



GIOVEDÌ 29

Impiego delle gliflozine nell'infarto miocardico acuto

Fabrizio Oliva, *Milano*





CONTINUING MEDICAL EDUCATION DISCLOSURE FORM:

In accordance with the National-Regional Regulation of 2 February 2017, art. 76, page 34 and the Legislative Decree No. 165 of 30 March 2013 and the Presidential Decree No. 62 of 2013

The undersigned, **Fabrizio Oliva**, as Speaker in this CME activity

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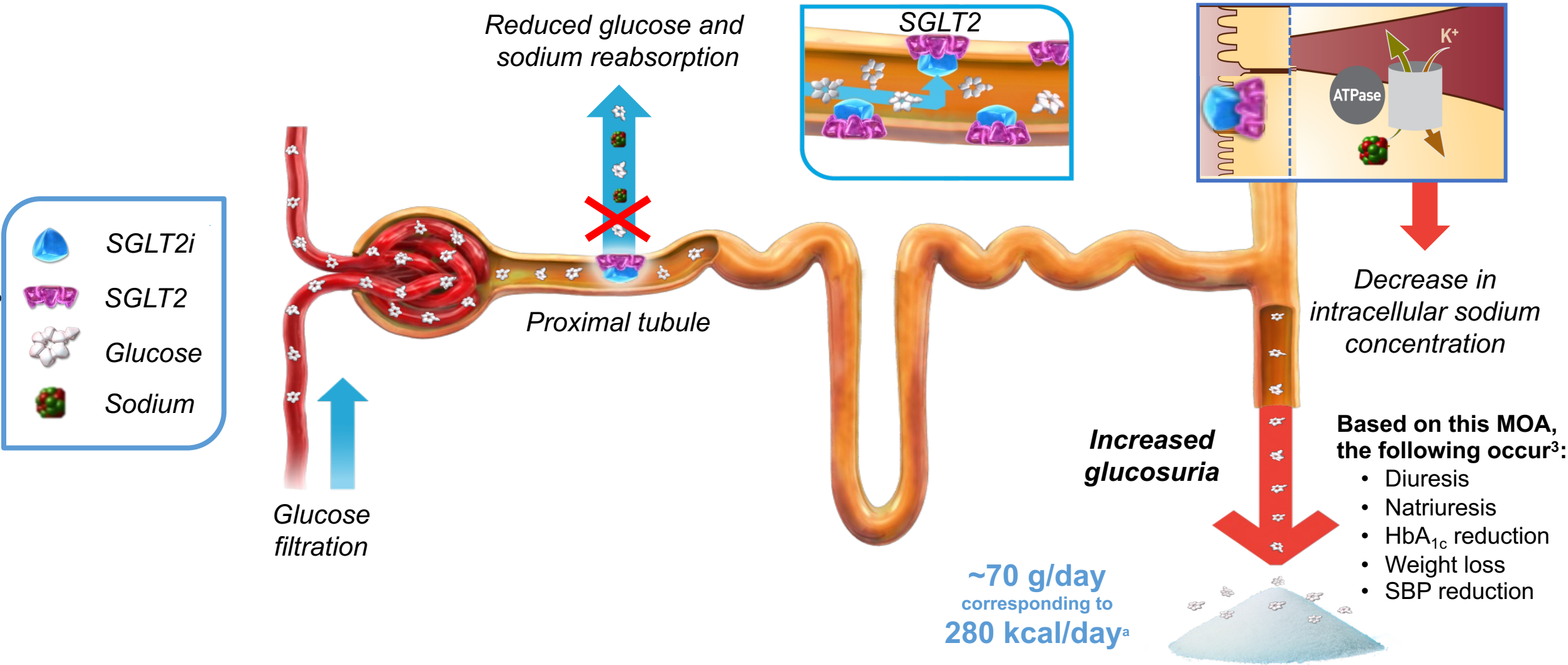


Agenda

- SGLT2i: meccanismo d'azione
- I risultati dei grandi trial nel Diabete, HF e CKD
- Il rischio di insufficienza cardiaca post-MI
- Dati sperimentali SGLT2i post-MI
- Dati clinici disponibili

SGLT2 inhibition: An insulin-independent approach to remove excess glucose by reducing the renal threshold¹⁻³

Ad esclusivo uso del Medical Affairs. Non divulgare al di fuori di AstraZeneca



SGLT2i nel Paziente Diabetico

EMPA-REG OUTCOME⁹

- Prevenzione secondaria 100%

Composito Renale

HHF

Mortalità CV

CANVAS Program¹⁰

- Prevenzione secondaria 66%

Composito Renale

HHF

Mortalità CV

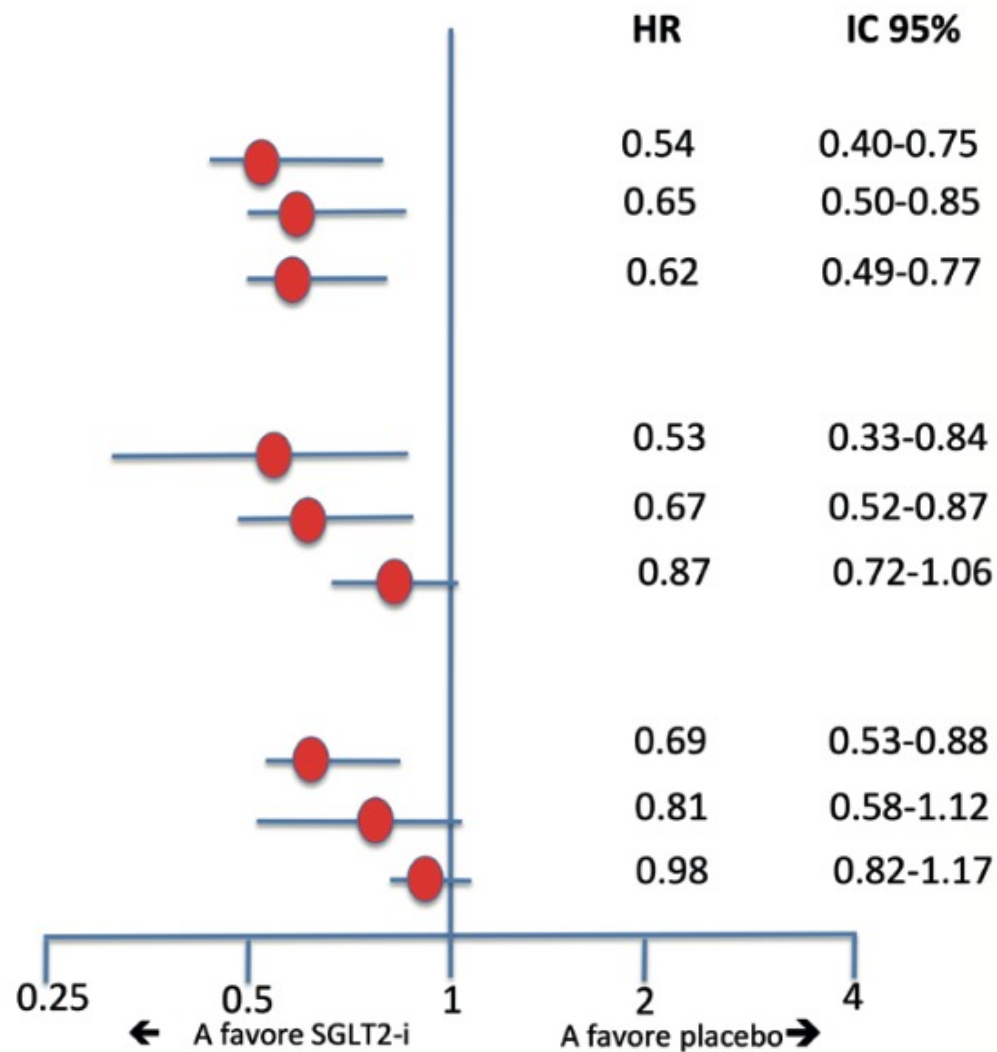
DECLARE – TIMI 58¹¹

- Prevenzione secondaria 39%

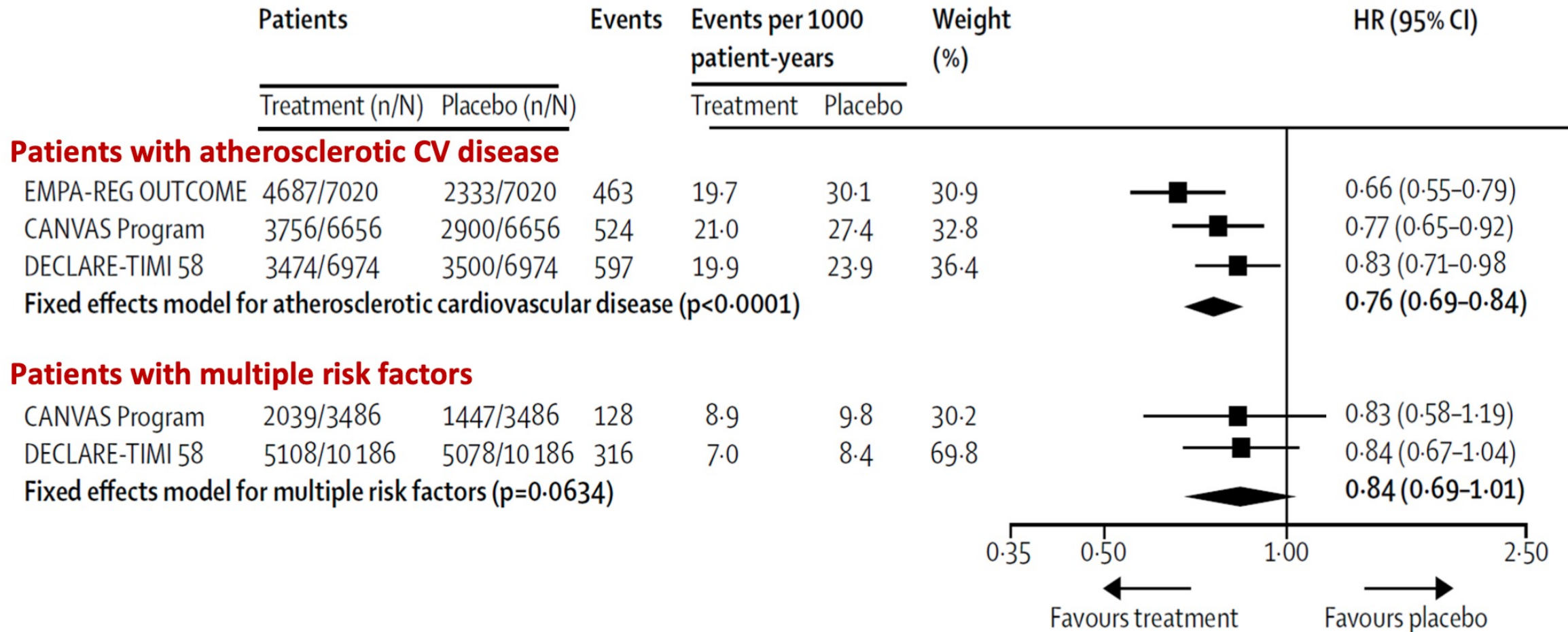
Composito Renale

HHF

Mortalità CV

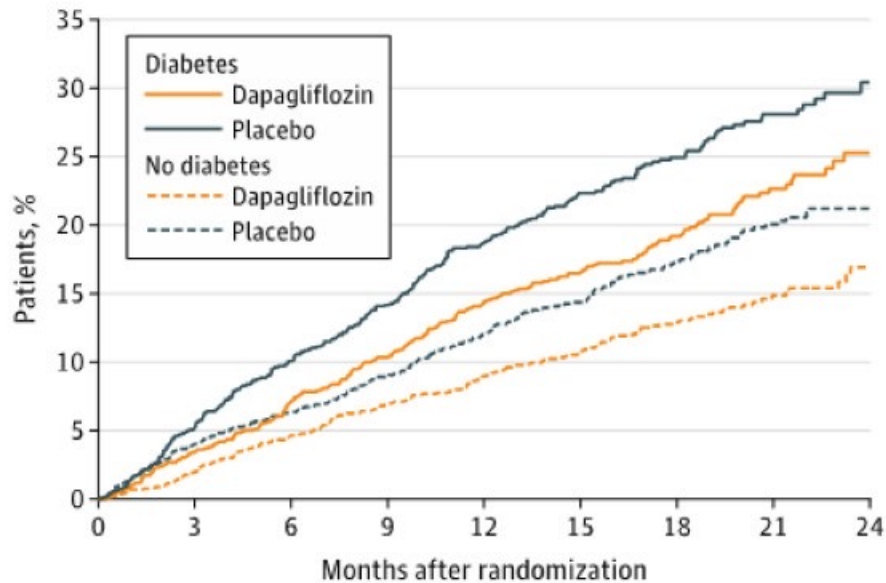


Large SGLT2 inhibitor RCTs: Effect on heart failure hospitalization



SGLT2 Inhibitor Treatment in HFrEF: Significant Reductions Regardless of Diabetes Status at Baseline

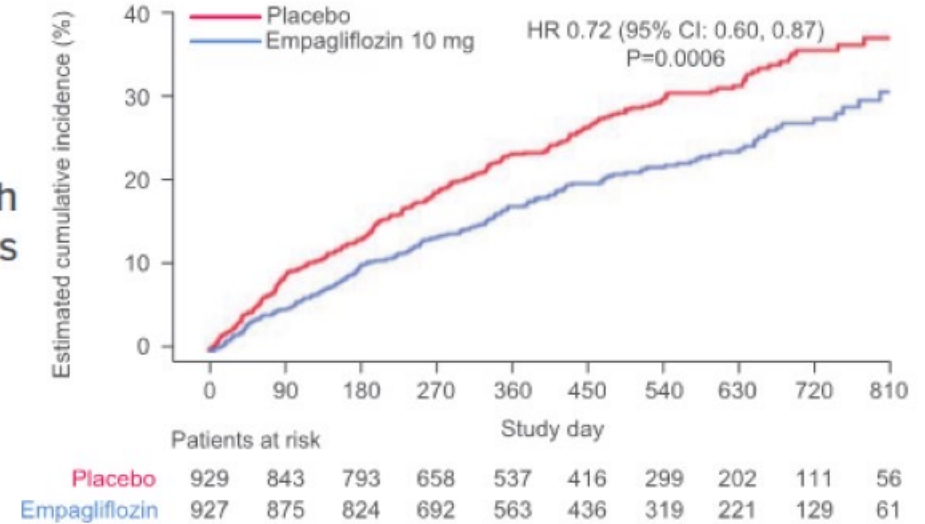
DAPA-HF^[a]



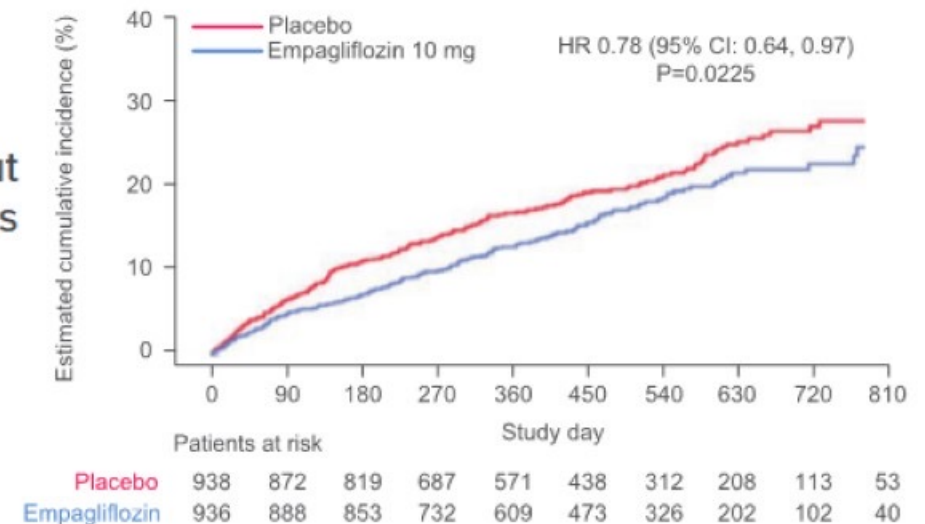
No. at risk									
No diabetes									
Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121
Diabetes									
Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

Emperor-Reduced^[b]

With Diabetes



Without Diabetes



SGLT2, sodium-glucose cotransporter 2.

a. Petrie MC, et al. JAMA. 2020;323:1353-1368; b. Anker SD, et al. Circulation. 2021;143:337-349.

