol . 2021 Jul 23;20(1):150.

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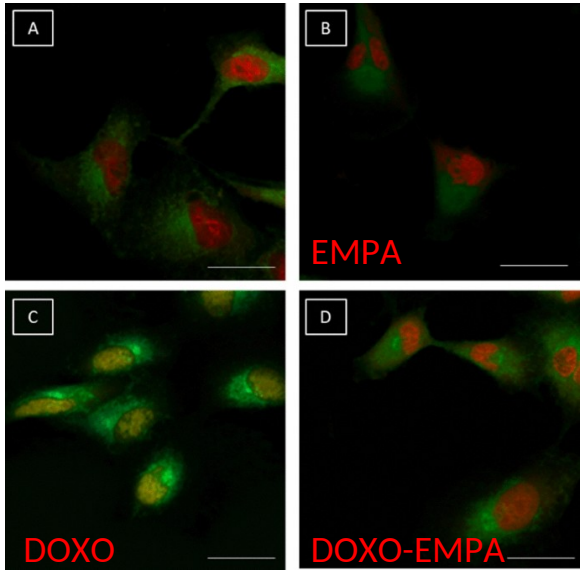
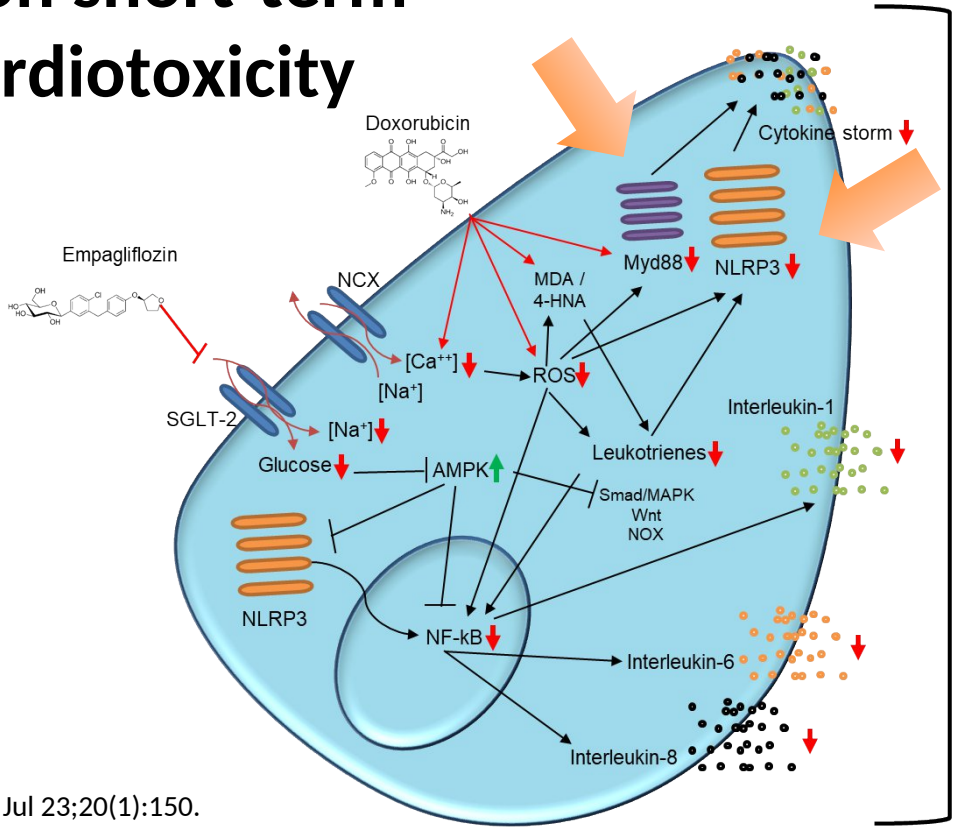
Preclinical studies on short-term DOXO-induced cardiotoxicity





- Heart Fibrosis
- Inflammation
- Mithocondrial biogenesis
- Oxidative stress
- Lipid peroxidation
- Necrosis
- Apoptosis
- Cardiomyocyte survival
- Left ventricular functions

Quagliariello V et al., Cardiovasc Diabetol . 2021 Jul 23;20(1):150.