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner-La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

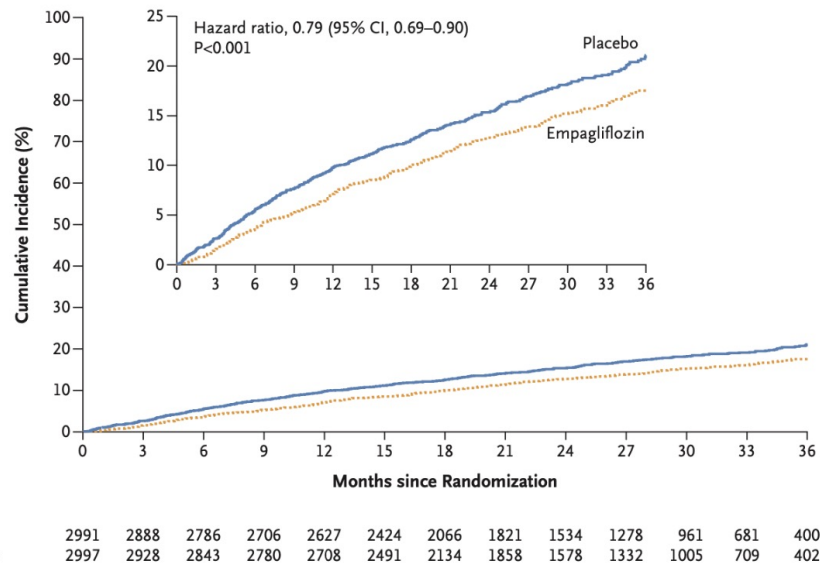
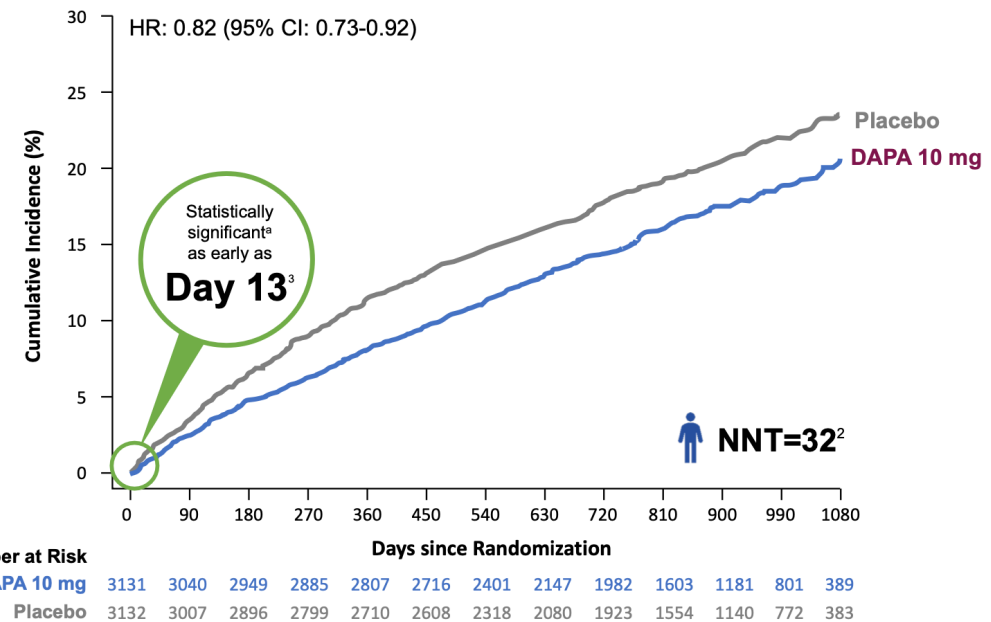


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.

The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

SGLT2i nel HFpEF

DELIVER- Primary Composite of CV Death, hHF or Urgent HF Visit¹



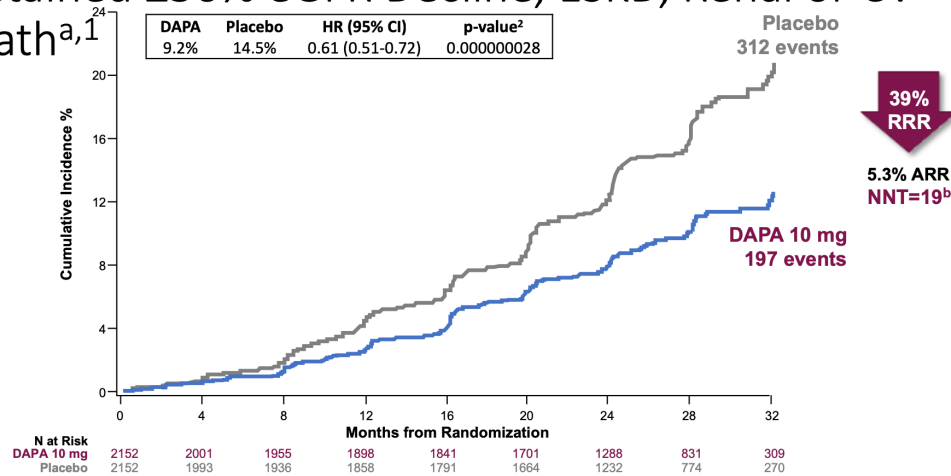
*Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; $p=0.046$), with sustained statistical significance starting at Day 15.

1. Solomon SD et al. *N Engl J Med.* 2022;387(12):1089-1098; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain; 3. Vaduganathan M et al. Online ahead of print. *JAMA Cardiol.* 2022.

SGLT2i nel CKD

DAPA-CKD

Primary Composite Outcome:
Sustained $\geq 50\%$ eGFR Decline, ESKD, Renal or CV
Death^{a,1}



^aESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR $<15\text{mL}/\text{min}/1.73\text{m}^2$ for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.¹; ^b95% CI, 15 to 27.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

Characteristic	Empagliflozin (N=3304)	Placebo (N=3305)
Cause of kidney disease — no. (%)		
Diabetic kidney disease	1032 (31.2)	1025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

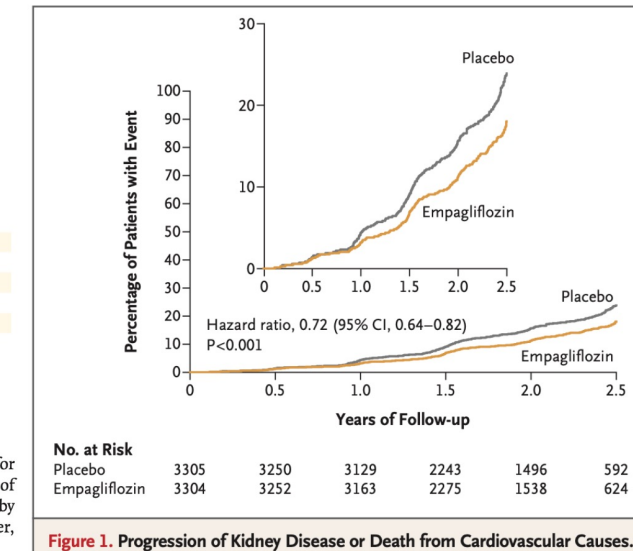


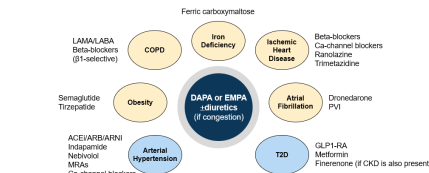
Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Ad esclusivo uso del Medical Affairs.



2023 ESC-HFA/EHRA/ESH Scientific Statement on Patient Profiling in Heart Failure with Preserved Ejection Fraction

**2023 ESC-HFA/EHRA/ESH Scientific Statement:
SGLT2 Inhibitors Are a Foundational Therapy for All HFpEF Patient Phenotypes**



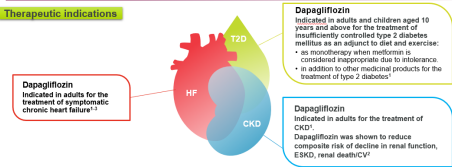
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARRA = angiotensin-receptor neoprilan analog; Ca = calcium; CKD = chronic kidney disease; CVD = chronic obstructive pulmonary disease; DAPA = dapagliflozin; ESRD = End-stage Renal Disease; EMPA = Empagliflozin; EMPA = Empagliflozin; ESC = European Society of Cardiology; ESH = European Society of Hypertension; GLP1-RA = glucagon-like peptide-1 receptor agonist; HFA = Heart Failure Association; HFpEF = heart failure with preserved ejection fraction; JAMA = long-acting muscarinic antagonist; LABA = long-acting beta agonist; MRA = mineralocorticoid receptor antagonist; PVI = pulmonary vein isolation; SGLT2 = sodium-glucose co-transporter 2; T2D = type 2 diabetes.

Author SD et al. Online ahead of print. *Eur J Heart Fail* 2023.

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Ongoing clinical trials beyond HF

Dapagliflozin provides patients protection from serious cardiac and renal outcomes associated with HF, T2D and CKD¹



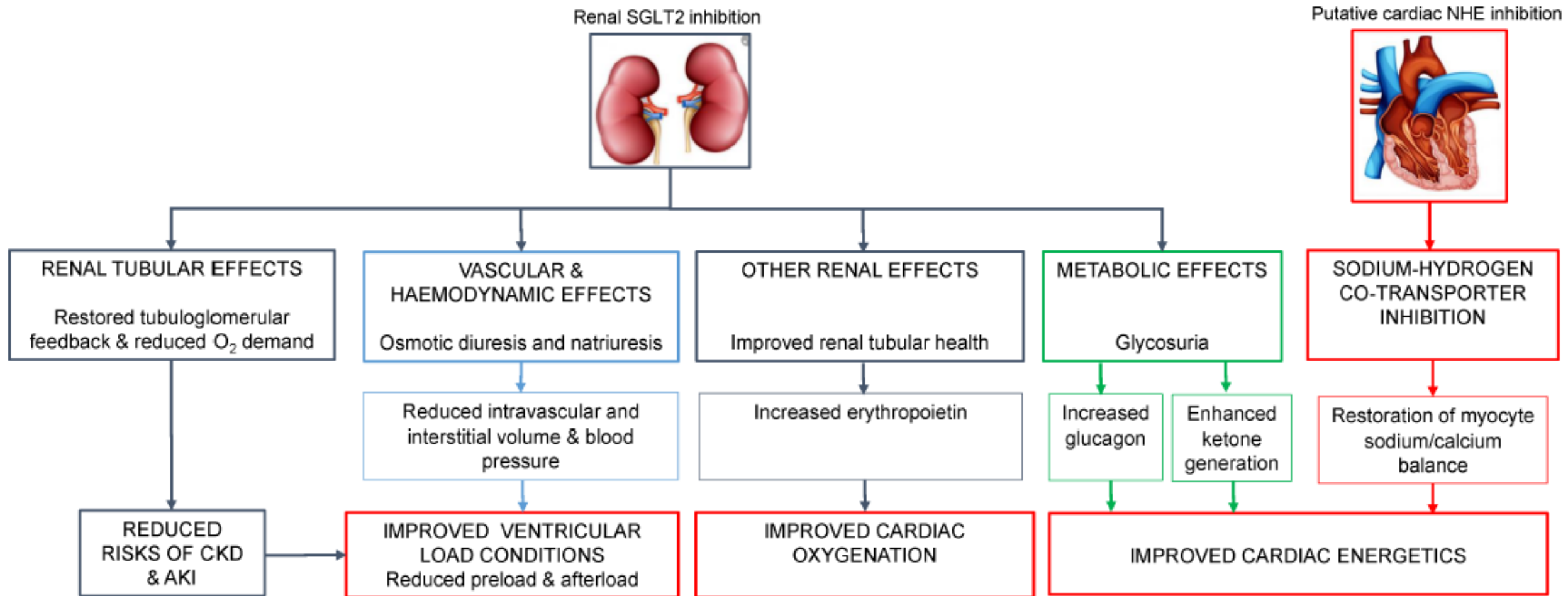
CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage kidney disease; GFR, glomerular filtration rate; HF, heart failure; **HFpEF**, heart failure with reduced ejection fraction; DM2, Diabetes mellitus type 2

1. AstraZeneca AS. Dapagliflozin EU Summary of Product Characteristics 2021. Available at: https://aoc.astra.com/assetdocuments/communitry-register/2021/02/18/005152430x_152433_en.pdf (Accessed August 2021). 2. Hembree HL, et al. *Endr J Med* 2020;303:1430–1440

3. "Baseline Characteristics of Patients With HF With Mildly Reduced and Preserved Ejection Fraction: ICDLIVER Trial."

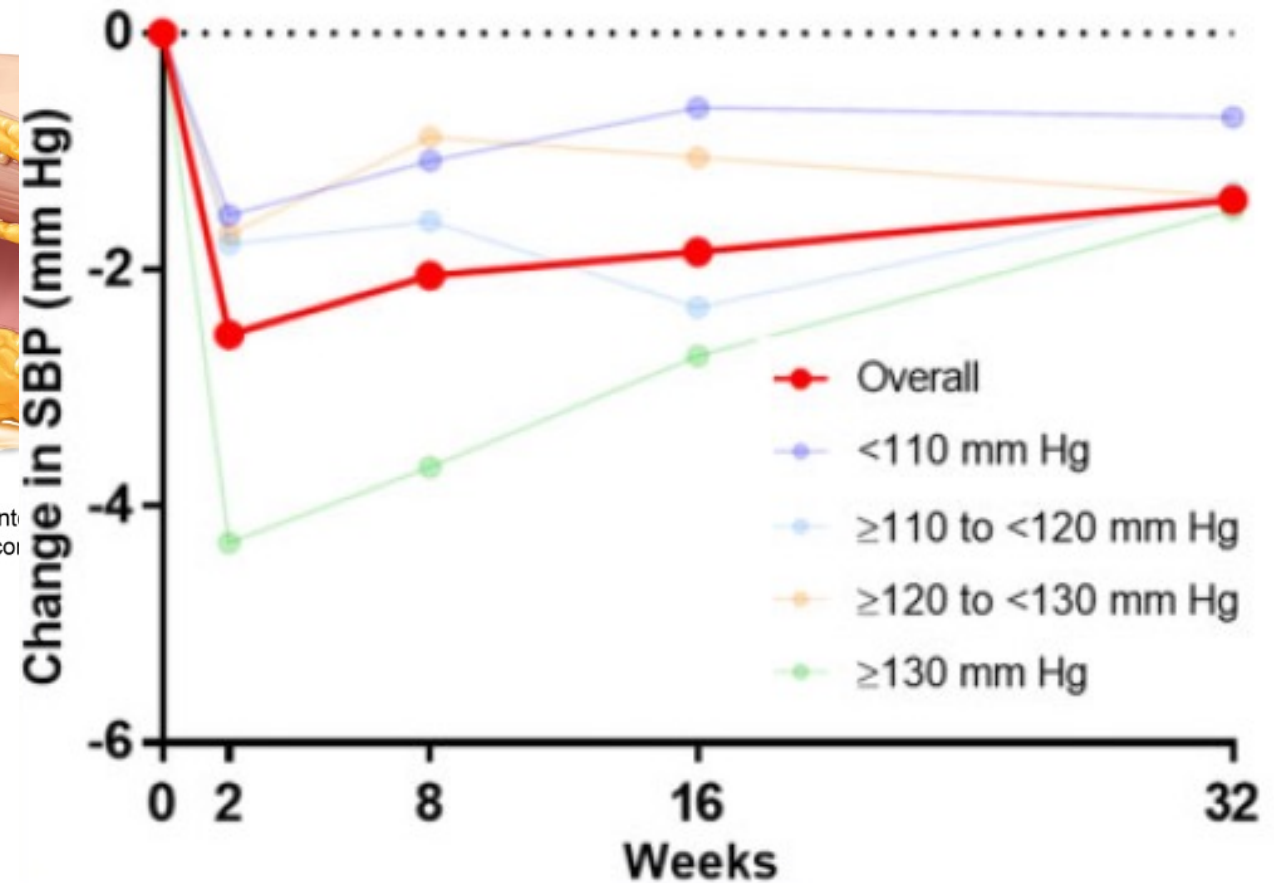
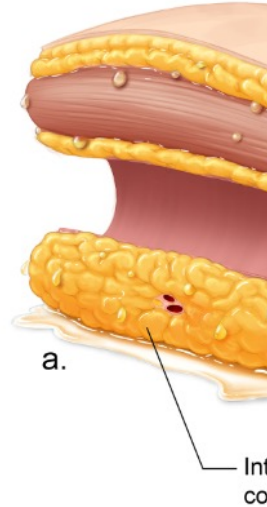
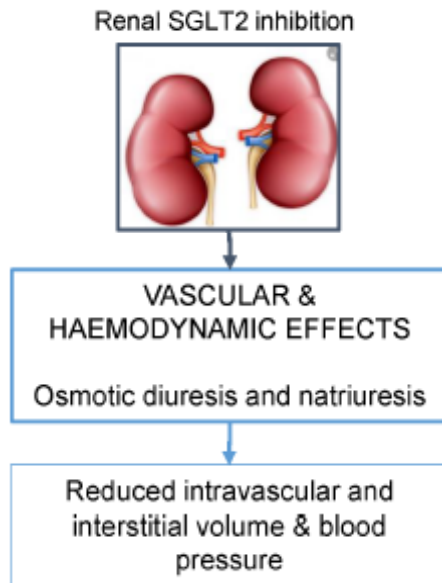
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Effects of SGLT2 inhibition on cardiorenal pathophysiology



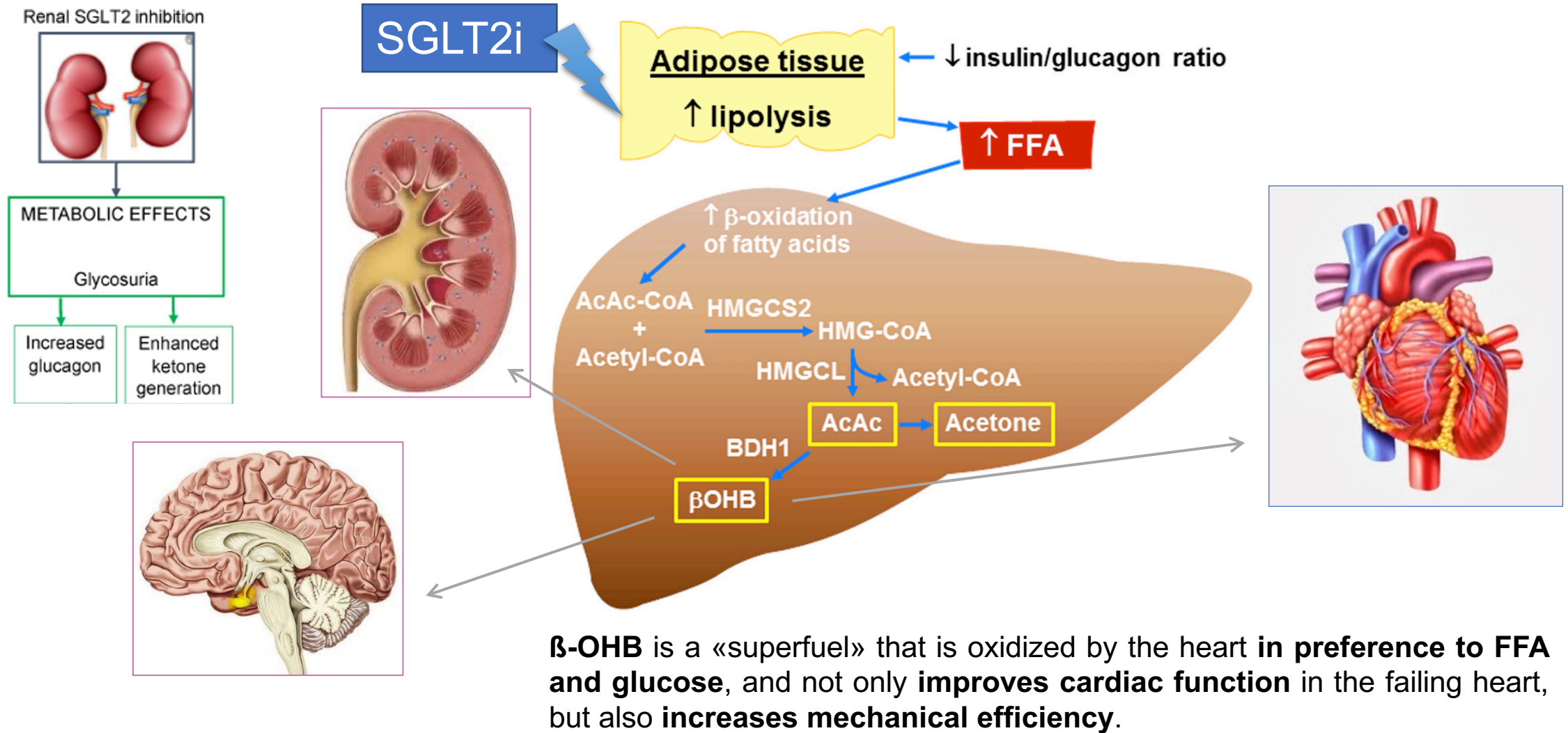
Effects of SGLT2 inhibition on cardiorenal pathophysiology

VASCULAR & HAEMODYNAMIC EFFECTS



Effects of SGLT2 inhibition on cardiorenal pathophysiology

METABOLIC EFFECTS





SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review

Subodh Verma¹ · John J. V. McMurray²

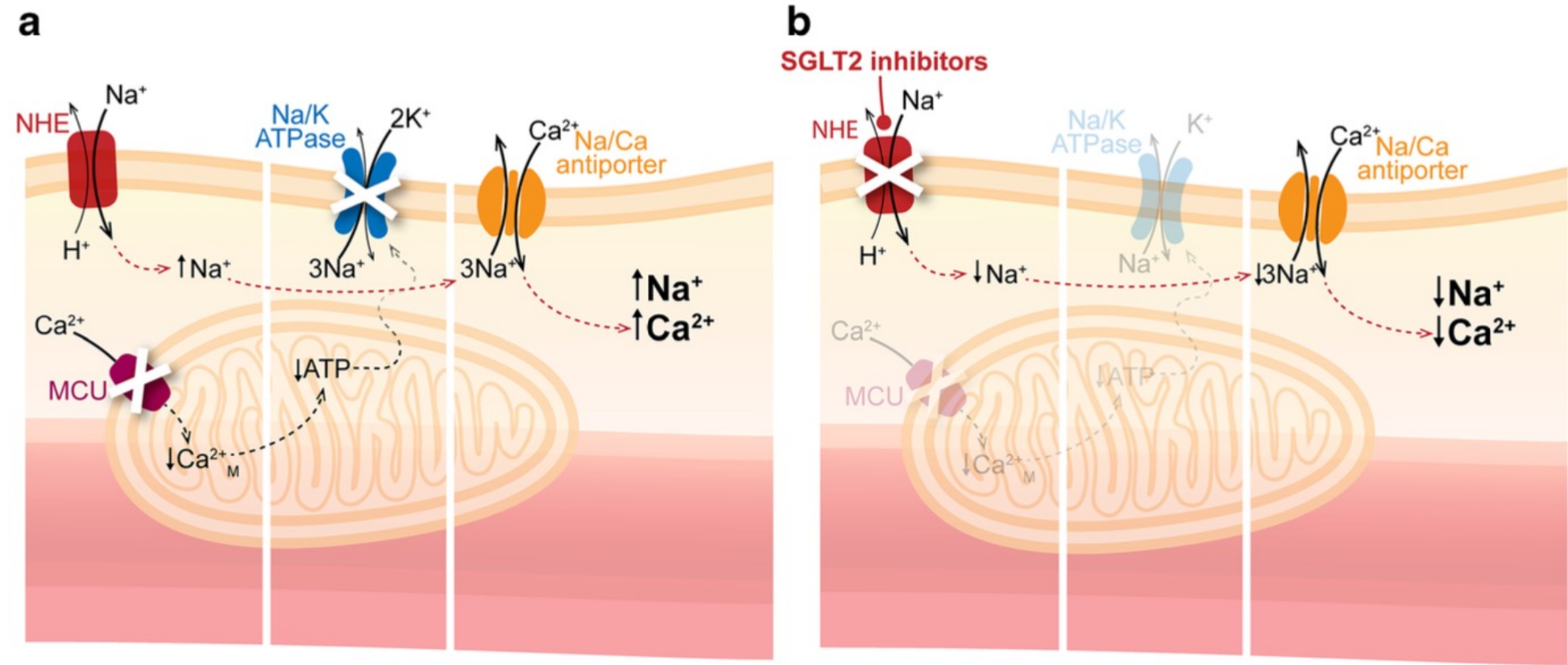
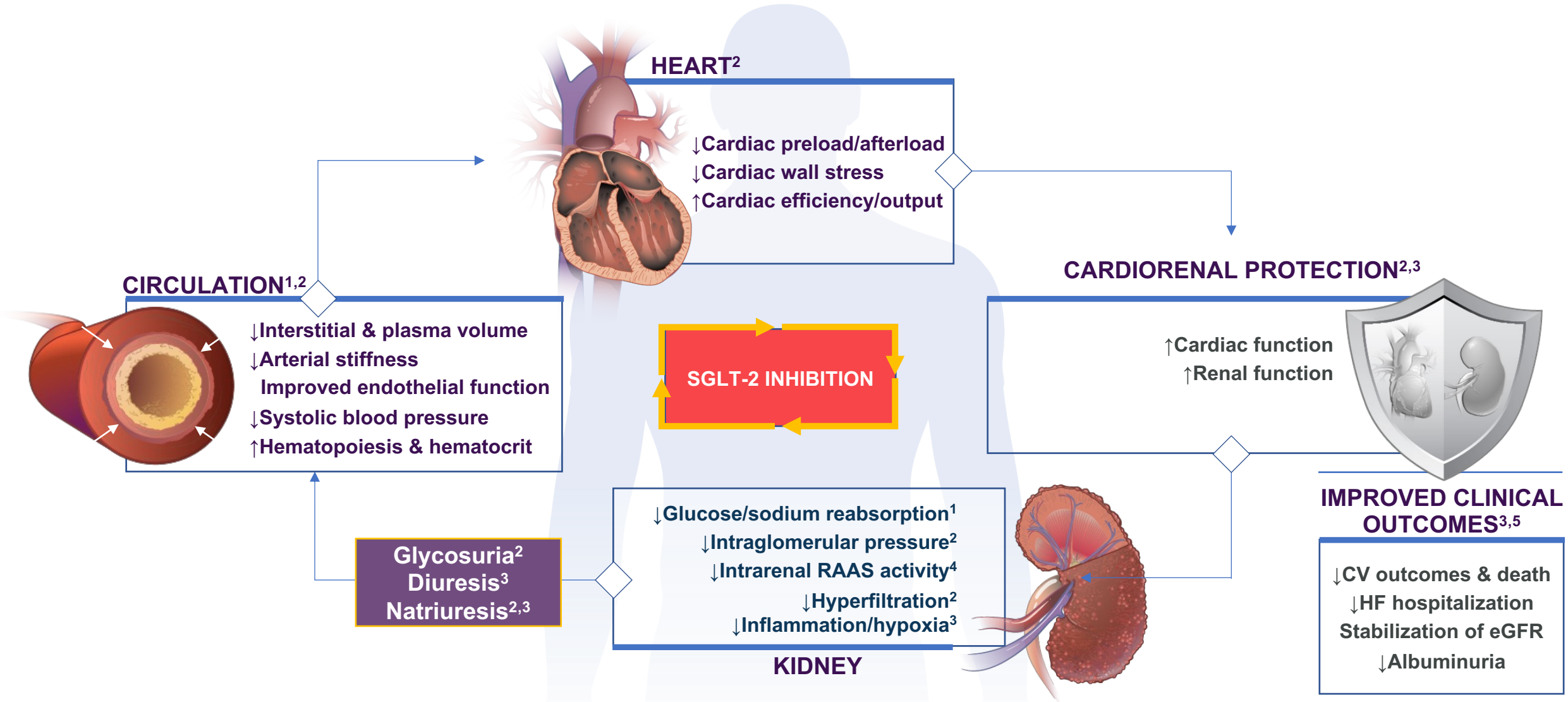


Fig. 5 (a) Diabetes-associated heart failure is characterised by an increase in myocardial expression of NHEs. This can lead to elevations in cytoplasmic sodium and calcium levels, which may contribute to the pathology of heart failure. (b) Recent data suggest that SGLT2 inhibitors

block NHEs, consequently reducing cytoplasmic sodium and calcium, thus offering cardioprotection. Ca²⁺_M, mitochondrial calcium; MCU, mitochondrial Ca²⁺ uniporter. © G. Oomen 2018. This figure is available as part of a [downloadable slideset](#)

SGLT-2i-mediated Adaptations to Glucose, Sodium and Fluid Dynamics Contribute to Cardiorenal Protection



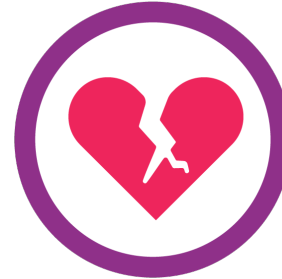
There is a significant unmet need for new and effective therapies in patients with acute MI at high risk of HF¹



Ischaemic heart disease, including acute MI, is one of the **leading causes** of disability in the world²



More than **7 million cases** of acute MI occur every year worldwide³



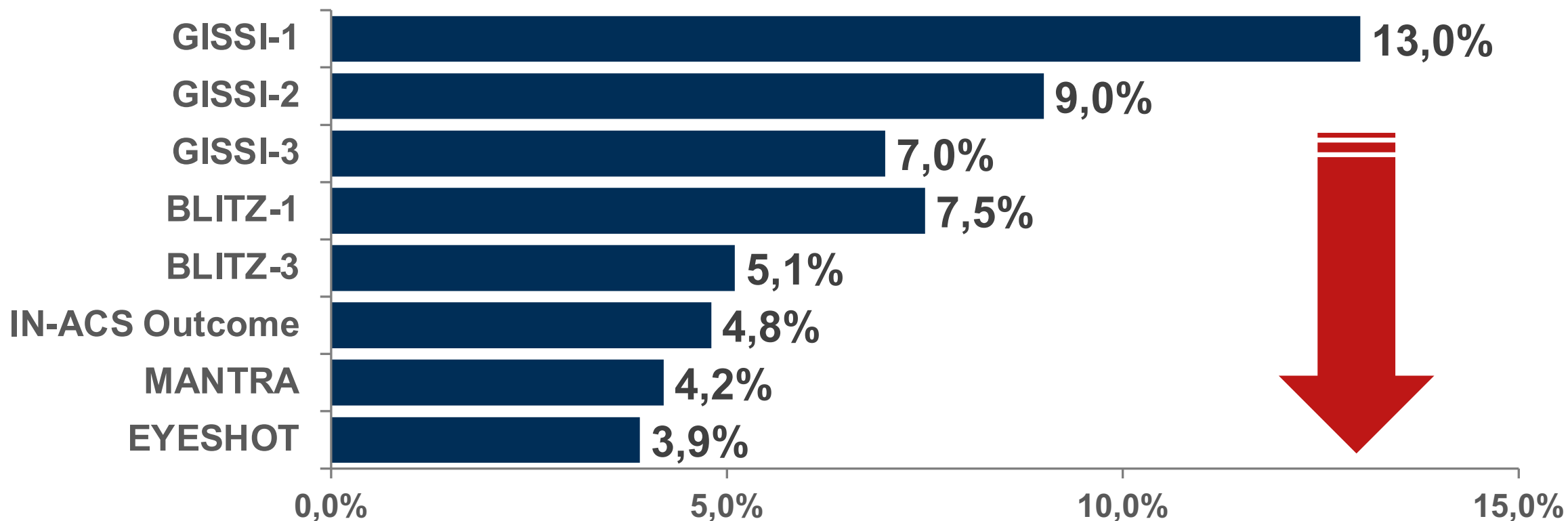
HF is one of the **most common** and **severe complications of acute MI** and is associated with a **3-fold increase in mortality**^{4,5}