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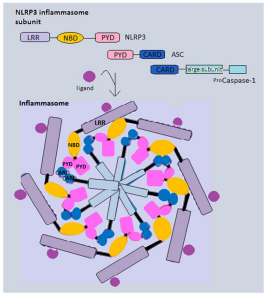
Hyperglycemia and Empagliflozin during CTLA-4 blocking agents

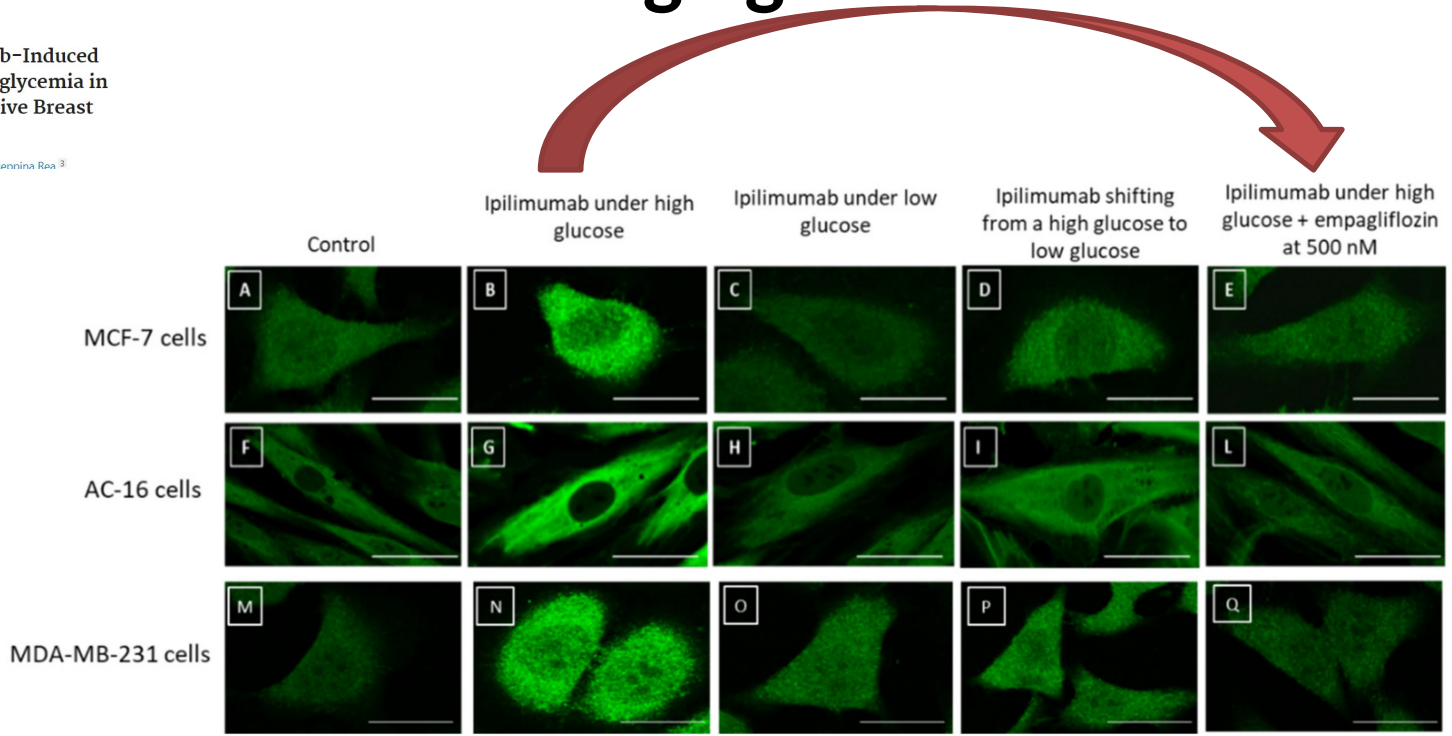
Int J Mol Sci. 2020 Oct 21;21(20):7802. doi: 10.3390/ijms21207802.