Approximately one-third of patients with acute MI are **hospitalized for HF** or have **died within 5 years after MI**⁶

IMPATTO DELLA RICERCA SULLA MORTALITÀ CV

In-hospital deaths for AMI in Italy: 1984 - 2014



Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective

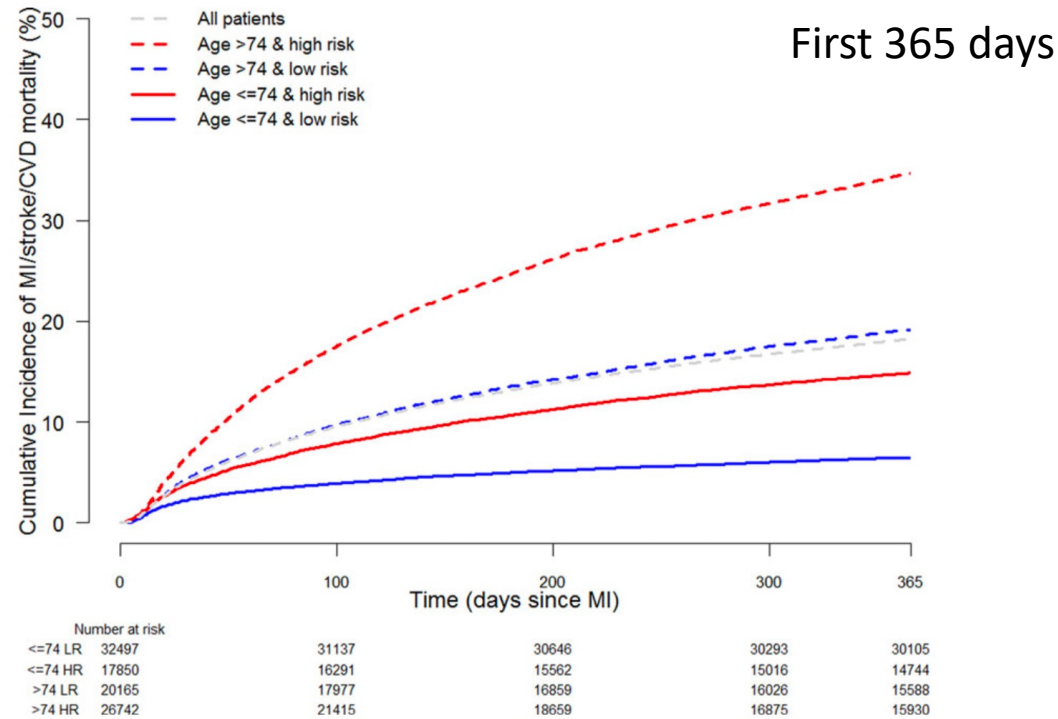


Figure 3 Kaplan–Meier estimate of the risk of the combined endpoint (myocardial infarction, ischaemic stroke, or cardiovascular death) during the first 365 days after the index myocardial infarction, stratified by age and high- vs. low-risk patients.

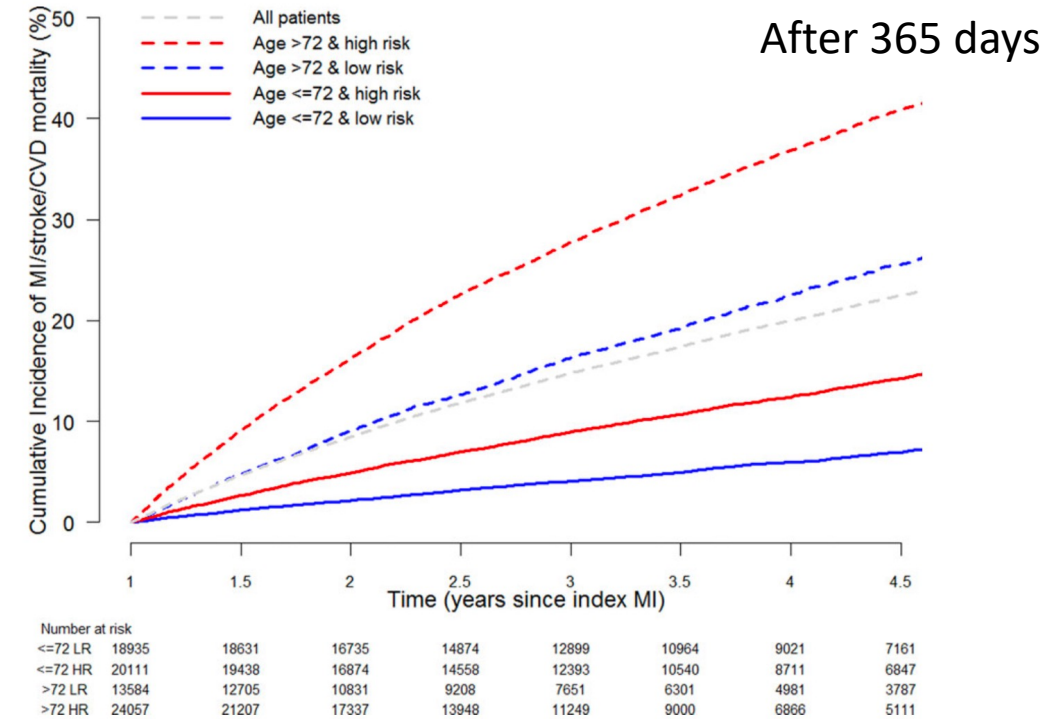


Figure 5 Kaplan–Meier estimate of the risk of the combined endpoint (myocardial infarction, ischaemic stroke, or cardiovascular death) after 365 days after index myocardial infarction until end of study for stable post- myocardial infarction patients, stratified by age and high- vs. low-risk patients.

Conclusions

Risk of cardiovascular events appeared high beyond the first year post-MI, indicating a need for prolonged surveillance, particularly in patients with additional risk factors.

BLITZ-HF: a nationwide initiative to evaluate and improve adherence to acute and chronic heart failure guidelines

Michele Massimo Gulizia^{1,2*}, Francesco Orso³, Andrea Mortara⁴, Donata Lucci², Nadia Aspromonte⁵, Leonardo De Luca⁶, Giuseppe Di Tano⁷, Giuseppe Leonardi⁸, Alessandro Navazio⁹, Giovanni Pulignano⁶, Furio Colivicchi¹⁰, Andrea Di Lenarda¹¹, and Fabrizio Oliva¹², on behalf of the BLITZ-HF Investigators[†]

¹Division of Cardiology, Garibaldi-Nesima Hospital, Catania, Italy; ²Heart Care Foundation, ANMCO Research Center, Florence, Italy; ³Heart Failure Clinic, Division of Geriatric Medicine and Intensive Care Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ⁴Department of Clinical Cardiology, Policlinico di Monza, Monza, Italy; ⁵Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ⁶Division of Cardiology, Department of Cardiosciences, A.O. San Camillo-Forlanini, Rome, Italy; ⁷Division of Cardiology, Ospedale di Cremona, Cremona, Italy; ⁸Heart Failure Unit, Policlinico Catania PO Rodolico, Catania, Italy; ⁹Cardiology Division, Arcispedale S. Maria Nuova, Azienda USL di Reggio Emilia – IRCCS, Reggio Emilia, Italy; ¹⁰Division of Clinical Cardiology, San Filippo Neri Hospital, Rome, Italy; ¹¹Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy; and ¹²Intensive Cardiac Care Unit, De Gasperi Cardiac Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Received 8 October 2021; revised 22 June 2022; accepted 25 June 2022

Aims

To assess adherence to guideline recommendations among a large network of Italian cardiology sites in the management of acute and chronic heart failure (HF) and to evaluate if an ad-hoc educational intervention can improve their performance on several pharmacological and non-pharmacological indicators.

Methods and results

BLITZ-HF was a cross-sectional study based on a web-based recording system with pop-up reminders on guideline recommendations used during two 3-month enrolment periods carried out 3 months apart (Phase 1 and 3), interspersed by face-to-face macro-regional benchmark analyses and educational meetings (Phase 2). Overall, 7218 patients with acute and chronic HF were enrolled at 106 cardiology sites. During the enrolment phases, 3920 and 3298 patients were included, respectively, 84% with chronic HF and 16% with acute HF in Phase 1, and 74% with chronic HF and 26% with acute HF in Phase 3. At baseline, adherence to guideline recommendations was already overall high for most indicators. Among acute HF patients, an improvement was obtained in three out of eight indicators, with a significant rise in echocardiographic evaluation. Among chronic HF patients with HF and preserved or mid-range ejection fraction, performance increased in two out of three indicators: creatinine and echocardiographic evaluations. An overall performance improvement was observed in six out of nine indicators in ambulatory HF with reduced ejection fraction patients with a significant increase in angiotensin receptor–neprilysin inhibitor prescription rates.

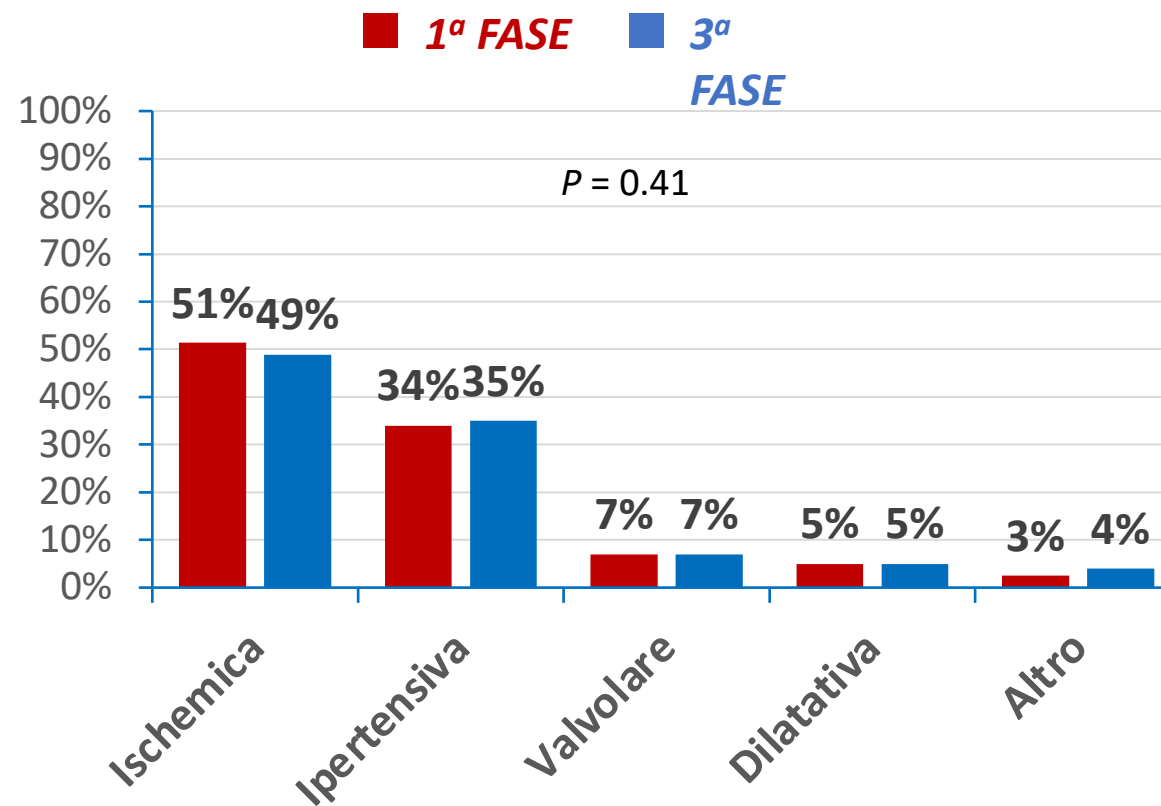
Conclusions

Within a context of an already elevated level of adherence to HF guideline recommendations, a structured multifaceted educational intervention could be useful to improve performance on specific indicators. Extending this approach to other non-cardiology healthcare professionals, who usually manage patients with HF, should be considered.

Keywords

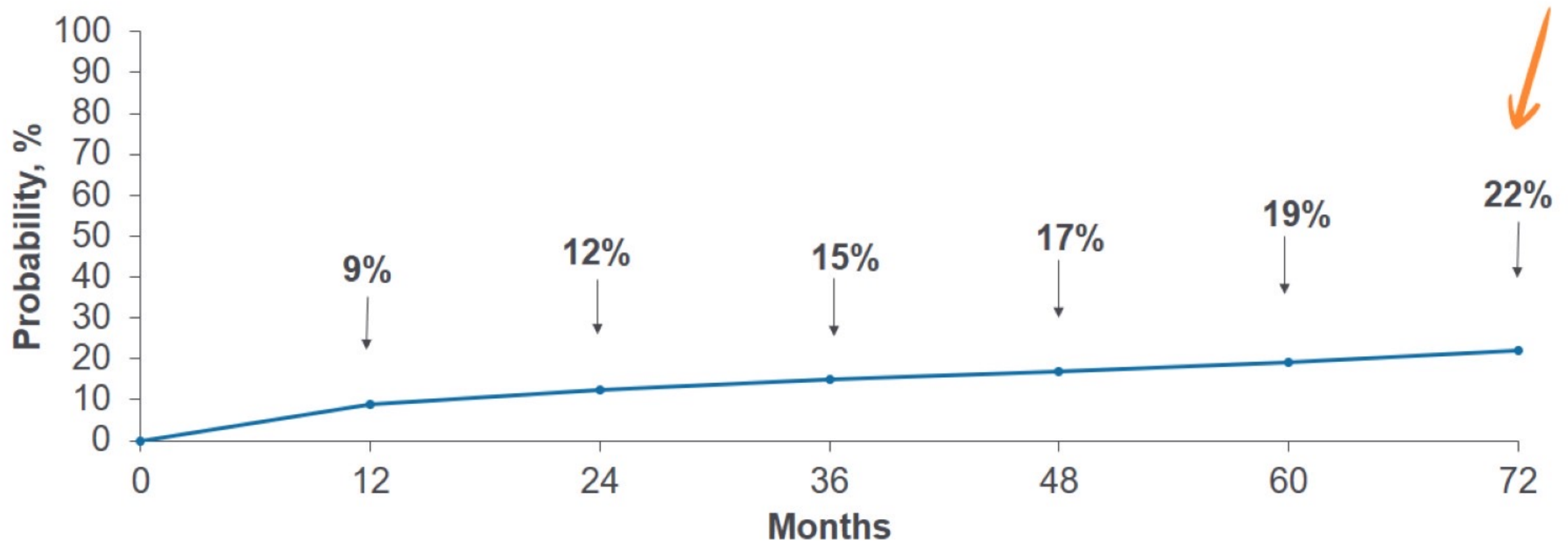
Acute heart failure • Chronic heart failure • Adherence • Registry • Guidelines

Eziologia principale in pazienti con HFrEF



Cumulative Incidence of HF After AMI in Patients With No Previous HF History

Among > 337,000 Patients Hospitalized With Acute MI and No Previous History of HF, Nearly 1 in 5 Patients Developed a Subsequent Diagnosis of HF Within 5 Years



Heart failure is one of the most common and severe complications in patients post-MI

Development of heart failure after MI is associated with an increased risk of mortality and impaired quality of life¹

The risk of heart failure is at its highest in the early post-MI phase²

Risk factors include MI size and timing of acute treatment²⁻⁴

There are several mechanisms that contribute to the risk of heart failure after MI³

All mechanisms include:³

- Myocardial stunning
- Inflammation
- Fibrosis
- Remodelling
- Neurohormonal activation
- Cardiomyocyte necrosis
- Reperfusion injury
- Microvascular obstruction
- Haemorrhage



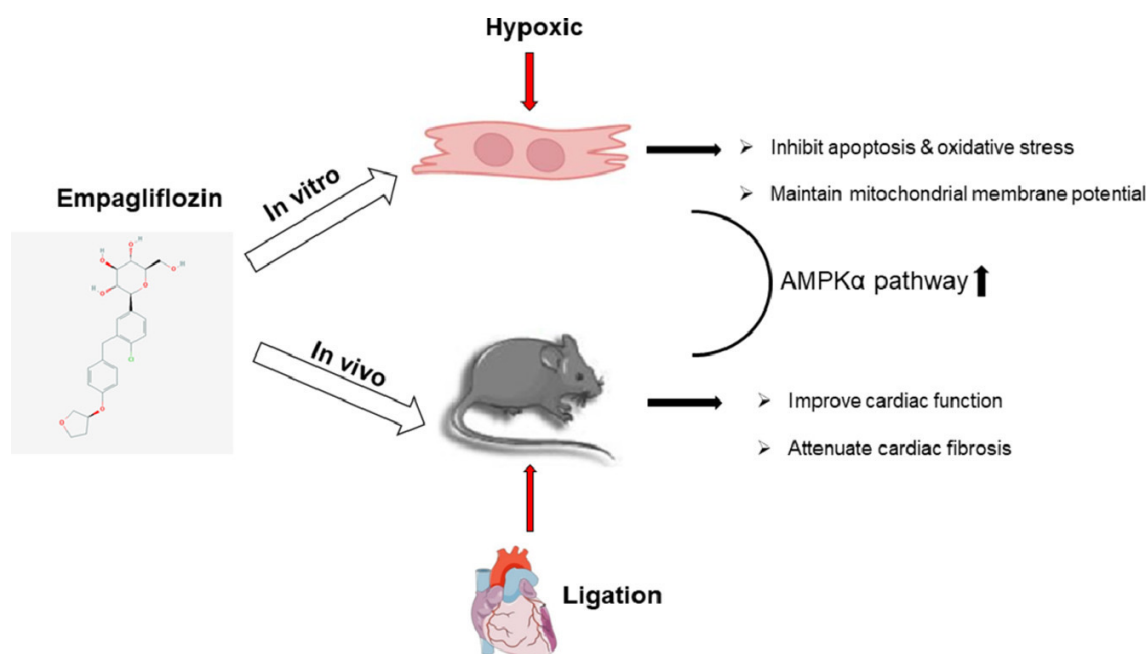
Conoscere, Curare, il Cuore 2024

Impiego delle Glifozine nell'Infarto Miocardico Acuto

Dati Sperimentali

Empagliflozin prevents from early cardiac injury post myocardial infarction in non-diabetic mice

Yihai Liu^{a, b, #}, Mingyue Wu^{a, #}, Jiamin Xu^a, Biao Xu^{a, b}  , Lina Kang^a  



Methods

C57BL/6 mice underwent left artery coronary artery descending (LAD) ligation to induce MI. Following the surgery, animals were randomized to receive saline or empagliflozin. Empagliflozin (EMPA) was administrated at 10mg/kg per day by oral gavage for 2 weeks. Echocardiography, histological staining and qualitative RT-PCR were performed to assess the cardiac remodeling post MI. In vitro experiments were performed to evaluate the effect of empagliflozin on apoptosis, oxidative stress and mitochondrial membrane potential of cardiomyocyte subjected to hypoxic treatment.

Results

Compared with MI group, the empagliflozin treatment group showed improved cardiac function, reduced infarct size and interstitial fibrosis. Empagliflozin also inhibited cardiomyocyte apoptosis by alleviating oxidative stress and restoring mitochondrial membrane potential. Immunoblotting analysis revealed activated AMP-activated protein kinase (AMPK) signaling may mediated the cardioprotective role of empagliflozin.

Conclusions

In summary, empagliflozin could inhibit cardiomyocyte apoptosis and improve cardiac remodeling early MI, which provided insights into the benefic effect of empagliflozin on MI patients without diabetes.

Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics



FIGURE 2 Empagliflozin Improves LV Systolic Function Post-MI

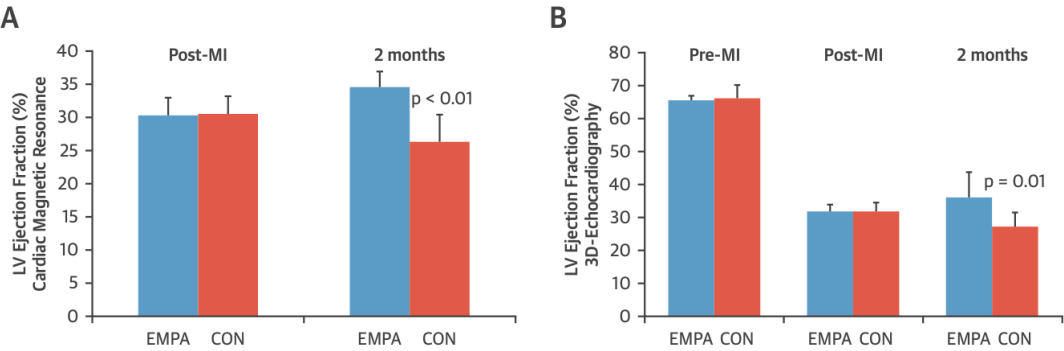


FIGURE 3 Empagliflozin Ameliorates Neurohormonal Activation

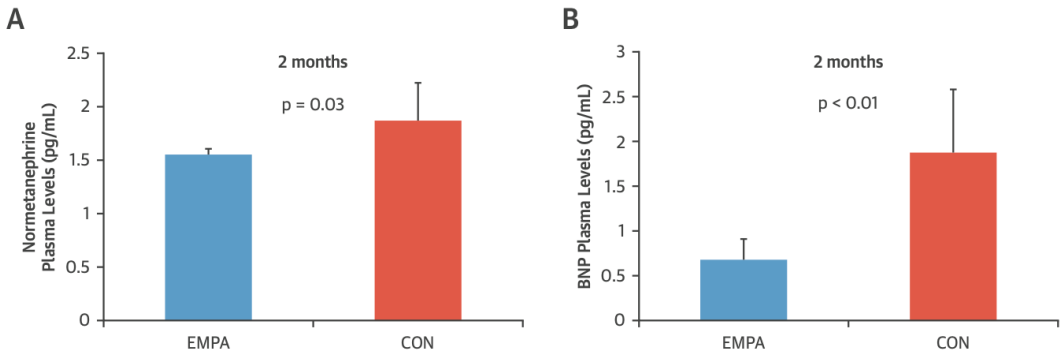


FIGURE 1 Empagliflozin Ameliorates Anatomical LV Remodeling

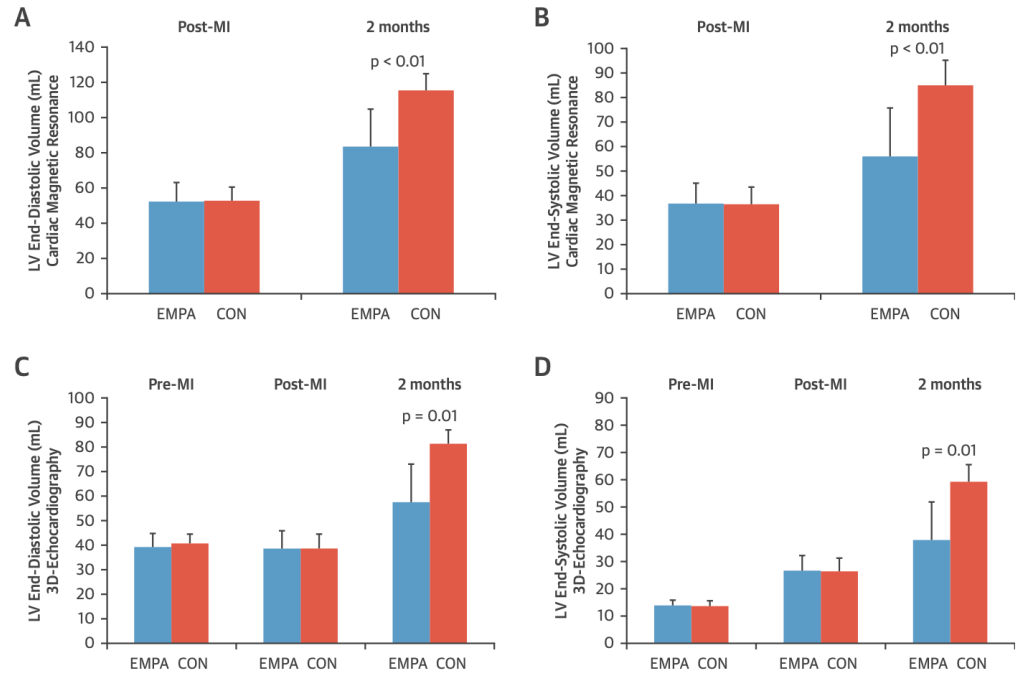
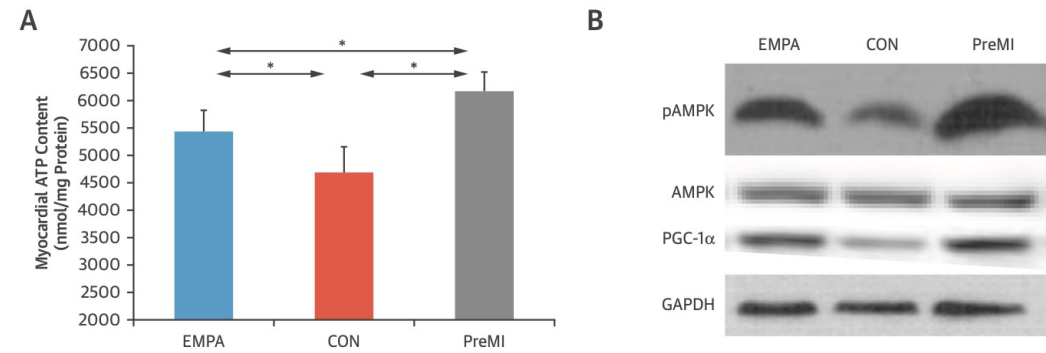
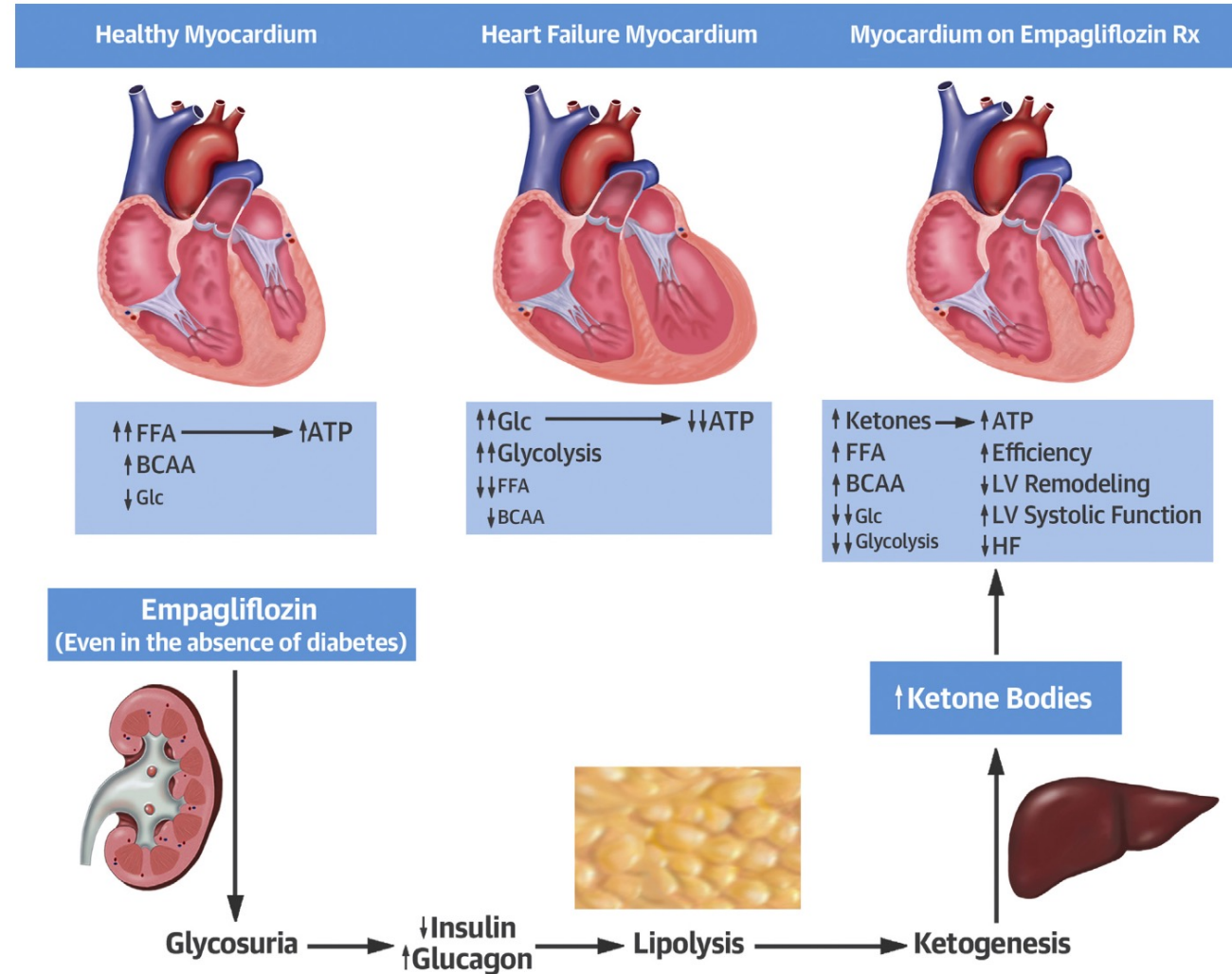


FIGURE 6 Empagliflozin Ameliorates Myocardial Energetic Metabolism



CENTRAL ILLUSTRATION Postulated Effect of Empagliflozin on Heart Failure

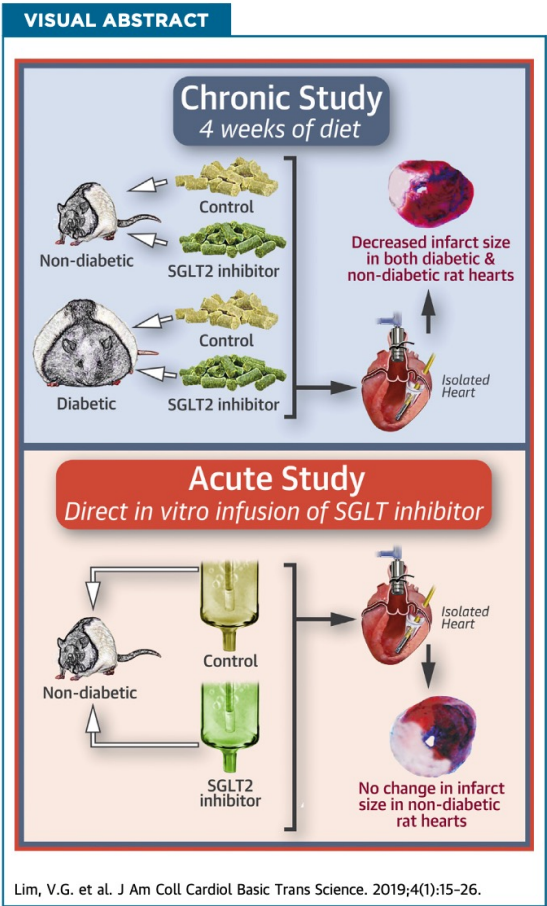


Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2019;73(15):1931-44.