NLRP3 as Putative Marker of Ipilimumab–Induced Cardiotoxicity in the Presence of Hyperglycemia in Estrogen–Responsive and Triple–Negative Breast Cancer Cells

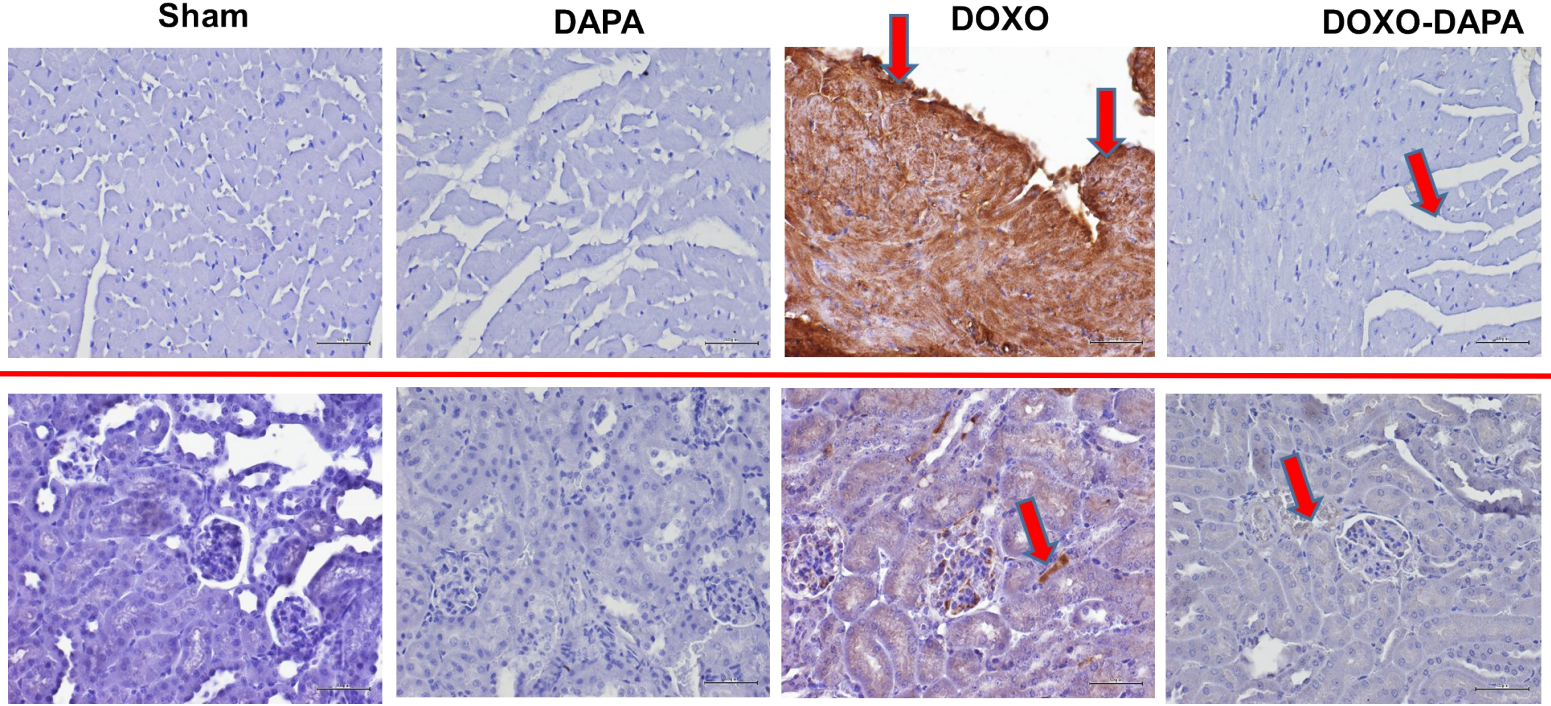
Vincenzo Quagliariello [1], Michelino De Laurentiis [2], Stefania Cocco [2], Giuseppina Rea [3], Annamaria Bonelli [1], Antonietta Caronna [1], Maria Cristina Lombari [1], Ga Massimiliano Berretta [4], Gerardo Botti [5], Nicola Maurea [1]