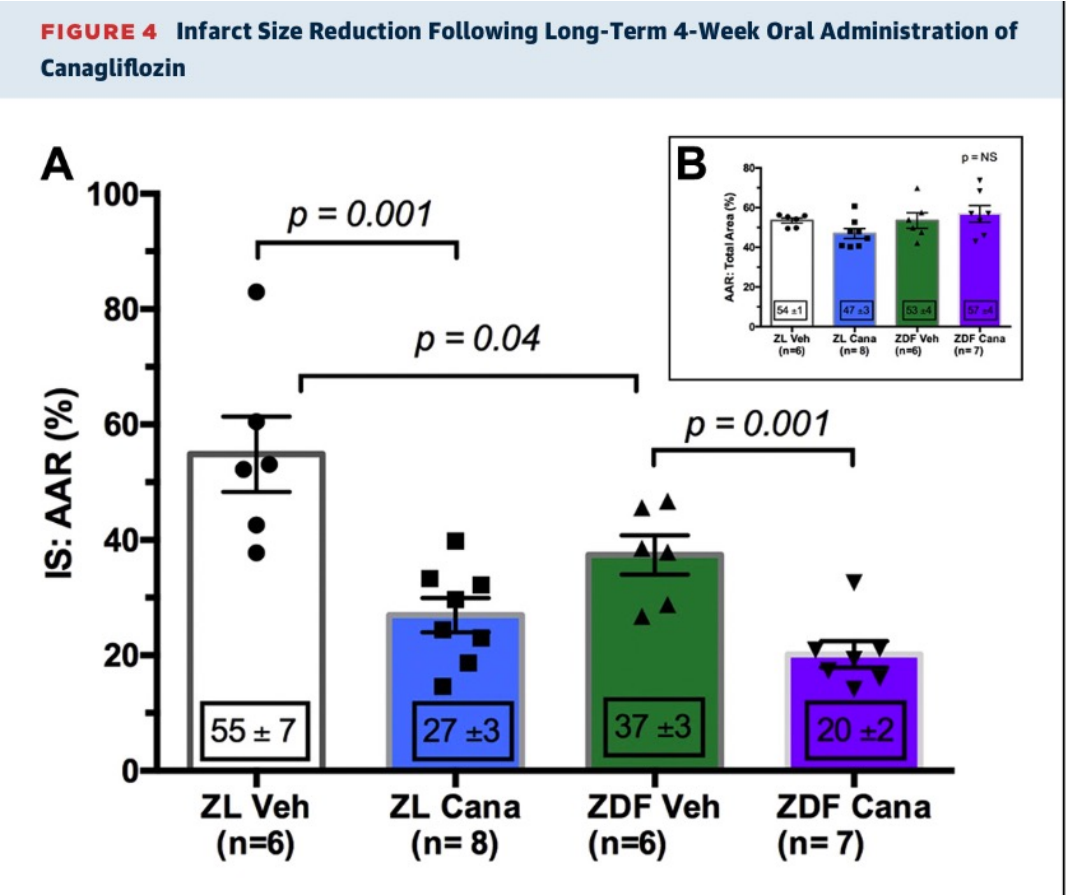
Empagliflozin improves cardiac function by switching away from glucose towards ketone bodies and free fatty acids as source of energy. AMPK = adenosine 5' monophosphate-activated protein kinase; ATP = adenosine triphosphate; BCAA = branched-chain amino acid; FFA = free fatty acid; Glc = glucose; LV = left ventricular; Rx = treatment.

SGLT2 Inhibitor, Canagliflozin, Attenuates Myocardial Infarction in the Diabetic and Nondiabetic Heart

Ven G. Lim, MBChB,^{a,*} Robert M. Bell, PhD,^{a,*} Sapna Arjun, PhD,^a Maria Kolatsi-Joannou, PhD,^b David A. Long, PhD,^b Derek M. Yellon, PhD, DSc^a



- HIGHLIGHTS**
- Long-term SGLT2 inhibition with dietary canagliflozin in diabetic and nondiabetic rats attenuates myocardial ischemia/reperfusion injury ex vivo.
 - This suggests that the improvement in myocardial infarct size by SGLT2 inhibition may occur independent of the glycemic status.
 - Canagliflozin improved hyperglycemia in diabetic rats but importantly did not cause hypoglycemia in nondiabetic rats.
 - Short-term perfusion of the nondiabetic heart with canagliflozin, solubilized in the Langendorff perfusion buffer, had no impact on the myocardial infarct size.



Original Research



Received: Jul 13, 2020
 Revised: Nov 9, 2020
 Accepted: Nov 11, 2020

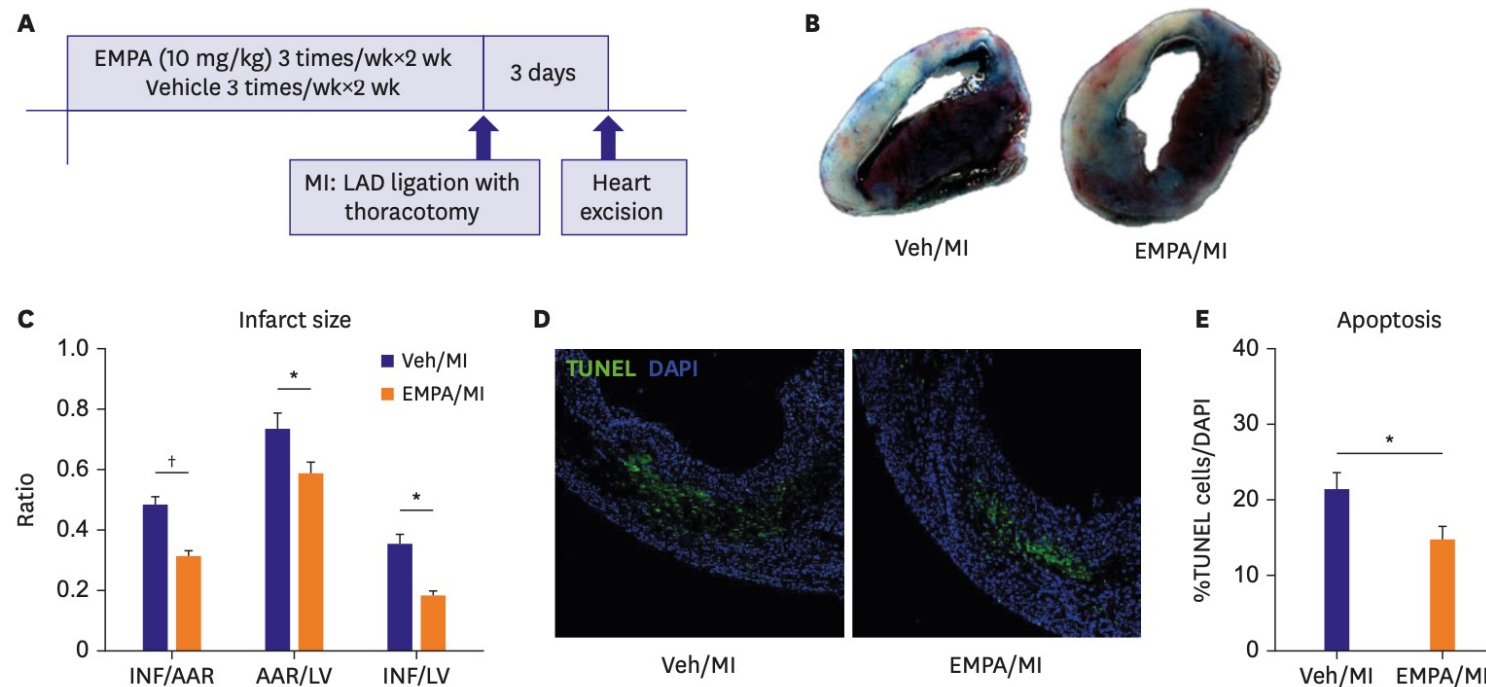
Sodium/glucose Co-Transporter 2 Inhibitor, Empagliflozin, Alleviated Transient Expression of SGLT2 after Myocardial Infarction

Soo Yong Lee , MD, PhD^{1,2}, Tae Wook Lee , PhD³, Gyu Tae Park , MS³, Jae Ho Kim , PhD^{2,3}, Hyun-Chae Lee , PhD⁴, Jung-Hwa Han , PhD^{4,6}, Aeseon Yoon , BS^{4,6}, Dahye Yoon , PhD⁵, Shukmann Kim , PhD⁵, Soon Myung Jung , MD¹, Jin Hee Choi , MD, PhD¹, Min Ku Chon , MD, PhD¹, Sang Hyun Lee , MD, PhD¹, Ki Won Hwang , MD¹, Jeongsu Kim , MD, PhD¹, Yong Hyun Park , MD, PhD¹, June Hong Kim , MD, PhD¹, Kook Jin Chun , MD, PhD¹, and Jin Hur , PhD^{4,6}

Methods: Mice pre-treated with empagliflozin (EMPA), an SGLT2 inhibitor, showed a significantly reduced infarct size compared with the vehicle group three days post-MI. Interestingly, we confirmed SGLT2 localized in the infarct zone. The sequential changes of SGLT2 expression after MI were also evaluated.

Results: One day after MI, SGLT2 transiently appeared in the ischemic areas in the vehicle group and increased until 72 hours. The appearance of SGLT2 was delayed and less in amount compared with the vehicle group. Additionally, there was a significant difference in metabolites, including glucose and amino acids in the ¹H nuclear magnetic resonance analysis between groups.

Conclusions: Our work demonstrates that SGLT2 is transiently expressed in heart tissue early after MI and EMPA may directly operate on SGLT2 to facilitate metabolic substrates shifts.



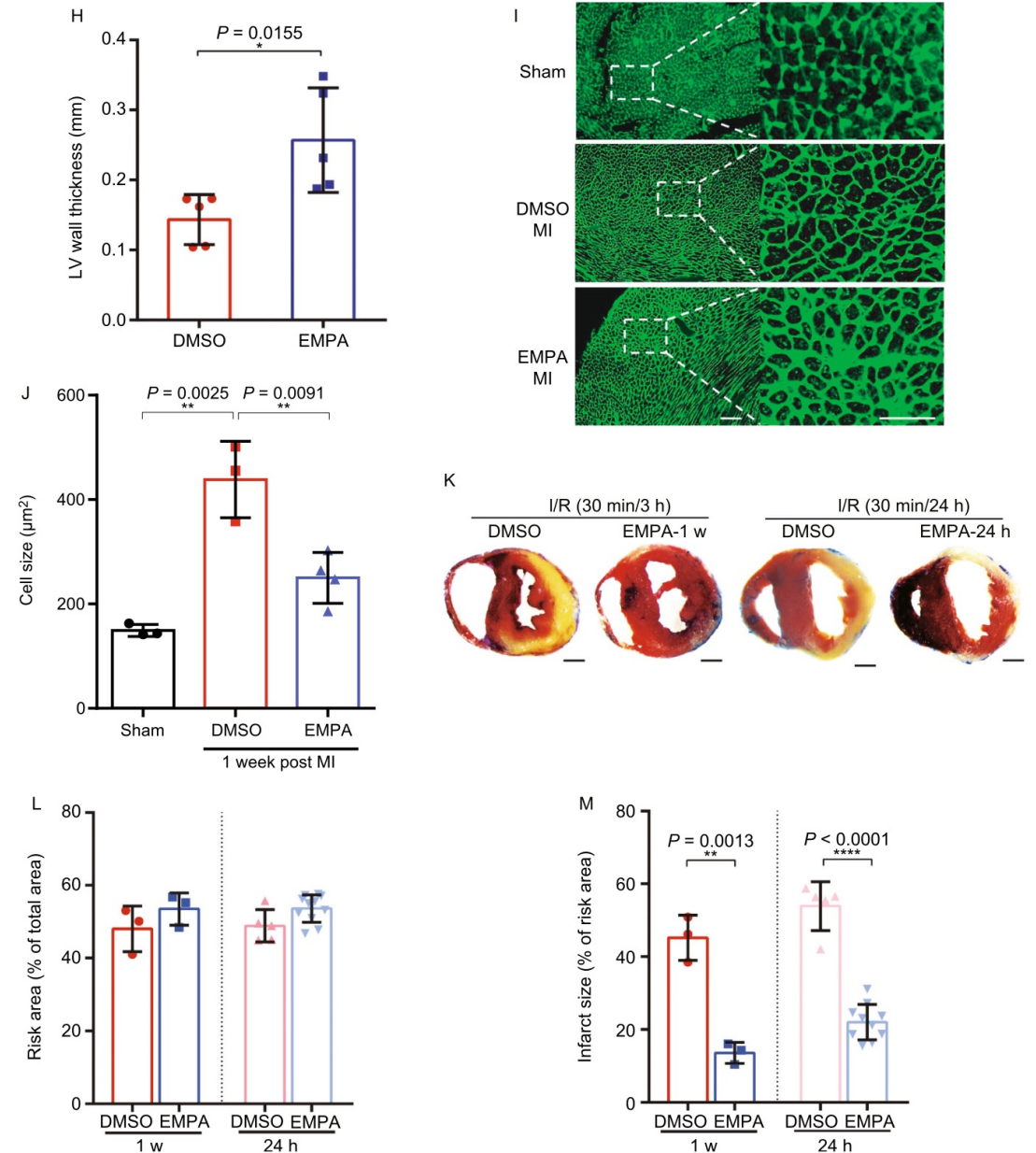


RESEARCH ARTICLE

Cardioprotective mechanism of SGLT2 inhibitor against myocardial infarction is through reduction of autosis

Kai Jiang¹, Yue Xu¹, Dandan Wang¹, Feng Chen¹, Zizhuo Tu¹, Jie Qian¹, Sheng Xu¹, Yixiang Xu², John Hwa³, Jian Li², Hongcai Shang⁴, Yaozu Xiang^{1✉}

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular mortality in patients with diabetes mellitus but the protective mechanism remains elusive. Here we demonstrated that the SGLT2 inhibitor, Empagliflozin (EMPA), suppresses cardiomyocytes autosis (autophagic cell death) to confer cardioprotective effects. Using myocardial infarction (MI) mouse models with and without diabetes mellitus, EMPA treatment significantly reduced infarct size, and myocardial fibrosis, thereby leading to improved cardiac function and survival. In the context of ischemia and nutritional glucose deprivation where autosis is already highly stimulated, EMPA directly inhibits the activity of the Na⁺/H⁺ exchanger 1 (NHE1) in the cardiomyocytes to regulate excessive autophagy. Knockdown of NHE1 significantly rescued glucose deprivation-induced autosis. In contrast, overexpression of NHE1 aggravated the cardiomyocytes death in response to starvation, which was effectively rescued by EMPA treatment. Furthermore, *in vitro* and *in vivo* analysis of NHE1 and Beclin 1 knockout mice validated that EMPA's cardioprotective effects are at least in part through downregulation of autophagic flux. These findings provide new insights for drug development, specifically targeting NHE1 and autosis for ventricular remodeling and heart failure after MI in both diabetic and non-diabetic patients.



SGLT2 inhibitors

Myocardial metabolism switch

SGLT2 transient expression

Na⁺/H⁺ exchanger inhibition

Activation of M2 macrophages

Improved loading conditions

Anti-inflammatory properties



↓ Adverse cardiac remodelling
↓ Infarct size



Conoscere, Curare, Cuore 24

Impiego delle Glifozine nell'Infarto Miocardico Acuto

Dati Clinici



	EMMY (2022) ¹⁴	DAPA-MI (2023) ¹⁵	EMPACT-MI ¹⁶
Design	RCT	Registry-based RCT	RCT
Intervention	Empagliflozin 10mg	Dapagliflozin 10mg	Empagliflozin 10mg
Number of patients	476	4017	6522
Study population	AMI	AMI	AMI
Additional features	CK > 800 IU/L and troponin > 10 x ULN	New Q waves on ECG New LV dysfunction	New LVEF < 45% and/or signs/symptoms of congestion
Primary endpoint	Changes in NT-pro-BNP at 6 months	Death, hospitalization for HF, nonfatal AMI, atrial fibrillation/flutter, type 2 diabetes mellitus, NYHA class, body weight decrease	All-cause mortality and time to first HF hospitalization



ESC

European Society
of Cardiology

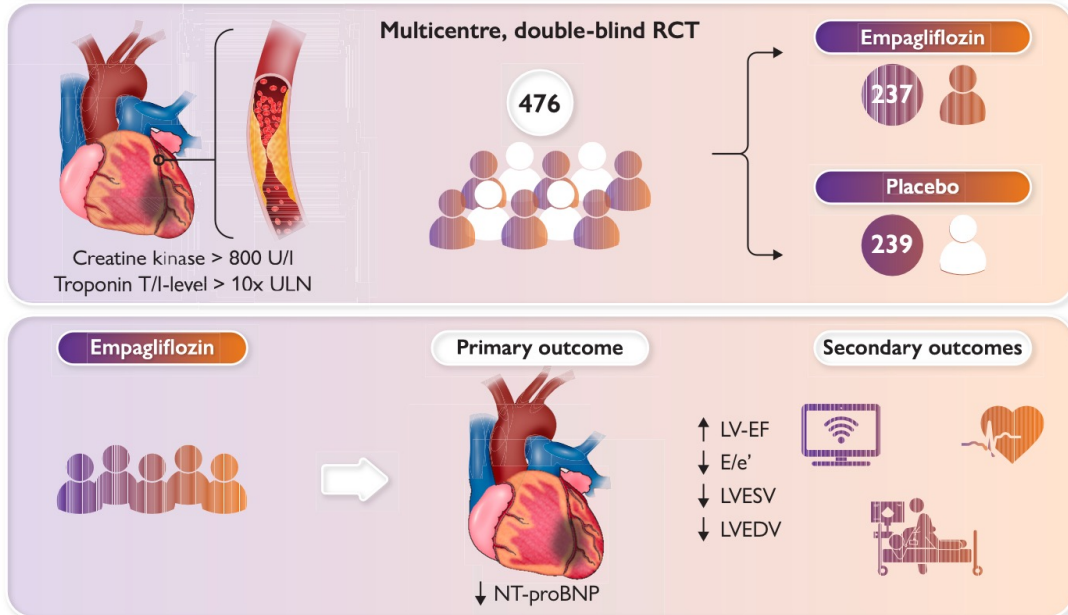
European Heart Journal (2022) 43, 4421–4432
<https://doi.org/10.1093/eurheartj/ehac494>

FASTTRACK CLINICAL RESEARCH

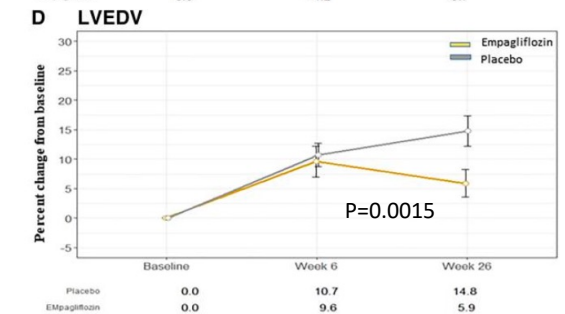
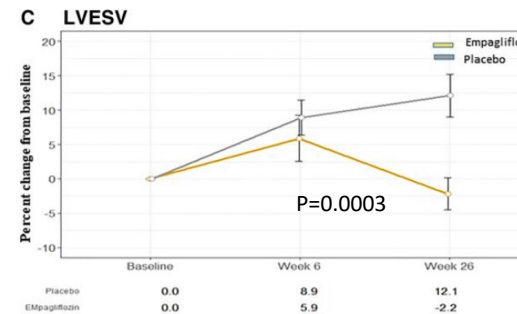
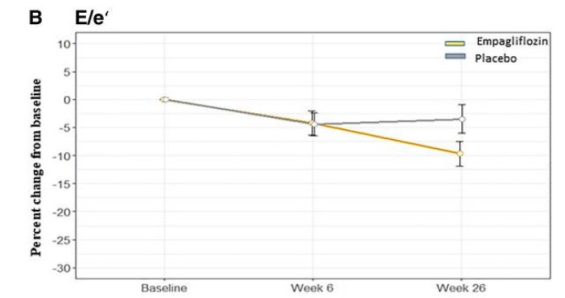
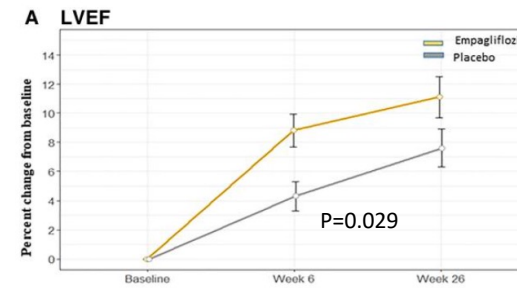
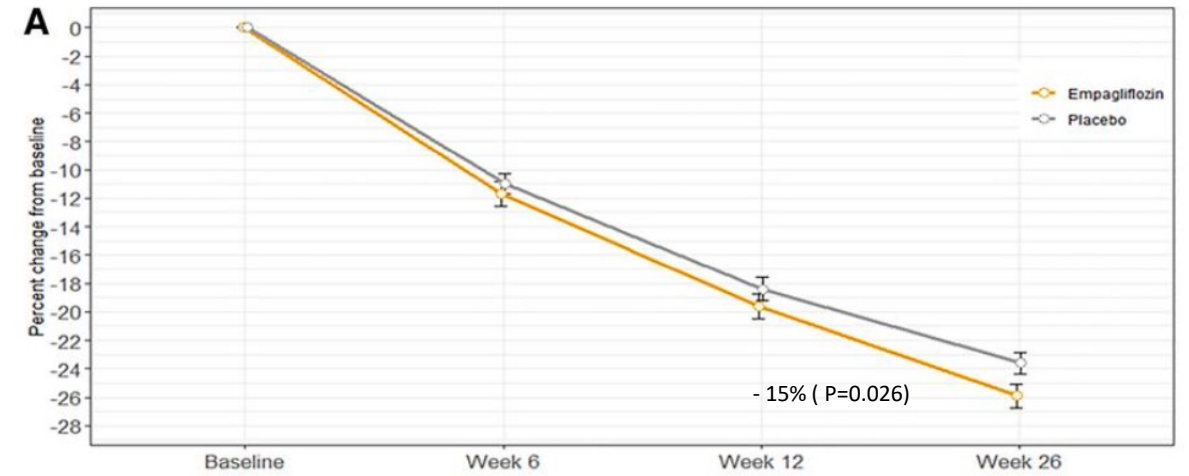
Clinical trials

Empagliflozin in acute myocardial infarction: the EMMY trial

Empagliflozin following severe myocardial infarction



D. von Lewinski et al.



ORIGINAL ARTICLE

Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

Stefan James, M.D., Ph.D.,^{1,2} David Erlinge, M.D., Ph.D.,³ Robert F. Storey, M.D., D.M.,^{4,5} Darren K. McGuire, M.D.,^{6,7} Mark de Belder, B.A. Cantab, M.B.B.S., M.A., M.D., F.R.C.P.,⁸ Niclas Eriksson, Ph.D.,¹ Kasper Andersen, M.D., Ph.D.,^{2,9} David Austin, M.D., F.R.C.P.,^{10,11} Gabriel Arefalk, M.D., Ph.D.,^{9,12} David Carrick, M.B.Ch.B., Ph.D., F.R.C.P.,^{13,14} Robin Hofmann, M.D., Ph.D.,¹⁵ Stephen P. Hoole, M.D., D.M.,¹⁶ Daniel A. Jones, M.D., Ph.D.,^{17,18} Kelvin Lee, M.R.C.P., Ph.D.,^{19,20} Hans Tygesen, M.D., Ph.D.,^{21,22} Peter A. Johansson, M.Sc.,²³ Anna Maria Langkilde, M.D., Ph.D.,²³ Wilhelm Ridderstråle, M.D., Ph.D.,²³ Ehsan Parvaresh Rizi, M.D., Ph.D.,²³ John Deanfield, C.B.E. F.Med.Sci. B.A. Hons. (Cantab), M.B., B.Chir., F.R.C.P., F.E.S.C., F.A.C.C.,²⁴ and Jonas Oldgren, M.D., Ph.D.,^{1,2} for the DAPA-MI investigators*

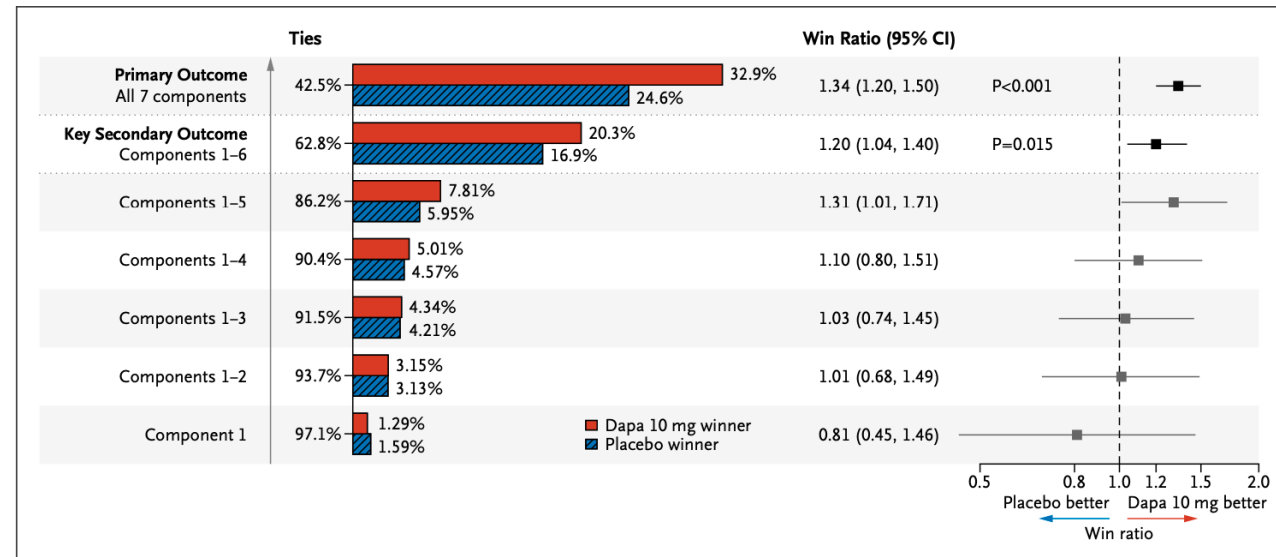


Figure 1. Primary and Key Secondary Hierarchical Composite Outcome, Assessed by the Win Ratio Method.

The results are presented as cumulative estimates where the number of components in the estimate is increased by one component at each step, according to the end point hierarchy, from the bottom and up (for per-component estimates in the hierarchy see Fig. S2). The gray arrow indicates the order of the end point hierarchy. Percentages are percent of 4,033,962 comparisons resulting in a win for Dapa 10 mg, tie, or win for placebo. The components in hierarchical order are as follows: 1. Death, 2. Hospitalization for heart failure, 3. Nonfatal MI, 4. Atrial fibrillation/flutter, 5. New diagnosis of type 2 diabetes, 6. NYHA class, and 7. Weight decrease of 5% or more.

Table 2. Secondary Outcomes.

Other Secondary and Exploratory End Points	Dapagliflozin 10 mg (n=2019)	Placebo (n=1998)	Hazard Ratio* (95% CI)
Composite of CV death/hospitalization for HF — n (%)	50 (2.5)	52 (2.6)	0.95 (0.64, 1.40)
CV death/hospitalization for HF/MI — n (%)	82 (4.1)	85 (4.3)	0.95 (0.70, 1.29)
MACE (MI, stroke, or CV death) — n (%)	68 (3.4)	72 (3.6)	0.94 (0.67, 1.31)
All-cause death — n (%)	41 (2.0)	33 (1.7)	1.22 (0.77, 1.92)
CV death — n (%)	27 (1.3)	23 (1.2)	1.15 (0.66, 2.01)
MI — n (%)	44 (2.2)	39 (2.0)	1.11 (0.72, 1.71)
Stroke — n (%)†	10 (0.5)	17 (0.9)	0.61 (0.28–1.34)
New diagnosis of type 2 diabetes — n (%)	42 (2.1)	78 (3.9)	0.53 (0.36, 0.77)
New diagnosis of atrial fibrillation/flutter — n (%)†	16 (0.8)	18 (0.9)	0.88 (0.45, 1.73)
All-cause hospitalization — n (%)	418 (20.7)	372 (18.6)	1.12 (0.98, 1.29)
Adjudicated hospitalization for HF — n (%)†	27 (1.3)	32 (1.6)	0.83 (0.50–1.39)
Placebo-Corrected			
Change in body weight — kg (mean)‡	–1.41 (–1.75, –1.07)	0.24 (–0.11, 0.58)	–1.65 (–2.12, –1.18)