Inflammasome type-3





Dapagliflozin reduces myocardial and renal NF-kB expression during Anthracycline therapy



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Evidences of cardioprotective effects against anthracycline, Trastuzumab and Immune-checkpoint - induced cardiotoxicity

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SESSION TITLE: CARDIOPROTECTION: IN CARDIO-ONCOLOGY - NOVEL MECHANISMS I

Abstract 9383: Dapagliflozin, an Sglt2 Inhibitor, Reduces Expression of Myd88, Nlrp3 and Nf-kb During Exposure to Doxorubicin and Trastuzumab in Cellular Models

Nicola Maurea, Andrea Paccone, Martina Iovine, Simona Buccolo, Francesca Cerrone and Vincenzo Quagliariello

Originally published 8 Nov 2021 | Circulation. 2021;144:A9383

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DAPAGLIFLOZIN ASSOCIATED TO SACUBITRIL/VALSARTAN (LCZ696) EXERTS ADDITIVE CARDIOPROTECTION IN HUMAN CARDIOMYOCYTES EXPOSED SEQUENTIALLY TO DOXORUBICIN AND TRASTUZUMAB THROUGH MYD88, NLRP3 MEDIATED PATHWAYS AND PRO-INFLAMMATORY CYTOKINES

Spotlight On Special Topics

Nicola Maurea, Marino Scherillo, Annamaria Bonelli, Simona Buccolo, Martina Iovine, Carlo Maurea, Andrea Paccone, Irma Bisceglia, and Vincenzo Quagliariello

J Am Coll Cardiol. 2022 Mar, 79 (9_Supplement) 1886

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Meeting Abstract | 2021 ASCO Annual Meeting I

DEVELOPMENTAL THERAPEUTICS—MOLECULARLY TARGETED AGENTS AND TUMOR BIOLOGY

The SGLT-2 inhibitor dapagliflozin reduces cell death and apoptosis in cardiomyocytes exposed to trastuzumab and doxorubicin through NLRP3-mediated pathways.

Check for updates

Nicola Maurea, Vincenzo Quagliariello, Michelino De Laurentiis, Ernesta Cavalcanti, Andrea Paccone, Simona Buccolo, ...

JOURNAL ARTICLE

SGLT2 inhibitor dapagliflozin against anthracycline and trastuzumab-induced cardiotoxicity: the role of MYD88, NLRP3, Leukotrienes/Interleukin 6 axis and mTORC1 /Fox01/3a mediated apoptosis FREE

V Quagliariello, M De Laurentiis, D Rea, A Barbieri, M.G Monti, G Botti, N Maurea

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ABSTRACT ONLY | VOLUME 33, SUPPLEMENT 7, S550, SEPTEMBER 01, 2022

13P Berberine associated to SGLT2i dapagliflozin synergistically reduces cardiac cell apoptosis during exposure to trastuzumab through induction of pAMPK and reduction of NLRP3 inflammasome, IL-6, methylglyoxal and leukotrienes-B4 levels

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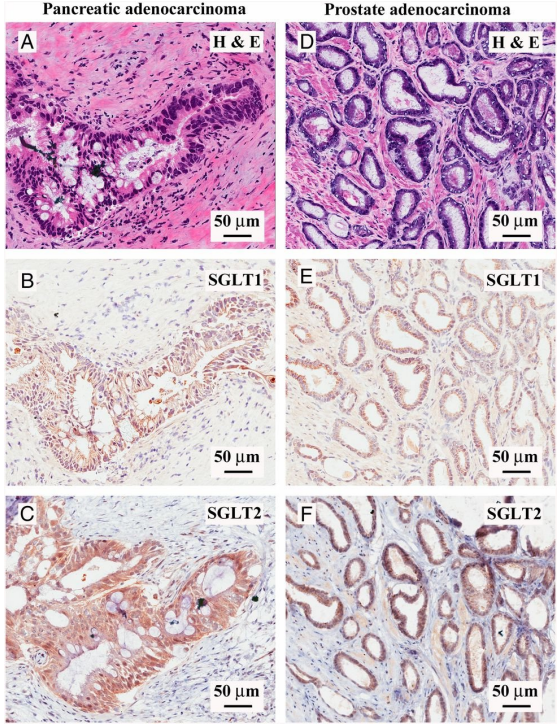
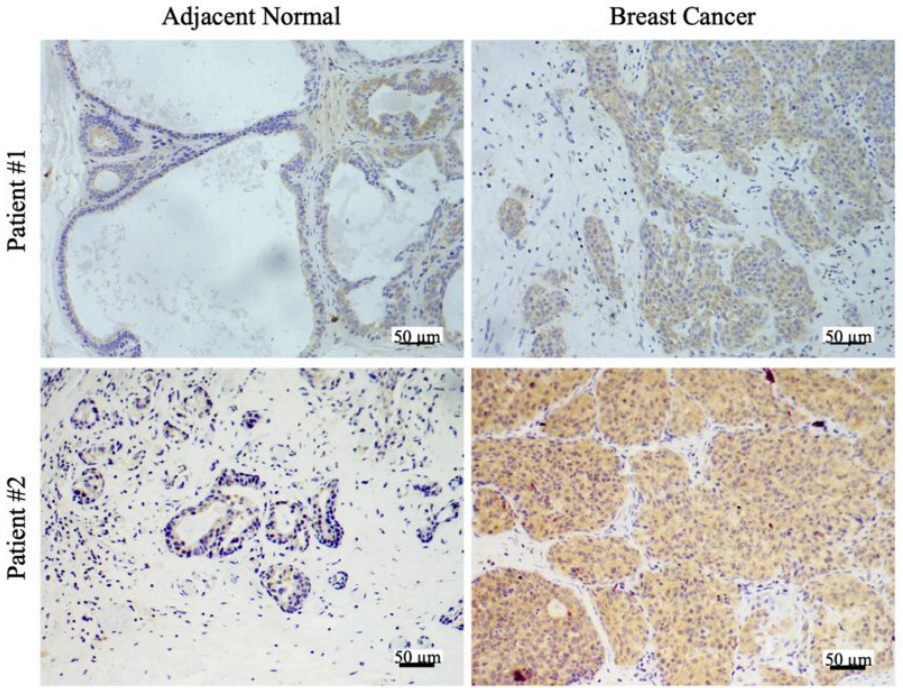
Functional expression of sodium-glucose transporters in cancer



Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):E4111-9.



Biomed Pharmacother . 2020 Dec;132:110821.

Conclusion and clinical perspectives

- **Large cardiovascular outcome trials (CVOTs): *SGLT-2 inhibitors have robust effects on reducing the risk of heart failure and renal outcomes which do not appear dependent on baseline atherosclerotic risk, prior HF, or renal function.***

- **Preclinical trials clearly demonstrated that gliflozins reduces cardiovascular events in several cardioncology models (doxorubicin, trastuzumab, cisplatin, ICIs, radiotherapy…)**

- ***A preliminar clinical study in cancer patients treated with anthracyclines indicates cardioprotective properties JACC Heart Fail 2022 Aug;10(8):559-567. (SGLT2 inhibitors were associated with lower rate of cardiac events among patients with cancer and DM who were treated with anthracyclines)***

Conclusion and clinical perspectives

Empagliflozin and Dapagliflozin demonstrated cardioprotective properties during several cardiotoxic anticancer therapies (i.e anthracyclines, HER-2 blocking agents, ICIs (i.e Ipilimumab).

Gliflozins improves Ca^{2+} homeostasis and inhibits the pro-inflammatory "NLRP3 – MyD-88- NF-κB –cytokines" pathways

Pathophysiological research turns the light on the cardioprotective properties of gliflozins in HER2+ breast cancer patients (with/without DM) in order to reduce incidence of heart failure and cardiomyopathies.

Grazie per l'attenzione