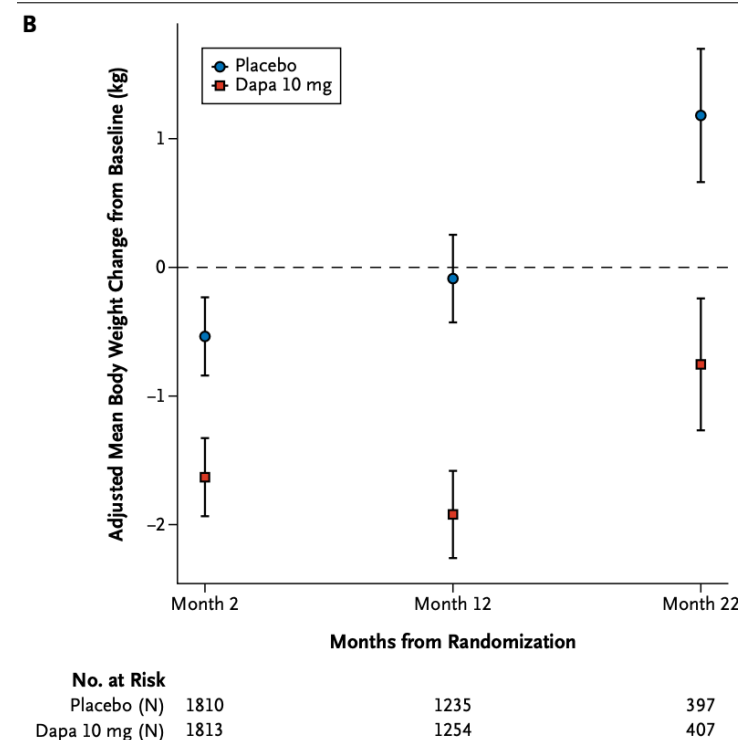
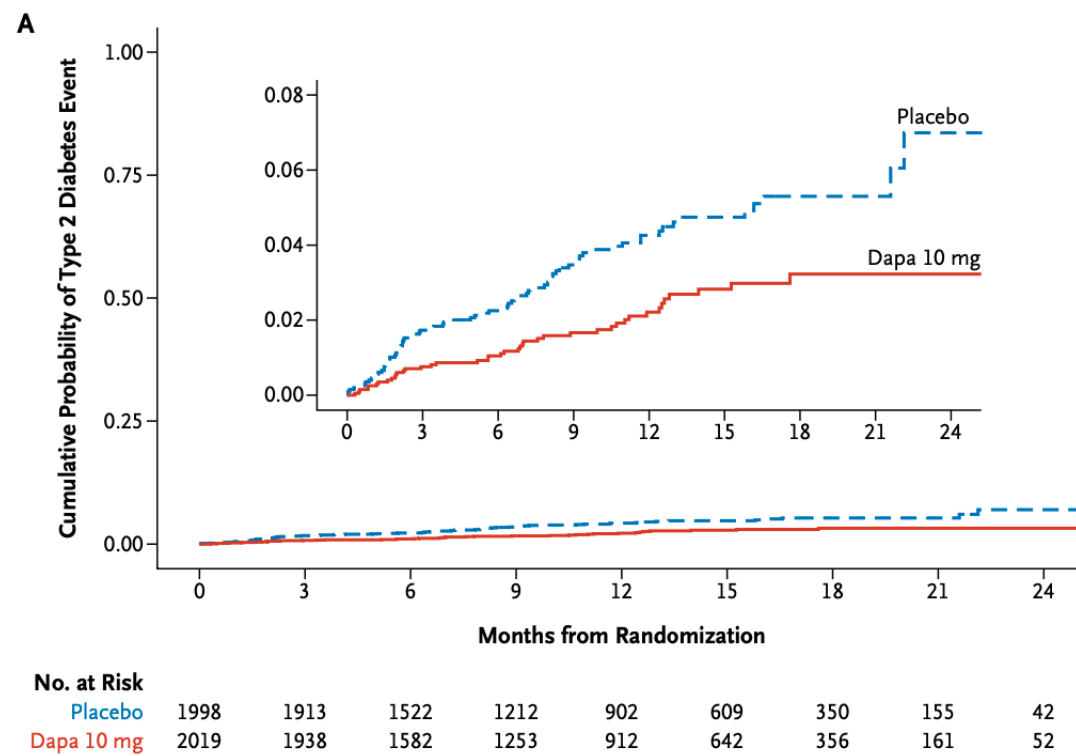
CONCLUSIONS In patients with acute MI as noted above, after approximately 1 year of treatment with dapagliflozin there were significant benefits with regard to improvement in cardiometabolic outcomes but no impact on the composite of cardiovascular death or hospitalization for heart failure compared with placebo. (Funded by AstraZeneca; ClinicalTrial.gov number, [NCT04564742](#).)

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The DAPA-MI trial extends the evidence from prior SGLT2 inhibitor trials and shows clinically relevant, largely cardiometabolic, benefits of dapagliflozin in patients hospitalized for acute MI with impaired LV function and without diabetes or prior chronic HF. Importantly, patients with any degree of globally or regionally impaired LV function were included and approximately 20% of patients had global LV ejection fraction greater than 50%. The primary outcome did not differ based on different degrees of LV function or level of troponin elevation.

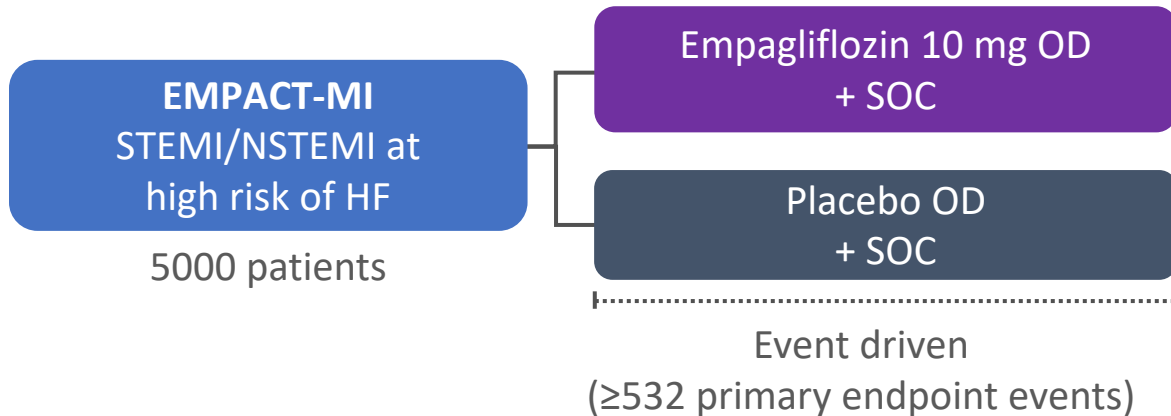


EMPACT-MI is designed to investigate the safety and efficacy of empagliflozin in patients after acute MI

Type of trial: Multicentre, randomized, double-blind, placebo-controlled trial

Population: Patients at high risk for developing new-onset HF after acute MI

Study design



Confirmatory endpoints

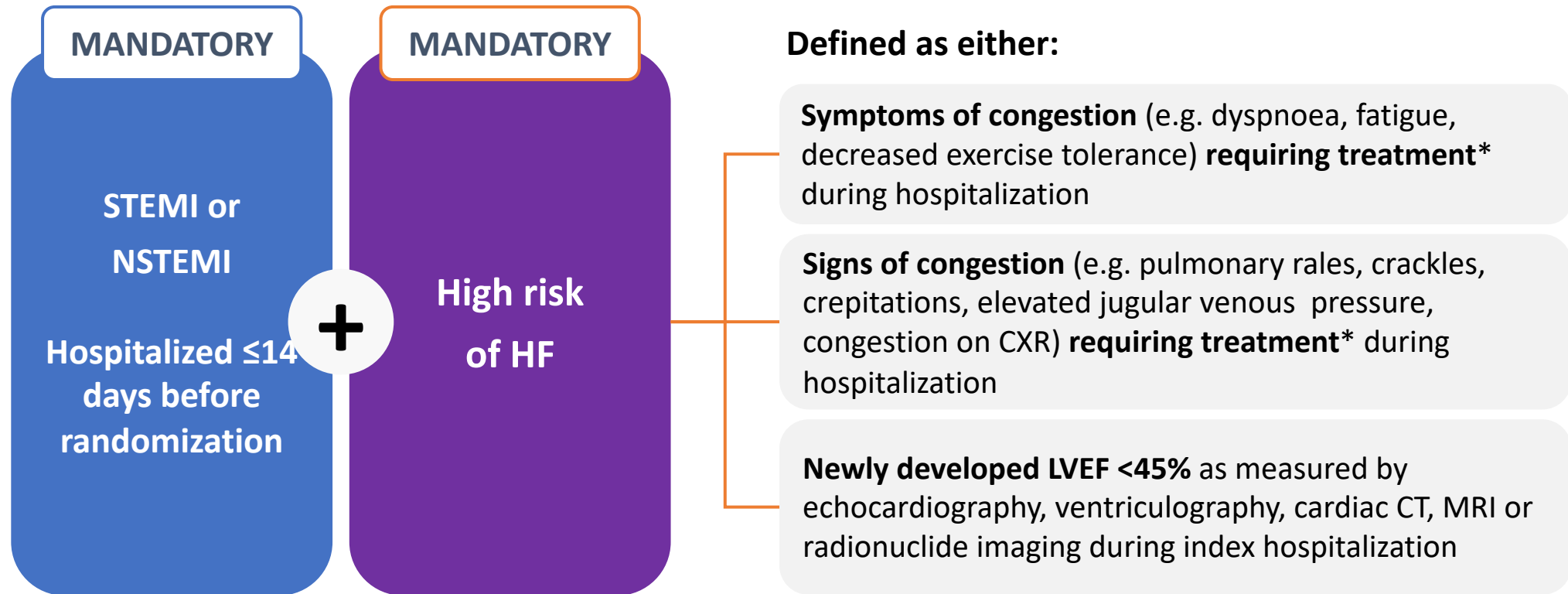
COMPOSITE PRIMARY ENDPOINT

Time to first HHF or all-cause mortality

KEY SECONDARY ENDPOINTS

- Total HHF or all-cause mortality
- Total CV hospitalizations or all-cause mortality
- Total all-cause hospitalizations or all-cause mortality
- Total MI hospitalizations or all-cause mortality

Inclusion criteria: High risk of HF



*Treatment included augmentation or initiation of oral diuretic therapy, IV diuretic therapy, IV vasoactive agent and mechanical intervention.
Harrington J *et al. Am Heart J.* 2022;253:86.

Inclusion criteria: Risk factors for development of HF

At least one of the following risk factors:

Age ≥ 65 years

AF (persistent or permanent)*

Uric acid ≥ 7.5 mg/dL

Newly developed LVEF $< 35\%$

Elevated NT-proBNP or BNP[†]

3-vessel CAD at time of index MI

Prior MI (before index MI)

Prior or new diagnosis of T2D

Patient not revascularized[‡]

Pulmonary artery systolic pressure ≥ 40 mmHg

eGFR < 60 mL/min/1.73 m²

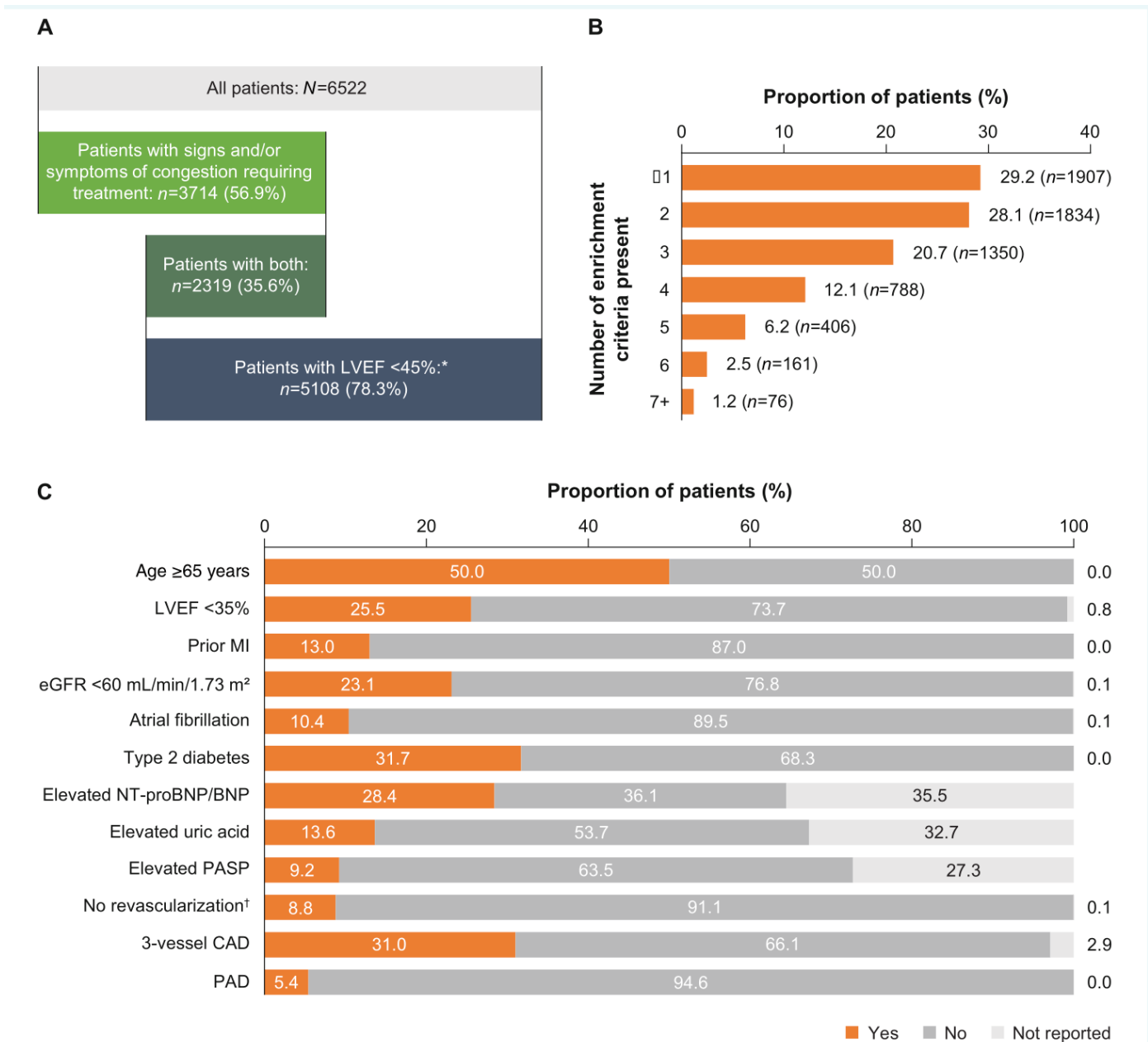
Diagnosis of peripheral artery disease

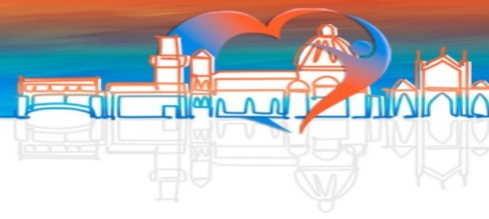
*If paroxysmal, only valid if associated with index MI. [†]Without AF: NT-proBNP ≥ 1400 pg/mL or BNP ≥ 350 pg/mL. With AF: NT-proBNP ≥ 2800 pg/mL or BNP ≥ 700 pg/mL.

[‡]Includes patients with no angiography performed, unsuccessful revascularization attempts, diffuse atherosclerosis not amenable to intervention, but does not include patients for whom no revascularization was performed due to non-obstructive CAD. Harrington J et al. *Am Heart J*. 2022;253:86.

Baseline characteristics of patients enrolled in the EMPACT-MI trial

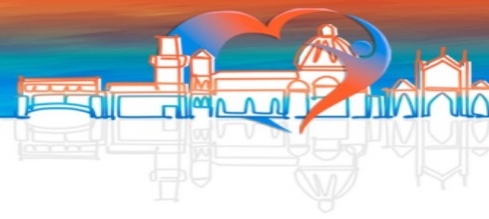
Josephine Harrington^{1,2}, Jacob A. Udell³, W. Schuyler Jones^{1,2}, Stefan D. Anker^{4,5}, Deepak L. Bhatt⁶, Mark C. Petrie⁷, Knut Robert Andersen⁸, Mikhail Sumin⁹, Isabella Zwiener¹⁰, Adrian F. Hernandez^{1,2}, and Javed Butler^{11,12*}





Conclusioni

- Gli SGLT2i hanno dimostrato importanti effetti cardio-renali-metabolici, con positivo impatto sugli outcome
- Rappresentano anche un potenziale strumento terapeutico nell'IMA (meccanismi fisiopatologici)
- Evidenze ancora limitate ma promettenti
- *EMMY trial*: riduzione livelli NTproBNP e miglioramento parametri ecocardiografici
- *DAPA-MI*: vantaggio nell' outcome composito, guidato dalla componente metabolica
- Necessità di dati più estensivi: *EMPACT-MI*...



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SGLT2i

Diabetes, HF and CKD Revolution

One for All...

All for one...



Grazie

Fabrizio Oliva

*Direttore SC Cardiologia 1-Emodinamica-UTIC
"De Gasperis" CARDIOCENTER
ASST GOM Niguarda, Milano
fabrizio.oliva@ospedaleniguarda.it*